20592

Zyprexa
(Olanzapine)

Lilly

NDA 20-592

1 VOLUME

APPROVAL PACKAGE

Antipsychotic

CATEGORY: 1S

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-592

Eli Lilly and Company
Attention: Timothy R. Franson, M.D.
Lilly Corporate Center
Indianapolis, IN 46285

SEP 30 1996

Dear Dr. Franson:

Please refer to your September 22, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) 2.5 mg, 5 mg, 7.5 mg, and 10 mg Tablets.

We acknowledge receipt of your amendment of September 16, 1996.

This new drug application provides for a new chemical entity indicated for the treatment of the manifestations of psychotic disorders.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in your submission of September 16, 1996. Accordingly, the application is approved effective on the date of this letter.

As discussed during the September 17, 1996, working meeting (telecon) with the Division, and as amended in several follow-up faxes and telephone conversations, the draft labeling was revised and is included as an attachment to this approval letter. These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-592. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitment, specified in the submission of September 16, 1996,

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitment, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

CDR Steven D. Hardeman, R.Ph.
Project Manager
(301) 594-5533

Sincerely yours,

Robert Temple 9/30/96

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: September 30, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approval Recommendation on NDA 20-592 Zyprexa® [olanzapine]

TO: File NDA 20-592
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

The NDA for Zyprexa was declared approvable on 8/30/96. My support for that action and my views of the evidence supporting it are provided in memoranda that I wrote to the file on 8/18/96 and 8/30/96.

This memorandum serves only to document my endorsement of the final approval action.

Dr. Andreason has now completed his review (9/26/96) of the firm's responses to requests made in the 8/30/96 approvable action.

The Product labeling presented in the approvable action letter has been modified to a minor degree as a result of negotiations with the firm over the past several weeks . How the final labeling proposal was developed is summarized in Dr. Laughren's memorandum of 9/27/96.

In addition to the documents prepared by Drs. Andreason and Laughren, I have personally reviewed the final product labeling.

Recommendation:

Issue the approval action letter and attached labeling.

Paul Leber, M.D.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 27, 1996

FROM: Thomas P. Laughren, M.D. TPL
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Zyprexa (olanzapine) for the treatment of psychotic disorders

TO: File NDA 20-592
[**Note**: This overview should be filed with the 9-16-96 submission.]

1.0 BACKGROUND

In our 8-30-96 approvable letter, we requested a safety update, a foreign regulatory update, a world literature update, and a commitment to conduct a relapse prevention study. In the biopharmaceutics area, we identified our preferred dissolution methodology and specifications, and we asked the sponsor to consider a further exploration of the population PK database as an approach to providing additional information regarding drug interactions. We also attached our proposal for labeling. Lilly responded formally to the approvable letter with the 9-16-96 submission.

The review team, up to the level of Team Leader, interacted with the sponsor over a period of several weeks to arrive at the version of labeling [LABOLNPS.AP3] that is included with the approval letter. The sponsor responded initially with an alternative labeling proposal on 9-6-96, including additional modifications on 9-9-96. We responded with a counterproposal that was faxed to Lilly on 9-16-96. The sponsor responded with faxes dated 9-16-96 and 9-17-96, and we held a teleconference with the sponsor on 9-17-96, reaching agreement on most of the disputed issues. Lilly provided language consistent with these agreements in faxes dated 9-18-96 and 9-19-96. Additional faxes dated 9-18-96 and 9-20-96

addressed remaining issues for pharmacology and a 9-18-96 fax addressed remaining chemistry issues. We faxed a final version of labeling on 9-23-96, and Gary Tollefson, M.D., from Lilly, confirmed late on that same day that this version of labeling, which is included with the approval package, was acceptable to them.

Dr. Paul Andreason reviewed the clinical sections of the 9-16-96 response to the approvable letter, including the safety update, the literature update, and the regulatory status update.

2.0 SAFETY UPDATE

The safety update included reports of deaths, serious adverse events, adverse dropouts, and patients experiencing potentially clinically significant changes in vital signs, laboratory values, and ECGs. This update covered a period from 7-15-95 through 8-14-96 for deaths and serious adverse events and from 7-15-95 through 2-14-96 for all other safety data. The safety update included data for 765 olanzapine patients from the primary database (690 ongoing patients for whom some safety data had already been reviewed in earlier submissions and 75 new patients) and for 148 total patients from the secondary database, including 14 olanzapine patients, and 134 blinded patients.

There were 5 deaths, 1 other serious adverse event, and 3 adverse dropouts, none of which could be reasonably attributed to olanzapine treatment. Dr. Andreason considered only 1 of the patients with potentially clinically significantly laboratory abnormalities to have likely had olanzapine-related changes. That patient had an increase in LFTs, an issue already addressed in labeling.

In summary, none of these reports contained new or unusual findings that would change my view about the approvability of this drug or necessitate further labeling changes.

3.0 WORLD LITERATURE UPDATE

The sponsor's literature update covered the period from the cutoff date for the original NDA submission to 9-4-96, and included 159 clinical and preclinical references. Dr. Andreason reviewed abstracts for all the clinical references and titles for all the preclinical references. These references contained no findings that would adversely affect the conclusions about olanzapine's safety.

4.0 FOREIGN REGULATORY UPDATE

The sponsor warranted in the 9-16-96 submission that Zyprexa is not approved in any countries at the present time, and that no negative regulatory actions have been taken with regard to olanzapine.

5.0 REQUEST FOR RELAPSE PREVENTION TRIAL

The sponsor has committed to conducting a phase 4 study to adequately address the question of long term effectiveness.

6.0 BIOPHARMACEUTICS

The sponsor accepted our proposed dissolution method and specifications.

7.0 LABELING

Lilly proposed numerous changes to the labeling for Zyprexa, many of which we found acceptable, while others were the subject of negotiations with the review team over the roughly 2-week time period described under Background. As noted, we were able to reach agreement at a Team Leader level on labeling. I will comment here on the resolution of labeling issues that required additional data review and discussion:

Suggested Starting Dose/Concerns About Orthostatic Hypotension:

In our labeling proposal, we had emphasized the possibility of orthostatic changes, and recommended a focus by clinicians and patients on initial titration as the period of greatest risk. We also recommended 5 mg as the initial dose, with an increase to 10 mg after several days.

Our view was based partly on theoretical grounds, i.e., olanzapine is a potent α_1 antagonist, and drugs with that property predictably have problems with initial titration. Common sense would lead one to be cautious based solely on this fact. Our recommendations were also based on finding (1) 5.5% of olanzapine vs 1.8% of placebo patients in a pool of 2 studies (HGAD and HGAP) having a potentially clinically significant postural change in systolic blood pressure ($\geq$ 30 mmHg decrease in systolic BP, supine to standing), and (2) spontaneous reports of hypotension in 5.2% of olanzapine patients vs 1.7% of placebo patients for this same pool. These patients also differed in the incidence of dizziness and

tachycardia. In addition, there were 15 instances of syncope in phase 2-3 trials, some of which occurred fairly early in treatment. Phase 1 data were also suggestive of a dose response relationship for syncope during initial titration.

The sponsor argued against a focus on initial titration as a period of risk, and also against a recommendation for 5 mg as a starting dose. They argued that their placebo controlled dose response studies did not show a difference between orthostatic effects between the 5 and 10 mg doses, however, these studies weren't designed to detect this effect, e.g., blood pressure wasn't monitored at a time most likely to reveal an effect. They also argued that olanzapine is 100-fold less potent as an α_1 antagonist than risperidone, and that a 10 mg initial dose was well tolerated in the vast majority of patients receiving this dose in the clinical trials.

Comment: After much discussion, we agreed to precautionary language that did focus on initial titration as a period of concern, and a recommendation for 5 or 10 mg as the starting dose, out of consideration of the possibility of dose dependency for the orthostatic effect. In addition, 5 mg will be the recommended dose for potentially vulnerable patients.

Data from Long-Term Trials Pertinent to Risk of Tardive Dyskinesia:

In our labeling, we had removed from the standard tardive dyskinesia warning Lilly's reference to data from a pool of haloperidol controlled long-term extension trials suggesting a higher rate of emergence of dyskinetic events for haloperidol compared to olanzapine. The pool was based on studies HGAD, E003, and HGAJ. It included 707 olanzapine and 197 haloperidol patients who were free of dyskinesia at entry into the extension phase, and were exposed to olanzapine or haloperidol for a median duration of 237 and 203 days, respectively. Using criteria that seemed reasonable, there did appear to be a greater incidence of dyskinetic symptoms for haloperidol compared to olanzapine, using several approaches.

Lilly objected, arguing that these are valid data that provide important information for prescribers. We acknowledged that, in the past, we have generally not permitted claims of reduced risk of tardive dyskinesia, but that such claims have generally been based either on theoretical considerations or on a lack of new cases in databases that were not adequate for detecting this event. While we further acknowledged that the data are suggestive of a possible difference between olanzapine and haloperidol regarding risk of treatment emergent dyskinesia, nevertheless, we argued that it is

difficult to know their usefulness in predicting the relative risk of tardive dyskinesia for the two drugs at later and possibly more relevant time points. Since the inclusion of such data in labeling would represent an important departure from our usual practice, we indicated that it would be a decision necessitating more work internally and likely consultation with outside experts.
Comment: We agreed to consider expeditiously a supplement that addressed a modification of the tardive dyskinesia statement, and the sponsor agreed to accept our decision not to include these data at this time.

Duration of Prolactin Elevation:

In our labeling proposal, we had noted the finding that prolactin levels are elevated by olanzapine treatment, and that "the elevation persists during chronic administration," since this phrase is in the standard prolactin statement for some antipsychotic drugs.

Lilly objected to this phrase, arguing that, while a modest increase is apparent early in treatment, endpoint analyses reveal no difference between olanzapine and placebo, unlike the data for haloperidol arms in these studies which reveal a persistent elevation for that drug. They wanted to add a sentence to the Hyperprolactinemia statement noting the finding of no difference at endpoint, and to note later in labeling that the elevation is transient. However, we disagreed with their argument that prolactin elevation with olanzapine has been demonstrated to be transient. The LOCF analysis is not the most pertinent, since it carries forward the levels for many placebo patients who dropped out very early. The most relevant analysis is observed cases at week 6, and here, the data show a clear dose response relationship, however, there is insufficient power given the attrition to achieve statistical significance. Furthermore, the data from extension trials revealed that prolactin levels are elevated compared to baseline, albeit to a modest extent and without a placebo control.

Comment: The sponsor agreed to our preference to characterize the effect as persisting, providing we acknowledged that the elevation during longer term treatment was modest. We agreed to this qualification.

Adequate Characterization of Weight Gain Observed with Olanzapine:

In our labeling, we added a Precautions statement describing overall the weight changes observed with olanzapine treatment. Lilly wanted to qualify this statement, by emphasizing that

the effect is most prominent in patients who are underweight at baseline, and they wanted to move the statement to Adverse Reactions.

We agreed with moving this statement to Adverse Reactions. We also agreed to acknowledging in the statement the fact that larger changes are observed in patients with lower BMIs at baseline. However, we noted that the statement must also acknowledge that, despite this differential effect on the basis of BMI, the weight gain was observed generally for olanzapine patients, despite the BMI category. In fact, the longer-term extension data revealed that the effect is even more prominent during longer-term use, with almost half of even the overweight patients taking olanzapine experiencing a $\geq$ 7% increase in body weight compared to baseline. This finding also needs to be incorporated into the revised statement.

Comment: The sponsor agreed to our revised statement, located in the Adverse Reactions section.

Recommended Monitored Regarding Concerns about LFT Increases:

In our labeling, we had recommended baseline transaminases in all patients being considered for treatment, with followup monitoring monthly for any patients having clinically significant baseline abnormalities. Lilly objected, arguing that routine screening of all patients is unnecessary. They proposed alternative language that recommends monitoring only in patients who already have significant hepatic disease. In reconsidering this issue, including an examination of a consult done for Lilly by Hy Zimmerman, we were inclined to agree that requiring baseline LFTs in all patients would be excessive, and in fact, would not be consistent with our labeling for other recently approved drugs with a similar profile of transient, asymptomatic transaminase increase.

Commment: We agreed to a slightly modified version of Lilly's proposed labeling that noted the finding and recommended that caution should be observed in patients with hepatic impairment.

Adequacy of Available Data Pertinent to Long-Term Efficacy of Olanzapine:

In our labeling, we had not permitted Lilly to describe the efficacy findings from patients extended from the short-term phases of their efficacy studies, even though these data were suggestive of an effect. We argued that studies of this design are basically flawed, i.e., the randomization is violated, since only responding patients are continued in the extension phase. They wanted to

distinguish between continuation effects and relapse prevention effects, however, we noted that this basic flaw would apply whether one is focusing on either. We indicated that is was our view that these studies cannot provide definitive data pertinent to the question of long-term efficacy, and to include these data would undermine our current approach to this issue in labeling. Further, we reminded the sponsor that the labeling acknowledges under Dosage and Administration the usual practice of continuing responding patients, so that including this information would not strengthen labeling in any way from the clinician's standpoint.

Comment: We discussed this matter at some length, but in the end, the sponsor agreed with our preference to not include this information in labeling.

8.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has submitted sufficient data to support the conclusion that Zyprexa is effective and acceptably safe in the treatment of psychosis. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling.

cc:
Orig NDA 20-415
HFD-120
HFD-120/TLaughren/PLeber/PAndreason/GDubitsky/SHardeman
HFD-100/RTemple

DOC: MEMOLNPS.AP1

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

Review and Evaluation of Clinical Data
NDA # 20-592

Sponsor:	Eli Lilly and Company
Drug:	ZYPREXA™ (olanzapine)
Material Submitted:	Response to Approvable Letter and Safety Update
Correspondence Date:	September 16, 1996
Date Received:	September 17, 1996

I. Background

ZYPREXA™ (olanzapine) is an antipsychotic agent that belongs to the thienobenzodiazepine class. On August 30, 1996, FDA issued an approvable letter for the olanzapine NDA 20-592. In the approvable letter a number of revisions to the sponsor's labeling were proposed. FDA requested a safety update to include reports of deaths, serious adverse events, adverse dropouts, and potentially clinically significant changes in vital signs, laboratory values. and ECGs from clinical trials and any post-marketing safety data. FDA also requested a world-wide literature update, a foreign marketing and labeling update, and a commitment from the sponsor to perform a postmarketing study on the efficacy of olanzapine in preventing the relapse of the acute symptoms of schizophrenia. FDA also requested that the sponsor adopt a different dissolution specification.

II. Safety Update

A. Scope of the Safety Update

The initial safety update covered the period from 2/15/95 through 10/31/95 for deaths and serious adverse events and from 2/15/95 through 7/14/95 for all other types of safety data. The review of the first 4-month safety update was performed by Greg Dubitsky, M.D. in a review dated July 29, 1996. The current safety update covers from 7/15/95 through 8/14/96 for deaths and serious adverse events and from 7/15/96 through 2/14/96 for all other safety data.

Clinical trials contributing to this safety update were divided into a primary and secondary database by the sponsor. The primary safety database consisted of 4 open-label extension studies of Phase 2 and 3 multicenter clinical studies and 10 open-label phase

three studies that are enumerated in Table 1. The secondary database includes the following, which are enumerated in Table 2:

- three clinical pharmacology trials.
- four open-label studies done in Japan.
- eleven Phase 3 studies which are still blinded.
- five open-label Phase 3 studies in which <15% of the planned number of patients had been enrolled as of 2/14/96.

The sponsor states[1] that there are 765 patients represented in the primary database: 690 patients are ongoing patients from the clinical trials presented in the NDA 20-592 submission and 75 new patients from new protocols. Doses of olanzapine ran from 1-25 mg/day. The secondary database comprised studies enrolling 148 patients, 134 of whom remain behind the study blind. The sponsor did not provide estimates of cumulative exposure to olanzapine in these recent data.

The sponsor provided the following data for the primary database:

- Deaths
- Serious Adverse Events
- Adverse Dropouts
- Potentially Clinically Significant Adverse Events as defined in the original NDA submission.
- Potentially Clinically Significant Changes in Vital Signs and Weight
- Potentially Clinically Significant Changes in Clinical Chemistry Analytes
- Potentially Clinically Significant Changes in Hematology Analytes
- Potentially Clinically Significant Changes in Urinary Analytes
- Potentially Clinically Significant Changes in ECG Intervals and Heart Rate

The PCS criteria used to identify these patients was identical to the criteria applied in the previous safety update.

The sponsor provided the following data for the secondary database:

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[1]**The numbers of patients in the primary and secondary databases were conveyed to this reviewer via telephone by Anne-Marie Crawford of Eli Lilly and Company as this information was not in the safety update. The sponsor will prepare an addendum containing this information.**

- Deaths
- Serious, Unexpected and Possibly Causally Related Adverse Events ("Alert Events")

This data is more than adequate for this safety update.

B. Review methodology

Line listings of COSTART terms were examined for all deaths, serious or "alert" events, or events leading to discontinuation, to detect the occurrence of any adverse events judged to be clinically important. For any such event or any event with a non-specific COSTART term, the corresponding patient summary was reviewed. A judgement was made regarding possible causality to olanzapine.

For potentially clinically significant adverse events in the Primary Database, listings were examined to detect any events not previously observed in the original NDA database.

Line listings of patients with potentially clinically significant changes in laboratory, vital sign, and ECG parameters were not examined in detail for the following reasons. Changes in these parameters were more systematically evaluated in the original NDA database. Data in this update were largely uncontrolled and from long-term use; patient exposure was not known, which did not permit the calculation of even uncontrolled incidence rates. Furthermore, changes in these parameters which were associated with clinical events should have been detected under the reviews of important adverse events. In short, a useful interpretation of the line listings for these variables, as presented in this submission, would not have been possible.

C. Summary of Safety Findings

Deaths
There were five newly reported deaths of olanzapine treated patients (during treatment or less than 31 days after treatment termination) that occurred between the dates of 10/31/95 and 8/14/96. They are as follows:

HGAJ 045-1281 44 year old African-American female with a history of adult onset diabetes (insulin treated), morbid obesity, and medical non-compliance treated with olanzapine for 537 days (her usual dose was olanzapine 20 mg/day). She experienced acute respiratory distress at home which progressed to cardiac arrest. Paramedics efforts at resuscitation were not successful. At autopsy the patient was found to have sickled cells in the liver sinusoids but no evidence of liver disease. It is unlikely that this patient's death was related to olanzapine.

HGBT 241-2401 70 year old white female taking olanzapine 10 mg/day after 440 days of therapy. The last patient visit was January 2, 1996 and the date of death was May 21, 1996. The cause of death was listed as old age. It is unlikely that the patient's death is related to olanzapine therapy.

HGBT 241-2403 49 year old white male with a history of early onset Parkinson's Disease. The death, which occurred after 411 days on olanzapine 10 mg/day, was not witnessed and an autopsy was not performed. The cause of death is listed as a cardiac arrest. It is unknown if the patient had a previous history of cardiac disease and he was taking Permax and Sinemet (both of which are associated with cardiovascular events including "heart arrest".) It is felt to be unlikely that the patient's death is related to olanzapine treatment.

HGBG 160-1604 34 year old white male who was hit by a train 28 days after discontinuing olanzapine. The investigator believes that this most likely represents a completed suicide though the patient had not reported or demonstrated suicidal thoughts or behavior prior to his demise. The patient's death is unlikely to be related to olanzapine treatment.

HGDY 007-1308 31 year old white male who took olanzapine 10 mg/day for 11 days. Due to an increase in psychotic symptoms the patient was admitted to the hospital where olanzapine was discontinued and clozaril was started and increased to 400 mg/day. The patient was reported as doing "fine" in the hospital on 21 July 1996 at 7 P.M. but 30 minutes after this notation he was found dead. The presumed cause of death was "heart failure", but no autopsy was performed. The patient's death was unlikely to be related to olanzapine treatment. Sudden cardiorespiratory arrest has been rarely associated with clozapine treatment, according to Cloazaril labeling.

Serious Adverse Events

HGAJ 723-5541 45 year old white male with a history of heavy alcohol intake was hospitalized to work-up difficulty breathing and fever and the patient was found to have elevated GGT, elevated SGOT and SGPT. He was found to have a large apical thrombus and was placed on anticoagulants. It is doubtful that the patient's dyspnea and fever were related to olanzapine therapy, but transaminase elevations have been associated with olanzapine treatment.

Adverse Dropouts

HGCA 001-1001 was listed as dropping out due to leukopenia; however, the lowest reported WBC was 3.96K with a baseline of

5.56K. He had no signs of infection, fever, or other sequelae of leukopenia.
Patient **HGAJ 004-0023** was listed as experience hepatitis; however, he was found to have active hepatitis C.
Patient **HGCM 155-1588** was listed as experiencing jaundice; however, he was found to have active hepatitis C.

Potentially Clinically Significant Adverse Events
HGAJ 333-3288 was listed as experiencing leukopenia; however, the lowest WBC count was 2.39K with a baseline WBC of 3.82K and a last visit WBC of 2.77K. The patient continues on olanzapine and has had no symptoms of fever, infection, or other signs of sequelae of leukopenia. This is another case of benign leukopenia that was observed in a few patients in the NDA. In the review of the NDA this reviewer concluded that there was no evidence that there was any indication of clinically significant leukopenia, neutropenia, or agranulocytosis. Due to concerns about significant neutropenia (to include agranulocytosis) occurring with other atypical antipsychotics, rare cases of leukopenia in the olanzapine clinical trials database were carefully scrutinized. Though the occurrence rate of these cases was slightly numerically higher in the olanzapine treatment group compared to placebo, the aggregate data showed no statistically significant differences in mean change from baseline (a measure of central tendency) or the incidence of "potentially clinically significant" leukopenia (a measure focused on outliers). It could not be concluded that this benign leukopenia was related to olanzapine use.

Conclusions and Recommendations
Only one adverse event in this update was felt to be possibly related to olanzapine therapy.

- **Liver enzyme elevations (HGAJ 723-5541).** This is felt to be adequately described in currently proposed labeling for ZYPREXA.

III. Post Marketing Study

FDA requested that the sponsor perform a post-marketing study under IND The sponsor agreed to this request, but en lieu of providing a protocol, they wished to consult FDA as to acceptable study designs prior to doing so.

IV. Foreign Regulatory Update and Labeling

Olanzapine has yet to be approved in any country though it is under review in several countries throughout the world. The sponsors do

not report that any foreign regulatory agency has any safety or efficacy concerns that are impeding the approval process.

V. World Literature Update

The database of archival literature for olanzapine was created and is maintained as follows:

When the database was created and is updated, on-line bibliographic search databases are queried using a fixed search strategy. The search strategy is to query the databases through the Dialog service for any mention of olanzapine or LY170053. The databases used for this search are:

Medline	**Derwent Drug File**	**Toxline**	**SciSearch**
Embase	**PsycINFO**	**Biosis**	**Pascal**

The importation, storage, and retrieval of these references is performed using Reference Manager[2]. The initial search (for NDA 20-592 inclusion; 1995) was performed to include all historical references. After the initial search, the database has been and continues to be updated on a quarterly basis using the same search strategy. The date of the last on-line search to update the olanzapine database was September 4, 1996.

A listing of titles of all 159 references was reviewed by Charles M. Beasley, Jr., M.D., Clinical Advisor, Olanzapine Development Team, Lilly Research Laboratories, who has maintained copies of and is familiar with the majority of these citations.

The abstracts of the clinical references were reviewed by this reviewer along with the titles of the preclinical references. There was no information in these references that provided new information regarding the safety or efficacy of olanzapine that should be mentioned in labeling.

VI. Biopharmaceutics

The sponsor addressed both questions regarding a) dissolution methodology and specification and b) population pK and drug interactions. This reviewer will defer to the biopharmaceutic and chemistry recommendations on these issues.

VII. Labeling

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[2]This is a commercially available software program designed for the purpose of creating, maintaining, and searching bibliographic databases.

The sponsor submitted a proposed labeling that was edited and modified by Thomas Laughren, M.D., Greg Dubitsky, M.D., and this reviewer. These modifications were discussed with representatives of the sponsor on 9/17/96 and were acceptable to the sponsor; proposed labeling awaits further review by Drs. Leber and Temple.

Paul J. Andreason, M.D.
September 26, 1996

cc: NDA# 20-592
HFD-120
HFD-120/PAndreason
GDubitsky
SHardeman
TLaughren

9-27-96

I agree that this NDA can now be approved. See memo to file for my more detailed comments.

James P. Laughren, MD
TL, PDP

Table 1 Studies Included in the Updated Primary Safety Database	
Protocol Number	Title/Design/Dose Range
FID-EW-E003	A Fixed Dose Range Safety and Efficacy Study of Olanzapine Versus Open-Label Extension Haloperidol in the Treatment of Schizophrenia. Double-blind comparator controlled followed by open-label extension/ 50 centers in 15 outside US countries. Dose range 1.0-17.5 mg/day.
FID-MC-HGAJ	Olanzapine Versus Haloperidol in the Treatment of Schizophrenia and Other open-Label Extension Psychotic Disorders. Double-blind comparator controlled followed by open-label extension/174 centers international.
FID-MC-HGAD	LY170053 Versus Placebo and Haloperidol in the Treatment of open-Label Extension Schizophrenia. Double-blind, placebo and comparator controlled followed by open label extension/23 centers US and Canada. Dose range 2.5-17.5 mg/day.
FID-MC-HGAP	Fixed-Dose Olanzapine Versus Placebo in the Treatment of Schizophrenia Open-Label Extension. Double-blind, placebo controlled followed by open label extension/12 centers US. Dose range 1.0-10.0 mg/day.
FID-MC-HGBB	Open-Label Experience with Olanzapine. Open label, single center/ France, Dose range 5-20 mg/day.
FID-MC-HGBI	Open-Label Olanzapine. Open label, single center/ US, Dose range 5-20 mg/day.
FID-MC-HGBK	Open Label Olanzapine in Treatment-Refractory Schizophrenics. Open label, 5 centers/ Spain, Dose range 5-20 mg/day.
FID-MC-HGBM	Open-Label Clinical Trial on Antipsychotic Safety and Efficacy and Safety of Olanzapine in Schizophrenic Patients with Positive or Negative Symptomatology. Open label, single center/ Germay, Dose range 10-25 mg/day.
FLD-MC-HGBT	Olanzapine in Dopaminomimetic Psychosis in Patients with Parkinson's Disease. Open label, single center/ Netherlands, Dose range 1-15 mg/day.
FID-MC-HGBX	Open-Label Olanzapine. Open label, single center/ US, Dose range 5-20 mg/day.
FID-MC-HGCA	Open-Label Experience with Olanzapine. Open label, single center/ US, Dose range 5-20 mg/day.
FID-MC-HGCG	Open Label Experience with Olanzapine. Open label, single center/ US, Dose range 5-20 mg/day.
FID-MC-HGCM	Efficacy and Safety of Olanzapine in the Treatment of Chronic Schizophrenic Patients Not Responding to Clozapine. Open label, 5 centers/ Israel. Dose range 5-25 mg/day.
FID-MC-HGDI	Open-Label Experience with Olanzapine in Patients Who Have Completed a Previous Olanzapine Clinical Trial. Open label, 6 centers/ US, Dose range 5-25 mg/day.

Table 2 Studies comprising the secondary safety database (N=148: 134 still blinded)	
Study	**Title/Design/Dose Range**
Clinical Pharmacology/Pharmacokinetic Studies	
F1D-LC-HGFJ	Safety and pharmacokinetic study in patients with cirrhosis.
F1D-MS-E002	Interactions between olanzapine and levomepromazine.
F1D-MS-HGCI	Pharmacokinetic interaction betweeer. fluoxetine and olanzapine.
Open label, Japan	
F1D-JE-202E	Late phase-II clinical study: Dose finding study of schizophrenia
F1D-JE-203E	Long-term study: Extension study from the late phase II study
F1D-JE-204E	Assessment of the efficacy and safety of LY170053 in treatment resistant schizophrenic patients
F1D-JE-208E	The extension long-term study of treatment resistant schizophrenia
Open-Label Phase III Studies (<15% Enrollment as of 2/14/96)	
F1D-MC-HGBO	Cost effectiveness of olanzapine in treatment resistant schizophrenic patients.
F1D-MC-HGCS	Open-label trial of olanzapine in children with childhood onset schizophrenia.
F1D-MC-HGCT	Long-term open-label trial of olanzapine in children with childhood onset schizophrenia-extension.
F1D-MC-HGCY	Open-label experience with olanzapine. Open-label 15 centers
F1D-MC-HGDB	Open label experience with olanzapine in patients who had completed a previous olanzapine trial

Blinded Phase 3 Studies	
F1D-CA-P022	Olanzapine versus haloperidol and risperidone in the treatment of schizophrenia
F1D-MC-HGBA	Olanzapine versus chlorpromazine in the treatment of patients with therapy-refractive schizophrenia
F1D-MC-HGBF	Double-blind, Olanzapine versus clozapine in the treatment of schizophrenia
F1D-MC-HGBG	Olanzapine versus resperidone in the treatment of schizophrenia and other psychotic disorders
F1D-MC-HGBH	Olanzapine versus amisulpride in the traetment of negative symptoms and deficit states of chronic schizophrenia
F1D-MC-HGBJ	Double-blind clinical investigation of olanzapine versus perphenazine in patients with schizophrenia
F1D-MC-HGBL	Double-blind, Olanzapine vs. Flupenthixol in the Treatment of Schizophrenia
F1D-MC-HGBQ	Olanzapine vs. Haloperidol in Partial Responders Affected by Schizophrenia; Acute and Chronic Treatment
F1D-MC-HGBU	Double-Blind, Olanzapine vs. Risperidone in the Treatment of Schizophrenia
F1D-MC-HGCR	Olanzapine vs. Haloperidol in Childhood Onset of Schizophrenia
F1D-VI-HGCH	Efficacy and Safety of Olanzapine vs. Fluphenazine

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-592

AUG 30 1996

Eli Lilly and Company
Attention: Timothy R. Franson, M.D.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Franson:

Please refer to your September 22, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) 2.5 mg, 5 mg, 7.5 mg, and 10 mg Tablets.

We acknowledge receipt of your amendments dated:

September 26, 1995	September 27, 1995	September 28, 1995
October 3, 1995	October 19, 1995	October 31, 1995
November 20, 1995	November 27, 1995	December 4, 1995
December 7, 1995	December 15, 1995	January 12, 1996
January 19, 1996	January 29, 1996	February 1, 1996
March 21, 1996	June 4, 1996	June 10, 1996
June 14, 1996	July 22, 1996	July 26, 1996

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to respond to the following requests:

1. Labeling

   Accompanying this letter (Attachment 1) is the Agency's proposal for the labeling of Zyprexa. We believe it presents a fair summary of the information available on the benefits and risks of Zyprexa.

   We have proposed a number of changes to the draft labeling submitted in your original submission. We will be happy to discuss these proposed changes in detail, and to discuss any disagreements you might have with any part of the proposed labeling format or content.

2. Post-marketing Study

   Although the evidence submitted documents the short-term efficacy of Zyprexa in the management of the manifestations of psychosis, there is no evidence bearing directly on the effectiveness of this drug in the maintenance treatment of remitted/partially remitted

psychotic patients. Because it is likely that Zyprexa will be widely used for these purposes, it is critical that appropriate clinical studies be undertaken to evaluate its safety and effectiveness in long-term use. We request that you commit to performing a study of subsequent to approval. Division staff would be happy to discuss this and any other proposals with you. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to Phase 4 commitments must be clearly designated "Phase 4 Commitments."

3. Safety Update

Our assessment of the safety of olanzapine is based on our review of all safety information provided in your original and subsequent submissions, including your safety update (January 12, 1996 amendment). This original review was based on an integrated safety database with a cutoff date of approximately 2-14-95 and on additional serious events and deaths reported up to a cutoff date of approximately 10-31-95. Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you provide a final safety update focusing on deaths, serious adverse events, and dropouts for adverse events. This final safety update can be in the same general format as your 1-12-96 safety update.

4. World Literature Update

Prior to the approval of Zyprexa, we require an updated report on the world's archival literature pertaining to the safety of Zyprexa. This report should include only literature not covered in your previous submissions. We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Zyprexa. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

5. Foreign Regulatory Update/Labeling

We require a review of the status of all Zyprexa actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If Zyprexa is approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for Zyprexa along with English translations when needed.

6. Biopharmaceutics

a. Please adopt the following dissolution methodology and specification for all tablet strengths:

Apparatus:
Media:
Volume:
Speed:
Sampling time:
Specification: not less than

b. We ask that you consider a further exploration of the population PK database as a approach to providing additional information regarding drug interactions.

Please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact CDR Steven D. Hardeman, R.Ph., Project Manager, at (301) 594-5533.

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

DRUG STUDIES IN PEDIATRIC PATIENTS

(To be completed for all NME's recommended for approval)

NDA: **20-592**
Product: **Zyprexa (olanzapine) 2.5mg, 5mg, 7.5mg, 10mg Tablets**
Sponsor: **Lilly**
Project Manager: **CDR Steven D. Hardeman, R.Ph.**
Division: **HFD-120**

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 and #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

✓ a. The applicant has committed to doing such studies as will be required.

✓ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

Thomas P. Laughren 7-24-96

Signature of Preparer Date

cc:
Orig NDA
HFD-120 Division File
NDA Action Package

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

CERTIFICATION

NDA Application No.: **NDA 20-592**

Drug Name: Zyprex

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Timothy R. Franson, M.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: _____
Timothy R. Franson, M.D.

Title: Executive Director, North American Regulatory Affairs

Date: January 19, 1996

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 30, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Actions taken and not taken in response to your memorandum of 8/27/96, concerning HFD-120's review of NDA 20-592 Zyprexa® [olanzapine]

TO: File NDA 20-592
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

In your memorandum[1], you offer a number of comments. I have little to say about most of them, but there are a couple to which a response is necessary.

Before doing so, however, I want to acknowledge an oversight.

Dr. Greg Dubitsky had a prominent and important role in the development of the Division's review of the Zyprexa application, a point not obvious from a review of documents in the package originally forwarded to the Office. Greg served as Dr. Andreason's mentor and, as such, is a substantive contributor to that primary review document (e.g., by analogy, if this were an academic manuscript submitted to an archival medical journal, Greg would be the senior coauthor).

Now, I will turn to the substantive points I have about your comments concerning the Zyprexa application.

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[1] I am mindful that the memorandum cited was delivered with a stamp indicating it was intended as a draft. Because the memorandum offered a number of comments and suggestions requiring responses or actions to which the Division has now taken some form of response, the memorandum is functionally much more a preliminary communication that is relevant to the decision making process than a preliminary draft explicating your personal views. In short, there is no practical way I can respond to and/or explain our decisions to act upon and/or not act upon a point conveyed in your memorandum without making reference to it.

1. Dropouts

I'm somewhat surprised by your reaction to the "go open" provision of the HGAP protocol. In fact, in virtually any placebo controlled trial with actively psychotic patients, a high early dropout rate is expected for both "ethical" and "medical" reasons. The use of placebo is considered arguable in the first place. Next, for management reasons (e.g., staff morale, legal risk, etc.), there are few, if any, hospitals in which a study permitting actively psychotic patients to be assigned to placebo is going to continue for even a couple of weeks, let alone 4. Finally, a high early dropout rate attributable to therapeutic failure that differentially affects the placebo group is actually a finding we look for because it documents the assay sensitivity of the population admitted for study. Of course, the censoring biases the between treatment comparisons made at latter time points in the study, but this is the very reason that I consider these studies more as a source of proof of principle of a drug's antipsychotic effects than as a basis to estimate the "effect size" of the drug. Indeed, this is yet another reason that I find drug-drug comparative studies so difficult to assess.

Viewed from my perspective, therefore, HGAP was unusual for the extent it was able to retain subjects until week 4. (If I had the time, I could probably find examples to document this assertion --that is, of antipsychotic trials where dropouts rates at earlier times are very high.) In any case, although 80 % of those randomized in HGAP remained on drug for only the first for 4 weeks, among those who did drop out-- 74, 62 and 56 percent (pbo,1,10) did so for lack of effectiveness--the pattern was consistent with a dose related effect, and, therefore, provides additional proof in principle of Zyprexa's efficacy.

2. Comparisons.

Comparisons are odious. For this reason alone it is sensible to approach any nominal advantage claimed by a sponsor for his product relative to a competitor's with considerable caution, even if the claim seems to rest on evidence adduced in an adequate and well controlled clinical investigation. One concern is that an experimental design for determining whether or not a drug is effective for use may be totally inappropriate for obtaining a fair comparison of the utility and performance of two drugs. Moreover, even if great care is taken to check the conditions under which the experimental comparisons are made, the estimates of the comparative utility adduced in a given experiment may be biased for any number of reasons, many not obvious.

I believe that you share these views, at least insofar as the principle is concerned.

Accordingly, I am surprised at your dismissal of my reservations (discussed in footnote 3 of my August 18 memorandum) about the arguable validity of the instruments used to assess the comparative performance of antipsychotic drugs. Moreover, I find your explanation for doing so unsatisfactory.

You seemingly dismiss, out of hand, my concern that an outcome assessment instrument that is valid as a measure of antipsychotic effect in a drug placebo trial might not reliably measure antipsychotic effect in a drug-drug comparison trial. Perhaps, I failed to develop my argument well enough in my memorandum of August 18, 1996, but the concern cannot be dismissed so easily.

As with a lab test, the performance of an outcome assessment instrument lies as much, if not more, in its specificity as in its sensitivity. The problem in schizophrenia outcome assessment is that some of the so-called "negative" signs and symptoms of that illness are indistinguishable from the pseudoparkinsonian signs and symptoms that are known side effects of antipsychotic drugs like haloperidol. It would be reckless, therefore, to assume that a drug - haloperidol difference detected on an instrument that registers negative symptoms is actually measuring a difference in antipsychotic effectiveness. To be clear, it is in theory possible to look at individual scale items to see to what extent, if any, the difference in total scale scores is attributable to items that might register pseudoparkinsonian signs/symptoms. Unfortunately, we have neither the luxury in time or resources to do this now.

In sum, I believe you cannot dismiss fairly, or with reason, my view that the validity of a measurement must be evaluated in the context of the use to which it is put, or stated conversely, that its validity <u>cannot</u> be judged from its[2] properties examined in isolation. This view is hardly mine alone; in fact, it is the view celebrated in the guidance offered in the American Psychological Association's manual on psychometric test validity.

Accordingly, I believe your implication that my concern about the validity of the assessment instruments can be dismissed on your personal observation

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[2] it refers to the instrument that generates the measurement

that "Although ...a test could respond to some action of a drug other than its antidepressant action, that seems equally true for the comparison with placebo. The answer, I think, is to expect that a difference, to be considered real, will show upon on all (most) of the tests we use to evaluate antipsychotic, antidepressant, etc. findings."

By the way, I agree totally with your view about the value of products that work where others fail. That, however, is a very different comparative matter, one with very different implications for both labeling and advertising.

4. Deaths

On this subject, I have only an observation. I would be very wary of making very much of any extrapolations based on a pooling of data taken from the three drug development cohorts. I have no confidence, let alone a valid means, to know just how comparable they are, and therefore, whether it is appropriate to combine them. In short, any pooled estimate of a common attribute will be of uncertain validity.

Incidentally, as to 'p' values for these or any other post hoc comparisons, I doubt whether or not a correction for multiplicity is or is not made has any effect on their validity. I speak primarily of data conditioned contrasts among groups not formed by randomization. You can calculate a 'p' value for these contrasts, but it has no useful meaning. Such contrasts beg the identity of the null hypothesis being tested in the sense that even if a low 'p' is obtained, the cause of the difference that is too small to be attributed to chance remains uncertain.

Most of the other points covered in your memorandum are about specific issues and I have no comments to offer about them, although Dr. Laughren does in his memorandum. It also addresses issues raised in the course of our meeting. Dr. Laughren also explains why we have not followed certain of your suggestions.

In any event, my comments and observations notwithstanding, the NDA is approvable provided, of course, that Zyprexa is marketed under the draft labeling that is serves as attachment 1 to the approvable action letter now being forwarded.

Paul Leber, M.D. 8/30/96

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 18, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 20-592 Zyprexa® (olanzapine)

TO: File NDA 20-592
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my endorsement of the review team's unanimous recommendation that the NDA for Zyprexa be declared **approvable.**

Introduction

The review team's exposition of the evidence documents that the sponsor's application provides sufficient information to establish, within the meaning of the Act, that olanzapine will be "effective in use" and "safe for use" under the conditions of use recommended in the labeling developed by the Division's review team. In the course of its systematic review of the information and reports provided, the Review team uncovered no finding or issue that could be considered exceptional, disconcerting, or controversial. Accordingly, the NDA has not been presented to the Psychopharmacologic Drug Products Advisory Committee.

Our understanding of the data adduced in the 4 clinical studies deemed by design capable of providing evidence of Zyprexa's effectiveness in use was increased substantially by the analyses conceived of and executed by Dr. Hoberman, the mathematical biostatistician assigned to the review team. His innovative conceptualization of "dropout cohorts" that provide a visual display of the status of dropout's by treatment during each interval over the course of a randomized trial provides an evidence rich basis to assess the impact of censoring on analyses of the " intent to treat" samples upon which primary descriptions of clinical trial results ordinarily rest.

Incidentally, my singling out of Dr. Hoberman's work is in no way intended to

diminish the caliber of work done by other members of the review team. The team's workup was outstanding.

In sum, although I have no reservations about the regulatory decision being recommended to the Office, I do have a number of observations about olanzapine and the sponsor's development program that are of potential importance in regard to the kind of promotional claims that it may or may not be appropriate to allow Lilly to advance for Zyprexa.

Effectiveness (absolute and relative?)

The NDA provides "substantial evidence" that olanzapine is an effective antipsychotic drug product. This conclusion, however, is not intended to convey a judgment that the sponsor's development program has evaluated every important aspect of olanzapine's use in the treatment of psychosis that the agency might like to have available at the time an NDA is approved, or that a prescribing physician would prefer to possess.

The evidence adduced in the sponsor's short term (nominally 6 week long) studies, although it unquestionably provides compelling proof in principle of olanzapine's acute antipsychotic action, does not, because of 1) the highly selected nature of the patients admitted to study, 2) the high incidence of censored observations in the controlled trials, and 3) the indirect means used to assess the product's antipsychotic effects, provide a useful quantitative estimate of how effective[1] (even in the short run) olanzapine actually will be in the population for whom it is likely to be prescribed upon marketing.

The relatively short duration of the controlled clinical trials the sponsor relies upon, as might be anticipated, leaves us largely uninformed both about how effective a "maintenance" treatment olanzapine will be in extended use,

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[1] This acknowledgment is not an implication that some other information gathering strategy on drug performance/use can accomplish what randomized controlled trials of the sort now conducted in commercial drug development cannot. To the contrary, those who use the limitations of the RCT to promote the fatuous notion that observational outcome studies can provide insights that the RCT cannot are deluding themselves. It is a fact that the typical RCT's we rely upon have limited external validity, and that is weakness. It is one, however, that pales in comparison to those of outcome "studies" that have, as a result of their uncontrolled comparisons and limitless undeclared assumptions, neither internal nor external validity.

and how best to administer it (i.e,. dose and regimen) for that use.

These limitations, of course, are hardly unique to the set of trials conducted by Lilly in its development of olanzapine. In fact, as development programs go, Lilly's evaluation of olanzapine is a reasonably good one in light of its primary intent.

Commercial drug development programs are intended to adduce, in the shortest interval possible, the evidence that will allow the approval of an NDA. Accordingly, sponsors do not ordinarily attempt to provide answers in their NDA submissions to every question that may arguably provide useful information about their product.

Moreover, it is not only economic considerations, but the prevailing political environment, one which places great weight on the pace of drug development (i.e., achieving the shortest possible latency between drug discovery and drug availability at the bedside), that undermines the incentive to approach the development of a new drug with the kind of flexibility that allows for the adjustment of development plans to address questions and issues that were unanticipated at the start of a development program (e.g., issues identified during clinical testing)

There is, however, a force at work that operates to increase the volume of clinical testing: marketplace competition. This characteristic of the current health care economy virtually compels those developing new drugs, in particular those that will compete with already marketed products, to advance claims of superiority or advantage. It is this need that drives the conduct of comparative drug trials.

One aspect of this is quite paradoxical. In the midst of an epoch where much attention is being given to efforts to make both the drug development and approval process more efficient (i.e., to reduce the number of studies that, respectively, must be submitted and reviewed, to support NDA approval), sponsors are being driven to conduct more studies and, to boot, ones that are more complicated and difficult to conduct, at least validly. I write, of course, of studies intended to show a product's advantage to an already marketed drug.

Such studies are not only more difficult to design and conduct fairly, but are also more difficult to interpret. Indeed, their assessment requires that attention be given to a number of issues that the "proof of principle"

randomized, controlled effectiveness trials that regulators have long been accustomed to evaluating for assessing effectiveness do not pose.

The typical controlled trial intended to document the advantage of a new drug usually involves some kind of comparison between the new drug and an already marketed product, typically one that dominates the market. Haloperidol, for example, is, if such a thing exists, pretty much the "standard" antipsychotic drug product; accordingly, it is the product against which new antipsychotic products are typically compared. Incidentally, these comparisons need not be performed only in "stand alone" comparison studies, but are often 'piggy-backed" onto the design of the more traditional effectiveness trial.

The review of NDAs, as a consequence, no longer focuses entirely on the relatively simple issue of whether or not the product is, within the meaning of the Act, "effective in use " and "safe for use," but on the much more vexing, perhaps unanswerable question, of whether or not the new drug is better than the standard, if not globally, then on some clinically important domain (ease of use, freedom from one or more untoward effects, etc.).

None of this is wrong, in principle. The comparative performance of a new drug is not only a legitimate question, but an important one. Who would not want to know which of several competing products is most effective and most safe? Who would not want to know that a particular drug, all things considered, gives a "bigger bang for the buck.?" The problem, of course, is that mere wanting is not sufficient. Valid comparisons of drug performance are not readily obtained. Moreover, even comparisons that on face appear compelling and reasonable can prove misleading.

A primary reason is that the information required to determine whether or not a particular comparison is fair and valid is rarely available[2].

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[2] This is an assertion. There are, as yet, no regulatory standards vis a vis comparative claims. I believe, however, that for a drug product comparison to be meaningful, the products involved must be compared at equi-effective doses under conditions that do not give one product an unfair advantage. I also believe that, because equi-effective doses may not be the same from sample to sample, that a valid comparative design must be able to show, from its internal results (not historical expectations), that the drugs compared are being administered at the an equivalent position along their response vs dose curve.

Another problem is that clinical studies, whether conducted by academicians or commercial corporations rarely, if ever, provide a valid estimate of the "effect size" of a product even when the estimate derives from the result of a clinical trial executed with care and competence. If one cannot know reliably what the effect size is, how can one judge the clinical importance of differences in the size of the effect measured among several products?

Moreover, one cannot always be confident as to what an observed between treatment difference adduced on an instrument is due. This concern reflects the oft ignored fact that validity cannot be ascribed to a rating scale in isolation, but to the use for which that scale is employed.[3]

These observations about the problems of comparative inference are not put forward solely for academic reasons. The fact that differences found in clinical trials comparing products have arguable external validity is of major regulatory importance vis a vis drug product labeling and advertising.

Given this background, I will explain why I believe the data adduced in the Zyprexa NDA is, although readily able to support the NDAs approval, insufficient to permit the sponsor to make claims asserting the product's superiority to haloperidol.

In study **HGAD**, a 23 center, study involving some 335 patients randomized to 3 dose ranges of olanzapine (5 +/- 2.5 mg/d, 10 +/- 2.5 mg/d, and 15 +/- 2.5 mg/d), haloperidol (15 +/- 5 mg/d) and placebo, there are no clear findings

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[3] The point made is that the validity of a test cannot be assessed without considering the use to which the test is put. A difference in outcome between drug and placebo assigned patients detected using a multi-item rating instrument may validly reflect a therapeutic effect the instrument was designed to measure. A difference found between two pharmacologically active drugs on the same assessment instrument, however, may not reliably speak to the differential effectiveness of the two products, but to some other consequence of drug action that is detected by the test instrument. The Hamilton Scale for Depression, for example, is sensitive to changes induced by established anti-depressants that have nothing to do with either drug product's therapeutic antidepressant action. Accordingly, caution is required in interpreting the meaning of between treatment differences even when they are detected using instruments that are widely accepted as "valid" for what may seem to be a very closely related use.

that can be claimed to show that olanzapine is more effective than haloperidol, although there are certainly some differences that could be described as "hints" of it. These hints, however, although they are consistent with common expectations predicted by the pharmacology of the two drugs[4] must also be considered in light of the patient sample's prior experience with haloperidol and the doses at which the products are compared. In sum, I would not interpret the results of HGAD as support for a comparative claim, either explicit or implied, because 1) its design is inappropriate,and 2) the sample of patients used is an inappropriate choice.

E003, is a basically failed study; moreover, by design and patient sample selection would, if positive, not prove what the sponsor's wants to show.

Study HGAJ, Lilly's very large[5] randomized trial comparing outcomes over a 6 week period among schizophrenic patients treated with olanzapine and haloperidol (the dose of each drug was permitted to range between 5 mg and 20 mg a day, being adjusted according to the clinical judgment of prescribers) is the second source that the sponsor can argue shows an advantage of olanzapine. The titration design of **HGAJ** makes it ill-suited for evaluating the comparative performance of two drugs, however. Moreover, like other studies in the sponsor's development program, it suffers in that it entered a sample of patients with a history of prior use of haloperidol, a factor, as noted earlier, that makes the study sample inappropriate for comparison purposes.

I am not, however, as concerned as Dr. Laughren is about what he characterizes as the small magnitude of the estimated between treatment difference, nor that fact that a very large study was required to show that the observed difference is unlikely to be due to chance.

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[4] Both the comparative neurotransmitter receptor binding profiles of the products and the electrophysiologic studies of the products would lead many experts to predict that olanzapine would be expected to exhibit less 'neuroleptic' activity than haloperidol. This, in turn, would not only be expected to influence the incidence and kind of ADRs reported, but any effectiveness instruments that are sensitive to the subset of psychotic phenomena (e.g., so-called negative signs/symptoms of Schizophrenia) that overlap with those of pseudoparkinsonism.

[5] 1950 or so subjects in 186 US and European centers: 1312 on randomized to olanzapine, 636 to placebo

The size of a drug's effect is, as my earlier comments indicate, an abstraction, a notion that is not yet fully reified. Importantly, the agency, wisely given the potential difficulties involved in reifying the concept, has steered clear of the issue. I believe we should do so in the arguments about HGAJ.

The allegedly "small" size of the measured difference, in my view, is not its fault, at least from a regulatory perspective. In fact, if I were convinced that differences observed in a study were truly a valid and accurate reflection of a real difference in therapeutic effectiveness of the products compared, I would willingly endorse the presentation of the evidence supporting the conclusion in product labeling, although, as a matter of truth in labeling, I would, if such hypothetical evidence did exist, require the sponsor to include a display of the empirical cumulative distribution of the between product difference in product labeling.

In sum, although I have no reservations at all about concluding, from the evidence adduced and reported, that olanzapine will be effective in use within the meaning of the Act, I would not go further.

Moreover, I believe it is proper to ask that the firm make a commitment to conduct clinical trials that can evaluate in a valid and meaningful manner Zyprexa's performance in extended use as a maintenance treatment.

Evidence of safety for use

Preclinical findings

The full panoply of preclinical tests required to support the approval of an NDA have been performed and reported. Review of the reports submitted has not detected any result that would preclude approval of the NDA, although some findings (e.g., those involving results of in vivo lifetime carcinogenicity testing) warrant description in product labeling.

Clinical findings

No pharmacologically active drug substance is absolutely free of risk. This caveat offered, the evidence adduced in clinical testing that has so far been reported to the Zyprexa NDA is more than sufficient to support the conclusion that olanzapine, within the meaning of the Act, is safe for use under the

directions of use given in the Division's draft labeling.

It bears note that this conclusion is strongly conditicned on the evidence so far adduced. No one should be surprised if, upon marketing, events of all kinds and severity not previously identified are reported in association with olanzapine's use. Moreover, post-marketing experience may easily provide a very different impression of what are or are not the primary considerations of importance to the clinician and patient who, respectively, use and take, Zyprexa. Again, these statements reflect a generic limitation on regulatory inferences of 'safety in use' that derive from limited clinical experience with samples of patients who do not fully reflect the population likely to be treated with a drug upon its approval.

The safety data base reported upon in the Zyprexa NDA, at the time this approvable action is being contemplated, involves approximately 2500 patients. While this is far above the minimum experience required for NDA approval, it is not as robust as it may appear, especially if Zyprexa proves to be, upon marketing, a very popular drug product. Under such conditions, a very low probability of risk, one too small to make it likely that we would see even one case of the event in the NDA, might be sufficient to generate substantial numbers of cases of the event upon marketing.

On the other hand, there are risks that seem certain to be realized; fortunately, they are not likely to be very different from those associated with other antipsychotic drug products that have a similar profile of receptor binding.

Olanzapine's dopamine receptor antagonist actions make it likely that the product will cause prolactin elevation, pseudoparkinsonian signs and symptoms, tardive dyskinesia and the neuroleptic malignant syndrome. It's potent anticholinergic activity may cause some distress and its relatively potent alpha adrenergic antagonism probably will be associated with orthostatic hypotension, syncope, and risks that can arise as a secondary consequence of these latter events.

In any event, the labeling text as proposed alerts the prescriber to these risks. If adopted as proposed and/or recommended (the sponsor still has work to do), the Zyprexa product labeling will be informative and not false or misleading in any particular.

Recommendation:

Issue the draft approvable action letter that is forwarded in the company of this memorandum and action package.

Paul Leber, M.D.
8/18/96

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA #:	20-592
Sponsor:	Eli Lilly and Company
Clock Date:	September 22, 1995

Drug Name

Generic Name:	Olanzapine
Trade Name:	Zyprexa

Drug Categorization

Pharmacological Class:	Dopamine/serotonin receptor antagonist
Proposed Indication:	Symptoms of psychotic disorders
NDA Classification:	6 S
Dosage Forms:	2.5, 5, 7.5, 10 mg capsules
Route:	Oral

Reviewer Information

Clinical Reviewer:	Paul J. Andreason, M.D.
Completion Date:	July 29, 1996

Table of Contents for Clinical Review of NDA 20-592

1.0 Material Utilized in Review

1.1 Materials from NDA/IND

The following items were examined during the course of this clinical review:

Table 1.1.1 Documents Utilized in Clinical Review

DATE	RECIPIENT	DESCRIPTION
7/20/95	Tom Laughren	Draft Integrated Summaries of Safety and Efficacy
8/10/95	Tom Laughren	Revised Table of all Studies
8/11/95	Tom Laughren	Adverse Event Listings
8/14/95	Tom Laughren	WP 6.1 formatted tables
9/1/95	Tom Laughren	Efficacy analyses
9/12/95	Tom Laughren	Draft ISS Bibliography
9/21/95	NDA 20-592	NDA Submitted
9/26/95	NDA 20-592	CD-ROMS 18 containing scanned case report forms, 1 installation CD and 1 upgrade disk
9/27/95	NDA 20-592	WP 6.1 15 diskettes containing ISE, ISS, selected tables and draft labeling
9/28/95	NDA 20-592	Listing of adverse events sorted by event and patient
10/4/95	NDA 20-592	Diskette of efficacy data for HGAD, E003, HGAP, and HGAJ
10/19/95	NDA 20-592	CD-ROMS containing NDA document reviewer
10/31/95	NDA 20-592	Correction of typographical errors in item 6 Table of contents
11/2/95	NDA 20-592	CD-ROM containing data browser
11/20/95	Paul Andreason	FAX of index to WP 6.1 diskette files
3/26/96	Steve Hardeman	FAX of trademark perspective
4/17/96	NDA 20-592	Revised trademark
5/13/96	Paul Andreason	FAXed response to 5/8/96 question

5/20/96	Paul Andreason	Diskette and letter re: ISS request of 5/14/96
6/4/96	NDA 20-592	Patient narratives requested by Paul Andreason re: Leukopenia/Neutropenia
6/10/96	NDA 20-592	Safety analyses from the placebo-controlled trials requested by Paul Andreason and Greg Dubitsky on 6/3/96
6/14/96	NDA 20-592	Response to 5/13/96 CM&C questions
6/27/96	IND	Letters re: Drs. Borison and Diamond
6/28/96	Greg Dubitsky	FAXed patient summary HGAJ 328-3070
7/12/96	IND	Information on re-evaluation of HGAD efficacy excluding Dr. Borison data

Table 1.1.2 Case Report Forms examined during review			
HGAD 002-1054	HGAJ 049-1257	HGAO 006-0615	HGAJ 307-2847
HGAD 002-1056	HGAJ 051-0319	HGAO 012-1208	HGAJ 307-3049
HGAD 002-1057	HGAJ 069-1309	HGAO 019-1903	HGAJ 049-1257
E003 103-1105	HGAJ 203-2409	HGAO 020-2003	HGAJ 049-0767
E003 105-1056	HGAJ 306-2837	HGAO 022-2210	HGAJ 027-0954
E003 105-1061	HGAJ 329-3158	HGAO 007-0712	E003 304-3069
HGAJ 035-0206	HGAJ 338-3266	HGAJ 025-0148	HGAJ 304-2825
HGAJ 040-0850	HGAJ 752-6057	HGAJ 025-0499	HGAJ 042-1464
HGAJ 042-0507	HGAJ 990-7728	HGAJ 810-6365	HGAP 002-1062

An audit of case report forms was made to compare the data contained therein with the information presented in the case summaries. All patient deaths in the olanzapine treatment groups of the primary integrated database, the olanzapine patients at study site 002 in study HGAD (Dr. Borison's site), and 12 randomly chosen adverse dropouts judged not to be drug related (as determined by the patient summary) were audited. Patient summaries were accurate representations of data contained in the case report forms and often contained follow-up information not included in the CRF (e.g. causes of death from autopsy reports, reports of death in patients who had dropped out, graphic summaries of laboratory data). The sponsor stated that follow-up information contained in the patient summary that did not appear

in the case repost form was reported through the "Drug Experience Network" (DEN). If a patient terminated a study the CRF could be picked up from the investigator as soon as within two weeks of the termination. If a death or serious adverse event occured within 30 days of termination but after the CRF had been closed, the investigator would report the death through the DEN (e.g.patients HGAO 019-1903 and 022-2210).

Case summaries were used to review all serious adverse events, adverse dropouts, and deaths (even when CRFs had been examined). Case summaries of all patients with any white blood count of less than 2.8 Gi/L or neutrophil count of less than 1.5 Gi/L were also examined.
IND 28,705, the sponsors IND for olanzapine, contained no additional pertinant safety or efficacy data that was not listed above.

1.2 Related Reviews
IND
Reviews from the sections on chemistry, biopharmacology, toxicology, and biometrics were read and considered as part of this clinical review.

2.0 Background
2.1 Indication
Olanzapine is a novel antipsychotic agent for the treatment of psychotic disorders, including schizophrenia. The pathophysiology of these disorders may include abnormal receptor density distribution and/or supersensitivity in several specific regional systems, eg dopamine (D). D_2 receptor antagonism is regarded as being predictive of clinical and pharmacological potencies of conventional antipsychotic drugs. More recently, the D_2 family has been shown to include the D_4 receptor, which is highly localized to the mesolimbic area. In vitro, olanzapine is a $D_4/D_1/D_2$ receptor antagonist.

There is also increasing evidence that a disturbance in serotonin $(5\text{-HT})_2$-like (and perhaps 5-HT_3 or 5-HT_6) receptors characterizes schizophrenia. It has been proposed that a distinguishing characteristic and, therefore, a desirable property of novel antipsychotics is antagonism of 5-HT_2-like receptors. This property may be responsible for the improved efficacy profile among patients refractory to conventional antipsychotics, in the treatment of negative symptoms, and in secondary dysphoric mood.

2.2 Related INDs and NDAs
IND is the sponsor's IND for the development of Olanzapine.

IND for the study of olanzapine and haloperidol in the treatment of

it was recommended to proceed on November 3. 1995, and there is no data from this IND available.

There are no other INDs or NDAs for olanzapine.

Olanzapine is most closely related to clozapine and respiridone in its pharmacologic action. Risperidone is indicated for the management of the manifestations of psychotic disorders. The antipsychotic efficacy of risperidone was established in short-term (6 to 8 weeks) controlled trials of schizophrenic inpatients. Clozapine use is associated with serious but usually reversible agranulocytosis. For this reason, a rigorous routine of hematologic monitoring accompanies the use of clozapine. The sponsor has not yet identified serious hematologic adverse events with the use of olanzapine.

2.3 Administrative History

The original IND application was submitted July 24, 1995. An end of phase II meeting was held with the sponsor on March 1, 1993. A pre-NDA meeting was held with the sponsor on February 16, 1995. There are no previous NDAs and the sponsor has never applied to market olanzapine in any other country.

2.4 Directions for Use

Olanzapine is indicated for the treatment of manifestations of psychotic disorders consisting of positive and/or negative psychotic signs and symptoms. The antipsychotic efficacy of ZYPREX was established in two 6-week controlled trials in schizophrenic inpatients and in schizophrenic, schizophreniform, and schizoaffective in- and outpatients. The suggested starting dose is 10 mg po per day, and the suggested daily dose range is 5-20 mg po per day. When clinically indicated, it is recommended for most patients that an increase to a dose $\geq$15 mg/day be made only after the patient has been treated with a starting dose for at least 4 days.

Chronic olanzapine treatment should generally be reserved for patients who suffer from a chronic illness that: 1) is known to respond to antipsychotic drugs, 2) requires maintenance therapy, and 3) for whom alternative nonpharmacologic treatments are not available or have not been effective alone. In patients who do require chronic treatment, the lowest effective dose for the shortest necessary duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered.

2.5 Foreign Marketing

Olanzapine has never been marketed nor have previous applications for marketing occurred anywhere in the world.

3.0 Chemistry

ZYPREX™ (olanzapine) is an antipsychotic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*]-[1,5]benzodiazepine. ZYPREX tablets are intended for oral administration only. Each tablet contains olanzapine equivalent to 2.5 mg (8.0 μmol), 5 mg (16 μmol), 7.5 mg (24 μmol), or 10 mg (32 μmol) olanzapine activity. There are no chemistry, manufacturing or control problems of clinical concern.

4.0 Animal Pharmacology

Olanzapine is a potent 5-HT_{2A}/5-HT_{2C}/5-HT_3/5-HT_6, $D_4/D_1/D_2$, and muscarinic cholinergic (M_1-M_5) antagonist. It also possesses α_1-adrenergic and H_1-histaminergic affinity. The compound's receptor binding profile is similar to that of the "atypical" agent clozapine. The likely clinical relevance of this pharmacologic profile (as also shown by the "atypical" neuroleptic agent clozapine) is also believed to be a reduction of the incidence and severity of drug-induced extrapyramidal symptoms and tardive dyskinesia.

Carcinogenicity studies were conducted in CD-1 mice and Fischer 344 rats. Olanzapine was administered orally to mice at doses of 3, 10, or 20 mg/kg for 19 months (males) or 21 months (females) in an initial study, and in a subsequent study at doses of 0.5, 2, or 8 mg/kg for 21 months (males and females). Rats received oral doses of 0.25, 1, 2.5, or 4 mg/kg (males) or 0.25, 1, 2.5, 4, or 8 mg/kg (females) for 24 months. These doses are equivalent to 2 to 70 times the maximum daily human dose (mouse studies) or 0.9 to 28 times the maximum daily human dose (rats). A maximum tolerated dose was achieved in both mouse and rat studies.

Increased mortality was seen in mice at doses of 10 and 20 mg/kg and decreases in circulating lymphocytes and neutrophils were seen at doses ≥0.5 mg/kg. In female mice treated with olanzapine, the incidence of mammary tumors was increased at doses ≥2 mg/kg. Female rats treated with 4 or 8 mg/kg had an increase in malignant mammary tumors, but the overall incidence of mammary gland neoplasia was unchanged. Olanzapine has been shown to chronically elevate prolactin concentrations in rodents. An increase in mammary neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated.

No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Mating performance was affected by administration of olanzapine due to sedation in male rats given doses greater than 18 times the maximum daily human dose, but the effect was quickly reversed when treatment stopped. Estrous cycles were affected in rats given doses greater than 4 times the maximum daily human dose. No adverse effects were observed on numbers of corpora lutea, implantations, fetal viability, or fetal weight, and there were no effects on litter size or on the survival, growth, or development of the offspring from parents given up to 18 times the maximum daily human dose. Although the reproductive process in female rats from mating through fertilization was not adversely affected by treatment, this evidence does not exclude a possible interference with maintenance of pregnancy at high doses of olanzapine.

Reproduction studies, performed in rats and rabbits at doses of olanzapine 3.5 and 7 times the maximum daily human dose (20 mg), respectively, have revealed no evidence of harm to the fetus. Maternal toxicity, developmental toxicity (indicated by fetal growth retardation and slightly delayed ossification at birth), and increased numbers of nonviable offspring occurred at higher doses (in rats at 14 and 63 times the maximum daily human dose and in rabbits at 28 and 105 times the maximum daily human dose). Fetal malformations were not increased. Transient decreases in offspring activity have occurred at all doses; however, there were no effects on body weight, growth, mating, fertility or live births in second-generation animals.

Olanzapine produced a dose-related delay in estrous in rats due to hyperprolactinemia from dopaminergic antagonism. Placental transfer of olanzapine occurs in rat pups. Olanzapine was excreted in milk of treated rats during lactation.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

A table describing and enumerating all of the studies performed in the development program of olanzapine for human use is in appendix 5.1.1 in table 5.1.1.1. The primary data cutoff date for information included in this integrated summary of safety was February 14, 1995 (integrated primary safety database, secondary safety database). The second data cutoff date for information about deaths and serious adverse events was June 30, 1995 (integrated primary safety database

Table 5.1.1.2. Patient Enumeration by Database, Study Type, and Study Design
Completed and Ongoing Studies

Database/Study Type/Study Design	Treatment Group		
	Olanzapine	Active Control	Placebo
Integrated Primary Safety Database			
(All multiple-dose studies)			
Placebo-Controlled Studies			
Fixed-Dose	102		50
Dose-Ranging	318	69	186
Active-Controlled Studies			
Dose-Ranging	1686[a]	741[a]	
Uncontrolled Studies			
All	939 (545)[b]		
Subtotal: Primary Database	**2500**	**810**	**236**
Secondary Safety Database			
Clinical Pharmacology Studies			
Single-Dose	283	6	11
Multiple-Dose	87	16	30
Subtotal: Clinical Pharmacology Studies	370	22	41
Open-Label Studies			
(All multiple-dose studies)			
All	319 (62)[c]	4	
Phase 3 Studies			
(All multiple-dose studies)			
All	12[d]		
Subtotal: Secondary Database	**639**	**26**	**41**
Total - Single-Dose Studies	283	6	11
Total - Multiple-Dose Studies	2856	830	266
GRAND TOTAL	**3139**	**836**	**277**

[a] Number does not include 198 patients randomized to olanzapine and 69 patients randomized to haloperidol in the three-treatment-group study HGAD; these patients are included in the counts given in the Olanzapine and the Active Control columns under Placebo-Controlled Studies, Dose-Ranging.

[b] Number in parentheses (545) represents olanzapine-treated patients participating in open-label extension studies, but already counted in the Olanzapine column under Placebo-Controlled Studies or Active-Controlled Studies.

[c] Number in parentheses (62) represents olanzapine-treated patients participating in open-label extension studies conducted in Japan, but already counted in the Olanzapine column under Open-Label Studies.

[d] An additional 14 patients had been enrolled in a controlled Phase 3 study (F1D-MC-HGBA), but the therapy was still blinded. These patients are not included in this enumeration table

5.1.2 Demographics

Characteristics of the patients assigned to treatment with olanzapine (patients who crossed over to olanzapine treatment included), placebo, or haloperidol in the integration of primary studies are summarized in Table 5.1.2.1. The mean age of patients assigned to treatment with olanzapine was 41 years, compared with a mean age of 37 years in the haloperidol group, and a mean age of 57 years in the placebo group. The corresponding age ranges for the three groups were 18 to 94, 18 to 79, and 18 to 93 years, respectively. The mean age was higher in olanzapine-treated patients and substantially higher in placebo-treated patients than in haloperidol-treated patients because of the influence of study HGAO. Study HGAO compared only olanzapine and placebo and was conducted in a geriatric population.

Table 5.1.2.1 Demographic Profile for Studies in Primary database

	Olanzapine (N=2500)		Haloperidol (N=810)		Placebo (N=236)	
Measure	No.	(%)	No.	(%)	No.	(%)
Sex: No. (%)						
Male	1608	(64.3)	537	(66.3)	134	(56.8)
Female	892	(35.7)	273	(33.7)	102	(43.2)
Origin: No. (%)						
Caucasian	2006	(80.2)	629	(77.7)	179	(75.8)
African descent	281	(11.2)	101	(12.5)	41	(17.4)
East/Southeast Asian	39	(1.6)	14	(1.7)	3	(1.3)
Western Asian	21	(0.8)	8	(1.0)	--	--
Hispanic	96	(3.8)	38	(4.7)	12	(5.1)
Other origin	57	(2.3)	20	(2.5)	1	(0.4)
Age (yrs)						
Mean	41		37		57	
Range	18 to 94		18 to 79		18 to 93	
Age: No. (%)						
<40 yrs	1395	(55.8)	503	(62.1)	79	(33.5)
40 to <65 yrs	842	(33.7)	292	(36.0)	40	(16.9)
≥65 yrs	263	(10.5)	15	(1.9)	117	(49.6)

5.1.3 Extent of exposure (dose/duration)

Patient exposure to olanzapine in the studies included in the integrated primary safety database, based on modal daily dose, is summarized in table 5.1.3.1. Studies included in the secondary safety database are not represented in this table. The modal dose is defined as the dose prescribed for or dose taken by the patient for the most number of days. (In studies HGAD, E003, HGAP, and HGAO information about the dose prescribed was collected; in study HGAJ information about the dose taken was collected.) The maximum dose of olanzapine permitted in any of these studies was 20 mg/day. Data from all study phases (including extensions) are included in the table. Some patients assigned to therapy did not have any study drug use recorded in their clinical report forms (olanzapine, 39 of 2500 patients assigned to therapy; olanzapine, 2 of 263 patients ≥65 years of age assigned to therapy). The patients may or may not have taken study drug, but are counted as having been exposed to study drug for safety analysis purposes. As study drug records are not available, these patients do not contribute to study drug exposure analyses and are not included in table 5.1.3.1.Exposure to olanzapine, based on the modal daily dose, is summarized in 5.1.3.1 for all patients. Data are pooled from all five studies in the overall integrated database (studies HGAD, E003, HGAP, HGAJ, and HGAO).

Table 5.1.3.1 Patient Exposure to Olanzapine Therapy Modal Daily Dose Integrated Primary Database

Duration (Days)	Dosage Range 0-<5mg	5-<10mg	10-<15mg	15-<20mg	>=20mg	Total	(%)
<=14	43	134	38	32	0	247	(10.0%)
14<-31	36	72	79	50	15	252	(10.2%)
31<-91	0	131	113	108	137	579	(23.5%)
91<-183	93	86	91	70	167	507	(20.6%)
183<-270	6	49	52	62	142	311	(12.6%)
270<-365	3	32	58	57	114	264	(10.7%)
>365	3	41	57	79	121	301	(12.2%)
Total	274	545	488	458	696	2461	
(%)	(11.1%)	(22.1%)	(19.8%)	(18.6%)	(28.3%)		

5.1.3.2 Total patient-years of exposure in primary database:

Olanzapine	1122.2
Haloperidol	192.4
Placebo	27.1

5.2 Secondary Sources of Clinical Information

5.2.1 Non-IND Studies

All studies performed by the sponsor with olanzapine (including non-IND studies) are listed in table 5.1.1.1. The primary clinical database is designated as studies HGAD, HGAP, HGAJ,

HGAO, and E003. The secondary database was reviewed for applications to specific safety questions (e.g. drug-drug interactions, drug-disease interactions), serious adverse events and deaths. Data from IND 48,944 has not been generated and therefore was not reviewed.

5.2.2 Post-marketing Experience
Olanzapine has not been marketed in any country thus far; this is the initial NDA.

5.2.3 Literature
The sponsor's process for selection, storage and retrieval of published articles is as follows: searches were performed on seven computer-databases with th search terms of "olanzapine" or "LY170053". All publications containing pre-clinical and clinical data were included in the reference section in volume 214. Databases searched by the sponsor were EMBASE, PSYCHINFO, BIOSIS, SCISEARCH, MEDLINE, RINGDOC, and PASCAL through August 25, 1995. The sponsors warranted that they had reviewed these references for potentially clinically significant adverse events and reported on all that they found. All abstracts of included articles were reviewed. No significant adverse events were found that were not addressed in the review of systems section 8.2; This is because all patient exposure is limited to the Lilly development program.

5.3 Adequacy of Clinical Experience
The sponsors have exposed an adequate number of patients to olanzapine, in appropriate dose ranges, and for appropriate durations to generate a significant safety database. The sponsor has exposed both men and women, whites and non-whites, and young, middle-aged and elderly patients. The sponsors have an adequate number of placebo-controlled clinical trials to judge efficacy.

5.4 Data Quality and Completeness
The data is complete in that the rating scales, laboratory values and other planned tests were performed and adequately documented. The data quality appears sound; however, the clinical investigator at site 002 in study HGAD resigned recently under allegations of "scientific misconduct". There were 17 patients at this site: 10 in the olanzapine group, 4 in the haloperidol group, and 3 in the placebo group. The Olanzapine patients were divided into 3 for the low group, 4 for the middle group and 3 for the high group. This information was received June 29, 1996 via FAX, and a statistical review of the study was performed by the sponsor wherein the study was re-analyzed after excluding the patients from this site. All clinical efficacy variables were re-analyzed and statistical significance was maintained. Medical quality assurance audits did not reveal "significant GCP [Good Clinical Practice] compliance issues" with this investigational

site.

6.0 Human Pharmacokinetics

Plasma concentrations of orally administered olanzapine were linear and dose proportional in trials studying doses from 1 to 15 mg. The maximum plasma concentrations (Cmax) of olanzapine after single oral doses of 5, 10 and 15 mg averaged 7, 14, and 21 ng/mL, respectively (20 ng/mL = 0.064 μM). The Cmax was attained 5 to 8 hours after dosing. After once-a-day repeated dosing, steady-state Cmax was approximately twice that achieved after a single dose (eg, 23 ng/mL versus 12 ng/mL for a 10-mg dose).

The half-life of olanzapine ranges from 21 to 54 hours (5th to 95th percentile), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile). Mean $t_{1/2}$ for male and females ,65 years old were 29 and 39 hours repectively; mean $t_{1/2}$ for males and females $\geq$65 were 49 and 55 hours respectively.

The relative oral bioavailability of olanzapine as a tablet in comparison to an oral suspension was equivalent. Food does not affect the rate or extent of olanzapine absorption.

Olanzapine is a very weak inhibitor of drug-metabolizing enzymes. Average steady-state plasma concentrations (40 ng/mL, 0.13 μM) are 100 times less than those necessary to inhibit the following enzymes: P450 CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A.

The plasma protein binding of olanzapine is about 93% and is concentration independent. Olanzapine is bound predominantly to albumin and α_1-acid glycoprotein. As such, the potential exists that it may displace drugs from their binding sites on plasma proteins or other drugs may displace olanzapine. The impact of protein binding interactions with other drugs has not been systematically assessed.

Renal Impairment

The principal mechanism by which olanzapine is eliminated is via metabolic transformation to metabolites that are excreted in bile or urine. The degree of renal function does not have a major impact on the pharmacokinetics of olanzapine. However, mass balance studies show that approximately 57% of radiolabeled olanzapine appears in urine and 30% in feces. The radioactivity in urine consists principally of metabolites. Therefore, renal dysfunction is unlikely to have a major impact on the pharmacokinetics of olanzapine, but may result in the accumulation of renally excreted metabolites. The dose of olanzapine does not need to be adjusted based upon a patient's renal function alone. The single dose PK characteristics of olanzapine were similar in patients with severe renal

impairment and normal subjects. However, multiple-dose studies in patients with renal failure have not been performed.

Hepatic Impairment
Olanzapine is metabolized by oxidative enzymes to a variety of metabolites. The effect of impaired liver function was evaluated in subjects with clinically significant (Childs Pugh Classification A and B) cirrhosis. The effect of impaired liver function on olanzapine metabolism was assessed by giving single oral doses to these subjects. The preliminary pharmacokinetic assessment indicates no major effect of cirrhosis upon the pharmacokinetics of olanzapine. More cirrhotic and normal control subjects are being recruited for study. Because there are multiple pathways, including glucuronidation, involved in olanzapine's metabolic routes, the overall impact of reduced liver function may be mitigated by alternative metabolic pathways and sites of metabolism. Based upon the available pharmacokinetic data, a dosage reduction for patients with impaired hepatic function is not warranted. The sponsors continue to enroll additional subjects in study F1D-LC-HGAU and a final summation will then be possible.

Smoking
In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was prolonged in elderly subjects compared with non-elderly subjects. The pharmacokinetic variability among the elderly was within the variability of their non-elderly counterparts.

Large-scale population pharmacokinetic analyses show that the clearance of olanzapine in females is approximately 30% lower than in males.

In vitro micro-enzyme studies
Results from in vitro metabolism studies of olanzapine using human microsomal preparation indicate that the cytochrome P-450 enzyme system (CYP) and the flavin-containing monooxygenase system (FMO) are responsible for metabolite formation. Olanzapine also undergoes conjugation with glucuronic acid. Metabolites of olanzapine in humans include 10-N-glucuronide olanzapine, 4'-N-glucuronide olanzapine, 2-hydroxymethyl olanzapine formed by CYP2D6, N-desmethyl olanzapine formed by CYP1A2, and N-oxide olanzapine produced by the FMO.

In vitro microsomal studies show that olanzapine is a weak inhibitor of the following human, drug-metabolizing, cytochrome (CYP) P-450 enzymes: CYP2C9 (Ki = 715 mM), CYP2C19 (Ki = 920 mM), and CYP3A4 (Ki = 490 mM). The Ki for CYP2D6 is 89 mM); and the Ki for CYP1A2 is 36 mM. Based upon these Ki values, little inhibition of these cytochrome P-450 enzymes is expected in vivo at concentrations below 10 mM (roughly 3000 ng/mL) because the olanzapine concentration will be less than 10% of

its Ki value. Observed steady-state plasma concentrations of olanzapine are rarely >150 ng/mL (approximately 0.5 mM).

In Vivo Drug Interaction Studies
Two studies showed pharmacodynamic, but not pharmacokinetic, drug interactions between olanzapine and diazepam and olanzapine and ethanol. Mild increases in heart rate, sedation, and dry mouth were accentuated by the diazepam combination. Single-dose ethanol administered with olanzapine also increased heart rate and accentuated postural hypotension.

In study F1D-LC-HGAQ involving healthy volunteers, minor effects were seen with the combination that were not observed with olanzapine 5 mg and imipramine 75 mg given alone. Human performance (HP) testing during the combination showed a minor depression in only one motor activity variable (HP Visual-Arm Random Forward Reach Speed, M4). Questionnaire data suggested that imipramine given with olanzapine counteracted an excited feeling after olanzapine administered alone. Although these effects were small, higher doses of these two agents in combination have not been evaluated.

Human studies of the potential for interaction between olanzapine and other drugs have focused on the potential effects of olanzapine and the pharmacokinetics of other drugs, or vice versa. The studies have utilized drugs with a known potential for interaction or those with a narrow therapeutic index. Pharmacokinetic interaction studies include imipramine, carbamazepine, ethanol, warfarin, lithium, cimetidine, diazepam, and biperiden. Olanzapine did not affect the pharmacokinetics of these drugs. Multiple doses of carbamazepine induced the metabolism of olanzapine leading to olanzapine plasma concentrations that were 30% lower.

None of these pharmacokinetic results led to a conclusion that the dose of either drug should be substantially modified when given concomitantly. The pharmacodynamic interactions observed within these studies were generally minor. However, rapid ingestion of 200-proof alcohol was associated with moderate clinically significant events, such as tachycardia and postural hypotension. Patients should be warned about this combination.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

The sponsors present 4 studies in support of olanzapine as effective in the treatment of the symptoms associated with psychotic disorders. All studies were multi-center, double-blind, randomized, parallel group by design. Study HGAD was multinational, placebo and active controlled with flexible dosing within three ranges. Study E003 was multinational, active controlled with flexible dosing within three ranges. HGAP is a US placebo controlled fixed dose study. HGAJ is a multinational, active controlled, fixed dose study. A fifth study in the primary database, HGAO, is a US, placebo controlled, flexible dose study of the efficacy of olanzapine in the treatment of psychotic symptoms associated with primary degenerative dementia of the Alzheimer's type with symptoms of psychosis. This study will not be considered in the review of efficacy of olanzapine in the treatment of psychotic symptoms associated with schizophrenia; however this study will be considered as part of the primary safety database.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1 Fixed Dose Study HGAP

Study HGAP, a multicenter, randomized, double-blind study, compared two fixed doses of olanzapine (1.0 mg/day; 10.0 mg/day) with placebo in the treatment of 152 patients who met the DSM-III-R criteria for schizophrenia.

The study had a placebo lead-in phase (Study Period I), an acute phase (Study Period II), and an open-label extension phase (Study Period III). The acute phase occurred between August 1993 and April 1994. A brief summary of the efficacy results of the acute phase of study HGAP follows.

Investigators and Location

The study was conducted at 12 sites in the United States. A list of the investigators and sites is listed in Appendix 7.2.1, table 7.2.1.1.

Objectives

The objectives of the study were 1) to evaluate the efficacy and safety of two fixed doses of olanzapine with placebo; 2) to study potential relationships between dose, plasma concentration of olanzapine, and clinical therapeutic effect; and 3) to allow open-label, potentially long-term treatment with olanzapine in the dosage range of 5 to 20 mg/day.

Study Population

Patients had to meet the diagnostic criteria for schizophrenia (295.1 to 295.3, 295.9) according to the DSM-III-R. Residual Type 295.6 was excluded. Patients suffered sufficient symptoms such that the initial score (Visit 1) of severity of illness on

the BPRS was at least 24 (0 to 6 scale).[1] The severity of illness as judged on the CGI Severity scale was at least moderate (score ≥4) at Visit 1.

Patients were excluded if they had a diagnosis of schizophreniform disorder/schizoaffective disorder or psychotic disorders other than schizophrenia. Other inclusion and exclusionary criteria are listed in Appendix 7.2.1 Table 7.2.1.2.

Design
HGAP consists of three phases, a placebo run-in phase (I), a 6 week treatment phase (II), and an open label extension phase (III). After a 4- to 9-day placebo lead-in phase (Study Period I), patients who were experiencing a clinically significant psychotic episode as part of schizophrenia were randomly allocated to one of three treatment groups (Study Period II). Patients were started on the assigned dose without titration (i.e. placebo, olanzapine 1.0 or 10.0 mg/day). Patients who wished to continue double-blind therapy and completed greater than 5 weeks of double-blind therapy during Study Period II (through Visit 8) could enter the open-label phase (Study Period III) at Visit 8 if they had not experienced any clinically serious adverse events. Patients who completed more than 3 weeks (through Visit 6) of double-blind therapy in the acute phase and failed to show adequate response could enter the open-label phase at Visit 6, 7, or 8.

Assessments
Efficacy evaluations were based on assessments of patient improvement on the PANSS, the BPRS extracted from the PANSS, CGI Severity, and PGI (Patient's Global Improvement) Improvement. All of these assessments, except the PGI Improvement, were made at each visit. The PGI Improvement assessment was made at every visit except Visit 1. The PANSS is a rating scale used to assess positive symptoms, negative symptoms, and general psychopathology, specifically in schizophrenia. It consists of 30 items scored on a scale of 1 to 7. The BPRS, extracted from the PANSS, was the primary efficacy criterion for the study and consists of 18 items. To calculate whether patients met percent improvement criteria, a rating system of 0 (normal) to 6 (extremely ill) was used when administering the BPRS. Since there are 18 items in the BPRS, this scoring scale produces a score which is 18 points less than the BPRS total score using the system of 1 to 7. The BPRS total scores used throughout this

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[1]The BPRS is an 18 item rating scale that measures the severity of psychotic symptoms. Each item is scored from 1 to 7; one is least severe (absent), seven is most severe. The sponsors chose to make this a 0 to 6 scale. The minimum criteria for illness would therefore be 24+18=42 if one were measuring by the standard scale.

study report, unless noted otherwise, are calculated from the 0 to 6 scale.

A full list of assessments and the schedule by which they are done is listed in Appendix 7.2.1 in table 7.2.1.3.

Analysis Plan
All analyses were done on an intent-to-treat basis, meaning all patients were included in the treatment groups to which they were randomized, even if a patient did not strictly adhere to the protocol. All randomized patients for which there was a baseline (Visit 2) and at least one postbaseline measurement were included in the analyses in accordance with an "intent-to-treat" principle.

When LOCF and OC change from baseline to endpoint was assessed, patients were included in the analysis only if a patient had a baseline and a postbaseline measure. The baseline measure was the Visit 2 observation, unless it was missing, then it was the Visit 1 measure. The endpoint measure was the last measure in the acute phase (Visits 3 through 8).

Treatment groups were compared with regard to change from baseline to endpoint in BPRS total, positive, and negative scores; PANSS total, positive, and negative scores; and CGI Severity score using ANOVA. The ANOVA model contained the terms for treatment, investigator, and treatment-by-investigator interaction. For all analyses, main effects were tested at a two-sided α level of 0.05, and treatment-by-investigator interactions were tested at an level of 0.10. Pairwise comparisons with no correction for multiplicity were performed for all treatment groups using least-squares means.

Patient Disposition
A total of 164 patients entered the placebo lead-in phase. Of these patients, 152 were randomly allocated to a treatment group at Visit 2. Table 7.2.1.4 in Appendix 7.2.1 summarizes the disposition of the randomized patients and the reasons the patients discontinued from the acute phase. Although a greater number of patients in the Olanzapine 10 mg/day treatment group completed the acute phase, the proportion of patients did not differ significantly among the treatment groups. Of the randomized patients, 27.0% completed the acute phase. A large proportion of the drop-outs occurred at week-4. 82% of the randomized patients continued in the open-label phase after either completing the acute phase or discontinuing at Visit 6, 7, or 8. Table 7.2.1.5 in appendix 7.2.1 summarizes the completion rates by week for each treatment group.

Baseline Demographics/Baseline Illness Severity
The 152 patients had a mean age of 37.7 years, and most were Caucasian (68.4%) and male (72.4%). In this study, 53.3% of the

patients were of the paranoid subtype, 98.0% had a chronic course, and 65.1% were experiencing an acute exacerbation. The treatment groups were comparable at baseline with respect to gender, racial origin, age, schizophrenic subtype, schizophrenic course, age of onset of psychosis, length of current episode/exacerbation, number of previous episodes/exacerbations, and length of current hospitalization. Group mean baseline rating scale scores were not statistically different. Patient characteristics are shown by treatment group in Table 7.2.1.6 in appendix 7.2.1.

Concomitant Medications
In general, concomitant medications with primarily CNS activity were not allowed in this protocol. Table 7.2.1.7 in appendix 7.2.1 contains a list of medications that were/were not allowed in this study. If a medication was not listed in Table 7.2.1.7, either specifically or by category, and if the medication did not possess primarily CNS activity, it could have been used by patients in this study. Should a medication for sleep or agitation have been required, lorazepam could have been given. In general, patients took a wide variety of concomitant medications. Concomitant medications that were used were analyzed by treatment group via ANOVA. There were no significant differences in the use of concomitant medications between groups.

Efficacy Results
Summary statistics and statistical analysis of the LOCF and OC by-visit and endpoint analysis are shown for BPRS total, positive, and negative scores; PANSS total, positive, and negative scores and CGI Severity score in Tables 7.2.1.8.-7.2.1.18. As stated in the protocol, the primary efficacy analysis was the mean change from baseline to endpoint in BPRS total score for the LOCF, ITT group. The LOCF Olz 10 mg treatment group experienced significantly greater mean improvement in BPRS total score than the placebo treatment group (p=.014).

The LOCF Olz10.0 treatment group experienced significantly greater mean improvement in BPRS positive score than the placebo treatment group (p=.003).

The LOCF Olz10.0 treatment group experienced significantly greater mean improvement in PANSS total (p=.002), positive (p=.004), and negative (p=.007) scores than the placebo treatment group at endpoint.

The LOCF Olz10.0 treatment group experienced significantly greater mean improvement in CGI Severity scores than the placebo treatment group (p=.036).

The OC data at week six did not support olanzapine as being effective. One must however view this in light of a large number

of drop-outs at week four. The sponsors were asked to explain why there wass such a high drop-out rate in this study versus HGAD which had the same protocol allowance for drop-out at week four. According to Charles Beasley, M.D., investigators in this study were concerned that 2/3 of the patients would be receiving either placebo or anersatz placebo dose of olanzapine (OLZ 1.0 mg). He reported that the investigators that he interviewed were anxious that the majority of the patients ran the risk of decompensation the longer that they remained in blinded groups. The protocol allowed that if patients completed at least 4 weeks then they could be changed to the open label group. Dr. Beasley believes that patients were dropped out of the study en mass at week four due to the investigators' anxiety of an odds on chance at being in a group that had a higher chance for relapse. Hence, the study might be more reasonably viewed as a four week study from an OC point of view; otherwise, OC data lacked statistcally significant change at six weeks in the OC database.

Conclusions
Study HGAP represents a positive study in the comparison of Olanzapine 10.0 mg po qd versus placebo in the treatment of schizophrenia. The dose of 1.0 mg/day was not superior to placebo and thus does not represent an effective dose.

A large number of patients dropped out of all the treatment groups at the end of week-4. The sponsors state that it was allowed in the protocol and the drop-out rates are roughly equal across groups. The explanation of investigators' anxiety of the majority of patients not receiving adequate drug led to the large drop-out rate seen at week 4 is reasonable. Study HGAD has a similar option to drop-out at week-4, but the retention rate is much better in this study; this is ostensibly because 80% of the randomized patients would be in an active treatment arm. One might better consider HGAP to be a 4-week study due to the high drop-out rate. If one does this the LOCF and OC data would still support olanzapine as being more effective than placebo in the treatment of chronic schizophrenia. The fact that patients could drop-out at week four and enter an open-label phase if they failed to show adequate response renders the OC analysis after week-4 invalid.

Endpoint versus baseline LOCF data supported olanzapine 10.0 mg/day while OC data does not. This is due to the high drop-out rate of placebo treated patients who could not remain in the study; this left the least symptomatic patients in all groups to compare against each other. It is for this reason that LOCF and not OC data represent a clearer picture of the true efficacy of olanzapine in this patient population.

7.2.2 Flexible dose range study HGAD
Study HGAD, a multicenter, randomized, double-blind study, compared three fixed dosage ranges of olanzapine (Olz-L, 5.0 ±

2.5; Olz-M, 10.0 ± 2.5; and Olz-H, 15.0 ± 2.5 mg/day) with one fixed dosage range of haloperidol (Hal, 15.0 ± 5.0 mg/day) and with placebo in the treatment of 335 patients who met the DSM-III-R criteria for schizophrenia. The study had a placebo lead-in phase (Study Period 1), an acute phase (Study Period 2), a double-blind extension phase (Study Periods 3 and 4), and an open-label extension phase (Study Period 5).

Investigators and Sites
The study was conducted at 23 sites in the United States and Canada. Table 7.2.2.1 in appendix 7.2.2 lists the investigators and sites where this study was performed.

The principal investigator for center #2, Richard L. Borison, Ph.D., M.D., is being investigated for research misconduct since participating in this study, according to a letter dated June 14, 1996, from the IRB at the Medical College of Georgia, Augusta, GA; he has since resigned his position at the Medical College of Georgia. One of his sub-investigators, Bruce I. Diamond, Ph.D., is also being investigated for this charge. Since Dr. Borison contributed a relatively small number of patients to this trial (total of 17 out of 335), a statistical review of the study was performed by the sponsor wherein the study was re-analyzed after excluding the patients from this site. All clinical efficacy variables were re-analyzed and statistical significance was maintained. Medical quality assurance audits did not reveal "significant GCP [Good Clinical Practice] compliance issues" with this investigational site. Nonetheless, this case is being referred to the Division of Scientific Investigation (DSI).

Objectives
The objectives of study HGAD were as follows: 1) to evaluate the safety and efficacy of olanzapine versus placebo and haloperidol in the treatment of patients with schizophrenia; 2) to determine any possible relationships between the dose, plasma concentration of olanzapine, and clinical therapeutic effect; 3) to evaluate the efficacy and safety of olanzapine versus haloperidol through 1 year's duration in patients who had shown a positive response during the acute phase; and 4) to assess the incidence and severity of extrapyramidal symptoms.

Study Population
Patients who met the diagnostic criteria for schizophrenia (295.1 to 295.3, 295.9) according to the DSM-III-R. Patients were experiencing an acute exacerbation of their illness (residual type 295.6 excluded). Initial score of severity of illness on the BPRS had to be at least 24 and CGI $\geq$ 4 (moderately ill). A complete list of inclusion and exclusion criteria are listed in appendix 7.2.2 in table 7.2.2.2.

Design
HGAD was a multicenter, randomized, double-blind, placebo- and

comparator-controlled study, three fixed-dose ranges of olanzapine were compared with placebo and one fixed-dose range of haloperidol. The study consisted of 5 phases by design but the results from phase 2 are those that are analyzed for acute efficacy.

Study Period 1 was the single-blind screening and placebo lead-in/washout period. Visit 1 consisted of screening tests, patient history, and psychiatric and physical examinations. The period between Visit 1 and Visit 2 consisted of placebo lead-in and washout of previous neuroleptic therapy. Patients were screened at Visits 1 and 2 to determine if they met entry criteria. The placebo lead-in period between Visits 1 and 2 was a minimum of 4 days and a maximum of 9 days. Placebo capsules were dispensed at Visit 1.

Study Period 2 was the double-blind, placebo controlled, acute therapy period of the study. Patients from the placebo lead-in period were randomized to one of five treatment groups: placebo, olanzapine 5.0 ± 2.5 mg/day (Olz-L), olanzapine 10.0 ± 2.5 mg/day (Olz-M), olanzapine 15.0 ± 2.5 mg/day (Olz-H), or haloperidol 15.0 ± 5.0 mg/day (Hal). The acute period began with randomization at Visit 2 and continued through Visit 9. There were 6 weeks of study drug treatment with visits occurring twice weekly for the first week, then weekly thereafter. For the first 2 weeks, patients were required to be inpatients; for the following 4 weeks, patients could be inpatients or outpatients. Once released to outpatient status, they were to remain outpatients. Rehospitalization during this period of active treatment, however, did not necessitate withdrawal of the patient from the study. At Visit 9, a psychiatric examination with rating scales was performed to determine a patient's continued eligibility for the phase 3 portion of the study.

Phase 3 was a continuation of double blind therapy for up to one year for patients who had a positive response and wished to continue. Phase 4 was an open ended continuation of phase three for patients to continue double-blind therapy (phase four lasted until the last patient finished phase 3). Phase 5 was an open label extension phase for patients who wished to continue olanzapine and who had previous exposure to olanzapine.

Assessments

Efficacy evaluations were based on assessments of patient improvement on the BPRS, the SANS, and CGI Severity, CGI Improvement, and PGI Improvement. The BPRS is the primary efficacy criterion for the study and consists of 18 items. Physicians within the US typically use the rating system of 1 = normal to 7 = extremely ill when administering the BPRS to patients. However, to calculate whether patients meet percentage improvement criteria, a rating system of 0 = normal to 6 = extremely ill was used when administering the BPRS.

Since there are 18 items in the BPRS, this scoring scale produces a score that is 18 points less than the BPRS total score using the 1 to 7 scale. The BPRS total scores used throughout this study report, unless noted otherwise, are calculated from the 0 to 6 scale.

A complete schedule of the assessments for safety and efficacy used in study HGAD are listed in appendix 7.2.2 in table 7.2.2.4.

Analysis Plan
All analyses were done on an intent-to-treat basis, meaning all patients were included in the treatment groups to which they were randomized, even if a patient did not strictly adhere to the protocol. Treatment groups were compared with regard to change from baseline to endpoint in BPRS total, positive, and negative scores; SANS summary score; and CGI Severity score using analysis of variance (ANOVA). The ANOVA model contained the terms for treatment, investigator, and treatment-by-investigator interaction. For all analyses, main effects were tested at a two-sided level of 0.05, and treatment-by-investigator interactions were tested at an level of 0.10. Pairwise comparisons with no correction for multiplicity were performed for all treatment groups using least-squares means.

Analyses of LOCF change from baseline to each acute phase visit were assessed for all efficacy variables. In the LOCF visitwise analyses, if a patient had a missing score at a visit, the last available (on treatment) score was carried forward to that visit.

Patient Disposition
A total of 419 patients entered the placebo lead-in phase. Of these patients, 335 were randomly allocated to a treatment group at Visit 2. Table 7.2.2.5 in appendix 7.2.2 summarizes the disposition of the randomized patients and the reasons patients discontinued from the acute phase. Of the randomized patients, 41.5% completed the acute phase. Although a greater number of patients in the Olz-H treatment group completed the acute phase, the percentage of patients who completed the acute phase did not differ significantly among the treatment groups (p=.380). Table 7.2.2.6 in appendix 7.2.2 summarizes completion rates by week for each treatment group. Table 7.2.2.9 in appendix 7.2.2 enumerates the mean dose by visit in each of the treatment groups.

Baseline Demographics/Baseline Illness Severity
The 335 patients had a mean age of 36.0 years, and most were Caucasian (68.7%) and male (87.8%). In this study, 59.4% of the patients were of the paranoid subtype, and 90.7% had a chronic course with an acute exacerbation. The treatment groups were comparable at baseline with respect to gender, racial origin, age, schizophrenic subtype, schizophrenic course, age of onset of psychosis, length of current episode, and number of previous episodes. The baseline BPRS total score s were statistically

significantly different between the treatment groups (p=0.048). The placebo group had a mean score of 39.7; OLZ-low 40.7; OLZ-med 42.8; OLZ-high 42.6; Hal 41.8. Though these are statistically significantly different, the clinical difference is negligable. Other baseline comparisons of rating scale scores were not significantly different. Patient characteristics are shown by treatment group in table 7.2.2.7 in appendix 7.2.2.

Concomitant Medications
In general, concomitant medications with primarily central nervous system (CNS) activity were not allowed in this protocol. Table 7.2.2.8 in appendix 7.2.2 contains a list of medications allowed and those prohibited in this study. Medications not listed in Table 7.2.2.8, either specifically or by category, that do not possess primarily CNS activity, may have been used by patients in this study.

If a medication for sleep or agitation was required, lorazepam could be given during the placebo lead-in period, and for up to a maximum of 21 cumulative days of treatment during the acute period and 60 cumulative days (additional) during the double-blind extension treatment period, in a dose of 1-10 mg/day. No other psychotropic drugs were permitted during the study If extrapyramidal symptoms occurred, benzotropine mesylate in a dose of 1 to 2 mg was permitted for up to 6 mg/day.

Most of the concomitant medications, other than the anticholinergics and/or benzodiazepine/hypnotics, were used for analgesia (ie, acetaminophen or ibuprofen) or gastric distress (ie, magnesium hydroxide). There was no significant difference in the pattern of concommitant drug use except that benzatropine was used significantly more often in the haloperidol group (patients receiving one or more doses benztropine p<0.001).

Efficacy Results
Summary statistics and statistical analysis of the LOCF and OC endpoint analysis are shown for BPRS total and positive scores; SANS summary score; and CGI Severity score in appendix 7.2.2, tables 7.2.2.10-17.

The LOCF and OC Olz-H and Olz-M treatment groups experienced significantly greater mean improvement in BPRS total score than the placebo treatment group (Table 7.2.2.10).

The LOCF Olz-H and Olz-M treatment groups experienced significantly greater mean improvement in BPRS positive score compared with the placebo treatment group (p=.004 and p=.010, respectively). Only the Olz-M group showed significant improvement over placebo in the OC BPRS positive score data set.

The LOCF Olz-H and Olz-L treatment groups experienced significantly greater mean improvement in SANS summary score than

the placebo treatment group (p= 001 and p=.041, respectively). The LOCF Olz-M treatment group did not show significant improvement over placebo; however, p-values steadily decreased over time and numerical clinical improvement was present. No endpoint OC SANS summary score were significantly better than placebo.

The LOCF Olz-H and Olz-M treatment groups experienced significantly greater mean improvement in CGI Severity scores than the placebo treatment group (p=.014 and p=.005, respectively). Six week OC analysis of CGI Severity scores was not significant.

Conclusions/Recommendations

Study HGAD represents a positive study in support of olanzapine as being effective in treatment of patients with schizophrenia. LOCF endpoint data for the primary and secondary efficacy measures were all significantly better than placebo for the highest olanzapine dose group (15 mg ± 2.5 mg/day). There could be a potential bias against the placebo group as this group had lower BPRS total scores than other treatment groups, but the difference in mean scores is quite small. The endpoint differences between the treatment and placebo groups overshadow this small baseline difference. In addition to this, the improvement that is evident using other rating scales, where no potential bias exsists, argues effectively in favor of the efficacy olanzapine in the treatment of psychotic symptoms. OC endpoint data did not show significant treatment benefit over placebo except on Olz-H and Olz-M total BPRS score, Olz-M BPRS positive score and CGI Severity scores; however, high drop-out rates of placebo treated patients who could not remain in studies leave the least symptomatic patients in the placebo group to compare against the treatment group. It is for this reason that LOCF and not OC data represent a clearer picture of the true efficacy of olanzapine in this patient population.

The study of serum concentration relationship with therapeutic response revealed no significant correlation.

Long-term efficacy results from study phases 3, 4, and 5 are discussed in section 7.3.

7.2.3 Flexible dose range study E003

Study E003, a non-IND, multicenter, randomized, double-blind study, compared three fixed dosage ranges of olanzapine (Olz-L, 5.0 ± 2.5; Olz-M, 10.0 ± 2.5; and Olz-H, 15.0 ± 2.5 mg/day) with one very low fixed dose of olanzapine (Olz1.0, 1.0 mg/day) and with one fixed dosage range of haloperidol (Hal, 15.0 ± 5.0 mg/day) in the treatment of 431 patients who met the DSM-III-R criteria for schizophrenia.

Investigators and Sites

This study was conducted at 50 sites in Europe, South Africa, Israel, and Australia.

Objectives

The objectives of the study were to:

- evaluate the acute phase efficacy and safety of olanzapine versus haloperidol,
- evaluate the acute phase efficacy and safety of the dosage ranges of olanzapine versus the very low fixed dose of olanzapine,
- establish the lowest effective dosage range of olanzapine,
- evaluate the efficacy and safety of treatment with olanzapine versus haloperidol through 1 year's duration in patients who had shown a positive response during the acute phase,
- study the possible relationships between the dose, plasma concentration of olanzapine, and clinical therapeutic effect,
- to assess the incidence and severity of extrapyramidal symptoms in various doses of olanzapine versus haloperidol.

Study Population

Male and female inpatients between the ages of 18 and 65 who met the diagnostic criteria for schizophrenia (295.1 to 295.3, 295.9) according to the DSM-III-R and who were in an acute exacerbation of illness were eligible. Residual Type 295.6 was excluded. Patients suffered sufficient symptoms such that the initial score (Visit 1) of severity of illness on the BPRS was at least 24 (0 to 6 scale). The severity of illness as judged on the CGI Severity scale was at least moderate (score ≥4) at Visit 1. Patients were excluded if they had a diagnosis of a psychotic disorder other than schizophrenia, an organic mental disorder, or a substance-use disorder. Other exclusionary criteria included serious and unstable nonpsychiatric disorders. A complete list of inclusion and exclusion criteria are listed in appendix 7.2.3.

Design
E003 was a multicenter, randomized, double-blind study, compared three fixed dosage ranges of olanzapine (Olz-L, 5.0 ± 2.5; Olz-M, 10.0 ± 2.5; and Olz-H, 15.0 ± 2.5 mg/day) with one very low fixed dose of olanzapine (Olz1.0, 1.0 mg/day) and with one fixed dosage range of haloperidol (Hal, 15.0 ± 5.0 mg/day). The study had a placebo lead-in phase (Study Period I), an acute phase (Study Period II), a double-blind extension phase (Study Periods III and IV), and an open-label extension phase (Study Period V).

After a 4- to 7-day placebo lead-in phase (Study Period I), patients who were experiencing an acute exacerbation as part of schizophrenia were randomly assigned to one of five treatment groups. Patients began therapy with the middle dose of the assigned dosage range. Investigators could titrate the dose up by one increment or down by single or multiple increments within the allowed dosage range to optimize clinical benefit. Patients who responded to therapy in the 6-week acute phase (Study Period II) could continue double-blind therapy for up to a total of 12 months (Study Period III). An addendum to the study allowed for patients who showed a positive response during Study Period III to continue double-blind therapy beyond 1 year (Study Period IV). Study Period IV lasted until the last patient completed Study Period III, and the reporting database, including data collected through that date, was created. Patients who had been previously treated with olanzapine in Study Period IV had the opportunity to receive open-label olanzapine for an indefinite period (Study Period V).

The data presented here in support of olanzapine's efficacy in the treatment of schizophrenia is from phase II.

Assessments
Efficacy evaluations were based on assessments of patient improvement on, the PANSS (BPRS data extracted from the PANSS), and CGI Severity, CGI Improvement, and PGI Improvement. The BPRS is the primary efficacy criterion for the study and consists of 18 items. Physicians within the US typically use the rating system of 1 = normal to 7 = extremely ill when administering the BPRS to patients. However, to calculate whether patients meet percentage improvement criteria, a rating system of 0 = normal to 6 = extremely ill was used when administering the BPRS. Since there are 18 items in the BPRS, this scoring scale produces a score that is 18 points less than the BPRS total score using the 1 to 7 scale. The BPRS total scores used throughout this study report, unless noted otherwise, are calculated from the 0 to 6 scale.

A complete schedule of the assessments for safety and efficacy

used in study E003 are listed in appendix 7.2.3 in table 7.2.3.3.

Analysis Plan
All analyses were done on an intent-to-treat basis, meaning all patients were included in the treatment groups to which they were randomized, even if a patient did not strictly adhere to the protocol.

When LOCF and OC change from baseline to endpoint was assessed, patients were included in the analysis only if a patient had a baseline and a postbaseline measure. The baseline measure was the Visit 2 observation, unless it was missing, then it was the Visit 1 measure. The endpoint measure was the last measure in the acute phase (Visits 3 through 9).

The main efficacy analysis was after 6 weeks of active treatment. BPRS total scores were the prime outcome measure: differences between the four olanzapine arms will be compared by analysis of variance (ANOVA). If the result indicated differences, then each of the olanzapine groups were compared with the haloperidol group by Dunnett's test. As a secondary end-point the same analyses were carried out on the total PANSS score and separately on the negative and positive symptoms. Patient and Clinical Global Impression and Improvement measured in 7 point scales were compared by non-parametric ANOVA. An endpoint analysis were done for the Quality of Life Scale to assess change in patient's overall sense of well-being.

Patient Disposition
A total of 508 patients entered the placebo lead-in phase. Of these patients, 431 were randomized to treatment groups. Table 7.2.3.4 in appendix 7.2.3 summarizes the disposition of the randomized patients and the reasons patients discontinued from the acute phase. Of the randomized patients, 57.3% completed the acute phase. Overall, both the Olz-M and Olz-H treatment groups had a greater number and percentage of patients completing the acute phase than the other treatment groups. Among the treatment groups, there were no statistically significant differences in the percentage of patients who completed the acute phase. Patient completion rates by visit are listed in table 7.2.3.5 in appendix 7.2.3.

Baseline Demographics/Baseline Illness Severity
The 431 patients had a mean age of 35.5 years, and most were Caucasian (86.3%) and male (63.8%). In this study, 56.6% of the patients were of the paranoid subtype, and 74.0% had a chronic course with an acute exacerbation. The treatment groups were comparable at baseline with respect to gender, racial or regional origin, age, schizophrenic subtype, schizophrenic course, age of onset of psychosis, length of current episode, and number of

previous episodes. Baseline group comparisons of clinical rating scale scores revealed no statistical differences in group mean scores. Patient characteristics are shown by treatment group in Table 7.2.3.6. Table 7.2.3.7 enumerates the mean dose by visit for all treatment groups.

Concomitant Medications
Patients who were using concomitant psychotropic medications except for benzodiazepines and anticholinergic/anti-pseudoparkinsonian medications were excluded from the study.

A list of approved and unapproved drugs as presented in the other pivotal studies was not present in this study. A fairly extensive dosing regimen for benzodiazepines was presented.

Use of concomitant medications taken by at least 10% of the patients was compared across treatment groups by chi-square tests. To account for protocol variations, all doses of benzodiazepine and/or hypnotics were converted to lorazepam equivalents. Similarly, all doses of anticholinergic medication were converted to benztropine equivalents (mg benztropine/day).

Mean daily benzodiazepine(expressed as "lorazepam equivalents") use was compared among the treatment groups using an ANOVA model including the terms for treatment, country, and treatment-by-country interaction. The proportions of patients taking at least one dose of lorazepam equivalent were compared across the treatment groups using a chi-square test. Similar analyses of anticholinergic use were also done.

The patients in the haloperidol group took biperiden significantly more often than any other group ($p<0.001$). Use of other concomitant medications was not significantly different among treatment groups.

Efficacy Results
Summary statistics and statistical analysis of the LOCF and OC endpoint analysis are shown for BPRS total, positive, and negative scores; PANSS total, positive, and negative scores; and CGI Severity score in tables 7.2.3.8-17. As stated in the protocol, the primary efficacy analysis was the mean change from baseline to endpoint in BPRS total score. There was no statistically significant improvement in the BPRS total score in any of the OLZ-L,M,H or haloperidol groups over the OLZ-1mg group. The OLZ-H LOCF and OC group showed significant improvement over the OLZ-1mg group on the CGI-Severity Scale . The OLZ-H LOCF and haloperidol OC groups showed significant improvement on the BPRS-positive symptoms scale. No other statistically significant differences in mean improvement in BPRS, PANSS, CGI, or PGI total score were observed between any of the other LOCF treatment groups.

Conclusions/Recommendations
Study E003 represents a failed study in that neither olanzapine nor haloperidol consistently show significant improvement over the OLZ-1mg group. In study HGAP, the olanzapine 1 mg group shows numerical improvement over placebo there is no statistical difference in therapeutic effect; however, study E003 is designed so that the olanzapine 1 mg group is an ersatz placebo group. Therefore, one can not assume that olanzapine 1 mg is an inactive dose.

7.2.4 Flexible dose range study HGAJ
Study HGAJ, a multicenter, randomized, double-blind study, compared one dosage range of olanzapine (Olz 5-20 mg/day) with one dosage range of haloperidol (Hal 5-20 mg/day) in the treatment of 1996 patients who met the DSM-III-R criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.

Investigators and Sites
The study was conducted at 186 sites in the United States and Europe. A list of study sites and principal investigators may be found in the sponsor's submission NDA 20-592 volume 1.129, pages 15-74.

Objectives
The objective of the study was to evaluate the safety and efficacy of olanzapine in a dosage range of 5-20 mg/day versus haloperidol in a dosage range of 5-20 mg/day through 1 year or more of treatment in patients who met the DSM-III-R criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.

Study Population
Male and female patients over 18 years of age were eligible. Patients had to meet the diagnostic criteria for schizophrenia (295.1 through 295.3, 295.6, 295.9), schizophreniform disorder (295.40), or schizoaffective disorder (bipolar type or depressive type [295.70]) according to the DSM-III-R. Patients had to experience clinically significant psychotic symptoms (positive and/or negative) while receiving no neuroleptic treatment or demonstrate less than a clinically optimal response to their then current neuroleptic treatment either by virtue of continued symptoms adverse events. This constituted clinical grounds for initiation or change in neuroleptic therapy. Patients must have had a total initial score on the BPRS of at least 18 (0 to 6 scale), or they could enter without the required minimum total score if they recently experienced (within 4 weeks of Visit 1 with depot neuroleptic therapy or within 6 days of Visit 1 with oral neuroleptic therapy) an adverse event that reasonably could have been attributed to their then current neuroleptic treatment (unless the neuroleptic was haloperidol) and who were no longer tolerating their current (immediately prestudy) treatment.

Patients were excluded if they had a serious, unstable illness including hepatic, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, hematologic disease, or any other DSM-III-R organic mental disorder or substance-use disorder. Other exclusionary criteria were a history of severe allergic adverse drug reactions including any adverse drug reaction to haloperidol of sufficient severity to discontinue haloperidol during the last 3 months. Full inclusion and exclusion criteria are listed in appendix 7.2.4 in table 7.2.4.1.

Design

Study HGAJ was a multicenter, randomized, double-blind study, comparing one dosage range of olanzapine (Olz 5-20 mg/day) with one dosage range of haloperidol (Hal 5-20 mg/day) in the treatment of patients who met the DSM-III-R criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.

The study had a screening phase (Study Period I), an acute phase (Study Period II), a double-blind extension phase for responders or an open-label extension for nonresponders (Study Period III), and an open-label indefinite extension (Study Period IV). After a 2- to 9-day screening phase (Study Period I), 1996 patients were randomized to a treatment group. The randomization ratio in the study was 2:1 olanzapine to haloperidol. Patients began therapy with one double-blind capsule (containing 5 mg of either drug) per day. Investigators optimized therapeutic benefit through dose increases of one capsule per day on a weekly basis and/or decreases to a minimum of one capsule per day at any time. Patients who responded to double-blind therapy in the 6-week acute phase (Study Period II) could continue double-blind therapy in Study Period III. Patients who did not respond to double-blind therapy during the acute phase could enter the open-label phase of Study Period III at Visit 6, 7, or 8 and receive olanzapine for 46 weeks.

Study Period III lasted until all patients had completed (or discontinued early) Study Period II and until at least 100 patients (cumulative, across multiple protocols) had been treated with olanzapine at doses ≥5 mg/day (including patients treated with a dosage range from 2.5 to 7.5 mg/day) for a duration of at least 1 year. Upon their completion of Study Period III, patients treated with double-blind medication could continue (Study Period IV). These patients continued to be treated with double-blind medication until the double-blind extension database had been finalized. At that time, treatment assignments were unblinded and patients treated with olanzapine were allowed to continue on open-label olanzapine in Study Period IV, if clinically indicated.

Assessments
Efficacy assessments included the PANSS, MADRS, CGI, and PGI rating instruments. Mean change in the investigator-rated BPRS served as the primary efficacy assessment. Secondary efficacy assessments included the PANSS, MADRS, CGI, and PGI.
A complete list of safety and efficacy assessments and their schedule of administration may be found in the sponsor's submission NDA 20-592 volume 1.126, pages 109-111.

Analysis Plan
All analyses were done on an intent-to-treat basis, meaning all patients were included in the treatment groups to which they were randomized, even if a patient did not strictly adhere to the protocol.
When LOCF and OC change from baseline to endpoint was assessed, patients were included in the analysis only if a patient had a baseline and a postbaseline measure. The baseline measure was the Visit 2 observation, unless it was missing, then it was the Visit 1 measure. The endpoint measure was the last measure in the acute phase (Visits 3 through 8).

When a patient discontinued the acute phase, patient disposition was determined by evaluating the patient's summary record. Patients who discontinued at Visit 8 for any reason other than a lack of efficacy, adverse event, or death were considered to be "reporting interval complete." Patients who completed Visit 8 and continued into either the double-blind extension phase or open-label phase were also listed as "reporting interval complete." Patients who entered the open-label phase at either Visit 6 or 7 were listed as discontinuing the acute phase for "lack of efficacy."

Treatment groups were compared with regard to change from baseline to endpoint in BPRS total, positive, and negative scores; PANSS total, positive, and negative scores; MADRS total score; and CGI Severity score using ANOVA. The ANOVA model contained the terms for treatment, treatment site, and treatment-by-site interaction. For all analyses, main effects were tested at a two-sided α level of 0.05, and treatment-by site interactions were tested at an α level of 0.10. The Wilcoxon signed rank test was used to test if the hypothesis that within-treatment group change from baseline to endpoint was significant. The cumulative distribution of LOCF change from baseline to endpoint in the BPRS total score was calculated for each treatment group. In the LOCF visitwise analyses, if a patient had a missing score at a visit, the last available score was carried forward to that visit.

Baseline Demographics/Baseline Severity of Illness
The 1996 patients had a mean age of 38.6 years, and most were Caucasian (80.2%) and male (64.9%). In this study, 83.1% of the patients were diagnosed with schizophrenia, 1.9% were diagnosed

with schizophreniform disorder, and 15.0% were diagnosed with schizoaffective disorder. The treatment groups were comparable at baseline with respect to gender, racial origin, age, diagnosis, schizophrenic course, length of current episode, and number of previous episodes. There was a significant difference (p=.026) between the treatment groups in mean age of onset of psychosis (mean ± standard deviation: Olz, 24.2 ± 7.9; Hal, 23.4 ± 6.7). There was no statistically significant difference between treatment groups in proportions of patients who had previously been treated with haloperidol (Olz, 38.0%; Hal, 38.3%). There were statistically significant differences in the BPRS total baseline score (33.1 Olz, 34.1 Hal, p=0.02), the PANSS total score (90.1, Olz, 92.1 Hal, p=0.01), and the PANSS general psychiatric score (44.9 Olz, 46.1 Hal, p=0.003). These differences are not clinically significant but become statistically significant due to the large numbers of patients in the study. Patients' characteristics by group is listed in appendix 7.2.4 in table 7.2.4.2.

Patient disposition
A total of 2223 patients entered the screening phase. Of these patients, 1996 were randomized to a treatment group at Visit 2. Table 7.2.4.3 in appendix 7.2.4 summarizes the disposition of the randomized patients and the reasons the patients discontinued from Study Period II.

A significantly greater proportion of patients in the Olz treatment group than in the Hal treatment group completed the acute phase of the study (p<.001). The proportion of patients from the Olz treatment group who discontinued the acute phase of the study because of adverse events was 4.5%, while 7.3% of the patients from the Hal treatment group discontinued because of adverse events (p=.010). The proportion of patients who discontinued because of lack of efficacy was significantly smaller (p<.001) in the Olz treatment group (20.7%) than in the Hal treatment group (32.1%). A significantly smaller proportion of olanzapine-treated patients (3.6%) than haloperidol-treated patients (7.4%) discontinued because of patient decision (p<.001). Table 7.2.4.4 in appendix 7.2.4 gives the patient completion rate by visit in this study. Table 7.2.4.6 enumerates the mean dose by visit for each of the treatment groups.

Concomitant Medications
In general, concomitant medications with primarily central nervous system (CNS) activity were not allowed in this protocol. Table 7.2.4.5 in appendix 7.2.4 contains a list of medications allowed and those prohibited in this study. Medications not listed in Table 7.2.4.5, either specifically or by category, that do not possess primarily CNS activity, may have been used by patients in this study.

Patients took a variety of concomitant medications. Concomitan'

medications used by at least 10% of the patients in one treatment were compared across groups using ANOVA to determine if there was a disproportionate use of a concomitant drug.

Overall, the Olz treatment group had a significantly smaller proportion of patients who took at least one concomitant drug than the Hal treatment group (81% vs 88%, p<.001). Medications which were taken by significantly smaller proportions of the Olz treatment group than the Hal treatment group included lorazepam (36% vs 41%, p=.028), benztropine mesylate (10% vs 29%, p<.001), and biperiden (3% vs 12%, p<.001). It is unclear exactly how these differences might have influenced the reported differences between olanzapine and haloperidol. Clinically anticholiergics and benzodiazepines are used to decrease drug related adverse events and in-so-doing increase efficacy of antipsychotics. The fact that these concomitant medications were used more often in the haloperidol group could conceivably bias the result toward haloperidol. If this were the case, it did not do so to the extent that haloperidol and olanzapine were equally effective, or that haloperidol was superior to olanzapine.

Efficacy Results
The primary efficacy analysis was a LOCF comparison of the Olz treatment group with the Hal treatment group in the mean change in BPRS total score from baseline to endpoint. The Olz treatment group had significantly greater mean improvement in BPRS total score compared with the Hal treatment group (p=.015).

PANSS negative scores were used in the assessment of negative psychopathology. Evaluation of the PANSS negative score demonstrated superior improvement in the Olz treatment group compared with the Hal treatment group in the analyses of LOCF and OC mean change from baseline to endpoint (p=.032 and 0.003 respectively).

CGI Severity scores were statistically significantly lower in the olanzapine treated patients by LOCF and OC analysis (p=0.03 and <0.001 respectively).

Tabular presentation of these results may be found in appendix 7.2.4 tables 7.2.4.7-16.

Conclusions and Recommendations
At face value, it would appear that the result of this study might suggest that olanzapine is significantly more effective at treating symptoms of psychotic disorders than haloperidol; however, there are several design flaws in the study that prohibit this reviewer from making any comparative conclusions between olanzapine and haloperidol that might be used in labeling.

The study is biased against haloperidol. The study enrolled

roughly 38% of a sample that had been previously treated with haloperidol while patients who had previously been exposed to olanzapine were excluded. Though the sponsors had exclusion criteria for patients who were treatment resistant to neuroleptics they did include patients who were previously treated with haloperidol. One must assume that the patients who had been previously treated with haloperidol were not completely satisfied with their treatment, or they would not have enrolled in the study. The dividing line between treatment resistant and unsatisfactory response is arbitrary and not defined in this study. The only way to resolve this issue would be to compare patients that had never been exposed to either haloperidol or olanzapine. Otherwise, this bias most likely deflates the haloperidol response rates.

The significant difference in rating scale means is clinically small but becomes significant due to the high numbers of subjects in the study (BPRS mean total change of 8-HAL vs 11-OLZ). The numerical differences between the mean changes in rating scales throughout the pivotal studies is similar and, in the balance, slightly superior in favor of olanzapine. The HGAJ study is overpowered.

Dosage ranges of the two drugs may not be comparable. Haloperidol has a vastly different drug-related-adverse-event profile than olanzapine. Dosing the two drugs on the same milligram for milligram basis and on the same schedule again potentially biases against haloperidol in the same way that dosing at lower doses and on a slower dose increase rate might bias against olanzapine. Multiple dosing levels and/or schedules would more realistically compare the two drugs.

I, therefore, can not recommend any labeling suggesting that olanzapine is more effective than haloperidol based on this study. This study takes nothing away from the positive results of two other studies in this submission and suggests that olanzapine would be more effective than placebo in the treatment of psychotic symptoms in schizophrenia.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

Subgroup analyses of efficacy measures common to studies HGAD and HGAP(BPRS total, positive, negative, and CGI Severity) were performed to examine the consistency of treatment effects over the strata of two demographic populations. These analyses were only performed when there was a minimum of 10% of the total sample in each of the subgroup strata. The subgroups that were analyzed were gender (male, female), and racial origin (African descent, Caucasian, other). Only gender and racial origin were analyzed because the age subgroup did not meet the criteria for analysis.

Comparisons were made between olanzapine and placebo. Comparisons between olanzapine and placebo were based on analyses of the acute phases of studies HGAD and HGAP which were similar in design. All olanzapine-treated patients from these two studies were pooled to form the olanzapine group, except for patients in the olanzapine 1 mg treatment group in study HGAP because olanzapine 1.0-mg/day dose was not demonstrated to be an efficacious dose. Patients from both placebo treatment groups were pooled to form the placebo group.

All efficacy measures were assessed using an ANOVA model that included the terms for treatment, study, subgroup, treatment-by-study interaction, and treatment-by-subgroup interaction. The treatment-by-subgroup interaction was tested to determine if the differences in the efficacy measures were consistent across subgroups. None of the efficacy variables exhibited a statistically significant treatment-by-strata interaction, indicating no significant differences between either gender or racial origin with respect to treatment effect (see volume 217 page 241, Attachment 4 to ISE: Summary of Subgroup Analysis for Placebo-Controlled Studies F1D-MC-ISE Placebo-Controlled Integrated Database AcutePhase). As previously mentioned, plasma olanzapine levels did not predict therapeutic response.

7.3.2 Size of Treatment Effect

This evaluation of treatment effect size will focus on the 10mg and medium and high olanzapine dose groups, and haloperidol of study HGAP and study HGAD. Treatment effect is defined as the change from baseline in the BPRS and CGI-severity scores among completers at the final (Week 6) visit. The unadjusted changes and placebo-adjusted changes are summarized in **Table 7.3.2** below, which includes corresponding efficacy data haloperidol in Study HGAD.

Table 7.3.2: Summary of Treatment Effect Sizes				
TX Group mg/day	BPRS		CGI-Severity	
	Unadj.*	Adj.**	Unadj.*	Adj.**
HGAP-OLZ 10	-15.6	-4.8	-1.47	-0.17
HGAD-OLZ 10± 2.5	-23.6	-8.2	-1.70	-0.43
HGAD-OLZ 15± 2.5	-22.7	-7.3	-1.42	-0.25
HGAD-HAL 15±5	-18.0	-2.6	-1.27	-0.10

* Calculated as: (Mean score at final visit) minus (Mean baseline score).

** Calculated as: (Mean active drug change from baseline) minus (Mean placebo change from baseline).

All treatment effect sizes were comparable with olanzapine being numerically but not statistically superior to haloperidol in the acute phase studies.

Overall, although the treatment effect sizes are not strikingly different, they can be considered to represent notable clinical improvement.

7.3.3 Choice of Dose

Efficacy data from studies HGAP and HGAD suggests that the mean effective dose begins at 10 mg/day. The efficacy of olanzapine in study HGAD at a fixed dosage range of 5 ± 2.5 mg/day was not demonstrated. The lower dose group mean was 6.6 mg/day or above after week 6. The middle dose group in HGAD, though effective, was at mean doses greater than 10 mg/day. The 10 mg/day dose group is the lowest effective dosage yet to be consistantly demonstrated. Individual differences may exist that allow lower dosing of olanzapine to be effective or may necessitate higher dosing of olanzapine before it becomes effective. The sponsors recommendation of 10 mg po qd as a starting dose is reasonable based on efficacy data.

The sponsor's recommended dose range is 5 to 20 mg po qd. The rationale is that individual patients may not be able to tolerate the 10 mg (lowest consistently effective dose tested) dose and that individual patients may require higher doses than 10 mg/day to receive adequate clinical response. This is consistant with good clinical practice and experience with other antipsychotic medication.

7.3.4 Duration of Treatment

The long-term effectiveness of olanzapine among acute responders was evaluated by assessing long-term completion rates, estimating the prevention of relapse at 1 year of double-blind therapy, estimating the time to relapse, and assessing the mean change in efficacy rating scale scores from baseline to endpoint. The efficacy data presented below are from the double-blind extension for responders in study HGAD. Data from study HGAD was used for comparisons of the olanzapine treatment groups with the placebo treatment group.

A survival analysis was performed to estimate the prevention of relapse at 1 year of double-blind therapy and the time to relapse for two definitions of relapse: primary and secondary. The analysis of time to relapse by primary and secondary definition only includes patients in the double-blind, responder extensions who were on outpatient status by their last visit in the acute phase. Patients classified as experiencing a relapse by primary definition were on outpatient status by the last visit in the acute phase (Visit 9) and later hospitalized because of an exacerbation of psychotic psychopathology and had an increase in CGI Severity score of at least 2 from their Visit 9 CGI Severity score. Patients classified as experiencing a relapse by secondary definition were on outpatient status by the last visit in the acute phase and later hospitalized because of an exacerbation of psychotic psychopathology, regardless of CGI Severity score.

The Olz-L (5.0 $\pm$ 2.5 mg/day) treatment group had the largest estimated percentage not relapsing according to the criteria outlined for primary definition of relapse. The survival curves for the Olz-L and Olz-H treatment groups were significantly different from the survival curve for the placebo treatment group (each, p=.026), indicating that fewer patients in the Olz-L and Olz-H treatment groups experienced a relapse by primary definition at any given point in time than patients in the placebo treatment group.

Table 7.3.3.1 Primary Definition of Relapse
F1D-MC-HGAD Double-Blind Extension Phase

Treatment Group	N	% Not Relapsing at 365 Days	p-Value[a] vs Placebo
Placebo	13	38.3	--
Olz-L	14	90.9	.026
Olz-M	9	76.2	.150
Olz-H	22	88.2	.026
Hal	10	71.4	.324

Abbreviations: N = patients who continued into Study Period 3 and were outpatients at Visit 9; Olz-L = olanzapine 5.0 ± 2.5 mg/day; Olz-M = olanzapine 10.0 ± 2.5 mg/day; Olz-H = olanzapine 15.0 ± 2.5 mg/day; Hal = haloperidol 15.0 ± 5.0 mg/day; vs = versus.

[a] p-Value from testing homogeneity of survival curves between treatment groups using log-rank test.

Table 7.3.3.2. Secondary Definition of Relapse
F1D-MC-HGAD Double-Blind Extension Phase

Treatment Group	N	% Not Relapsing at 365 Days	p-Value[a] vs Placebo
Placebo	13	32.8	--
Olz-L	14	69.3	.059
Olz-M	9	57.1	.174
Olz-H	22	77.8	.045
Hal	10	71.4	.223

Abbreviations: N = patients who continued into Study Period 3 and were outpatients at Visit 9; Olz-L = olanzapine 5.0 ± 2.5 mg/day; Olz-M = olanzapine 10.0 ± 2.5 mg/day; Olz-H = olanzapine 15.0 ± 2.5 mg/day; Hal = haloperidol 15.0 ± 5.0 mg/day; vs = versus.

[a] p-Value from testing homogeneity of survival curves between treatment groups using log-rank test.

Though the results of this study appear to support olanzapine as an effective longterm treatment of schizophrenia over placebo. This extension study is biased toward the olanzapine group. Patients in the placebo group were never exposed to olanzapine and therefore one can not answer the question of whether chronic olanzapine treatment prevents the relapse of schizophrenia symptoms after responding to acute olanzapine treatment. A preferable design would be to have studied patients who had responded to olanzapine then to have randomized these patients to either placebo or olanzapine then measure time to relapse. The only useful conclusion from this type of relapse study is that olanzapine's long-term effects appear to follow the same pattern as that of haloperidol.

7.4 Conclusions Regarding Efficacy Data

Table 7.4. summarizes the efficacy results for the two pivotal olanzapine clinical trials at week 6.

Table 7.4 Summary of efficacy results for pivotal olanzapine clinical trials program (significance of drug/placebo comparisons for mean change from baseline at week 6)[1].

Study	Active Drug Group	BPRS total		CGI-Severity	
		LOCF[2]	OC[2]	LOCF	OC
HGAD	OLZ-L	NS	NS	NS	NS
	OLZ-M	**	**	**	TR
	OLZ-H	**	**	*	NS
	HAL	**	NS	*	NS
HGAP	OLZ-1mg	NS	NS	NS	NS
	OLZ-10mg	*	NS	*	NS

1. Significance codes: **=very significant ($p<0.01$)
*=significant ($0.01 \leq p < 0.05$)
TR=trend toward significance ($0.05 \leq p < 0.10$)
NS=not significant ($p \geq 0.10$)
2. LOCF=Last observation carried forward. OC=Observed cases.

Studies HGAJ and E003 are not placebo controlled (sections 7.2.3 and 7.2.4). Study E003 included an olanzapine 1 mg/day group (designed as ersatz placebo); however, since the active control (haloperidol) group was not significantly therapeutically better than the ersatz placebo group, then it is this reviewer's opinion that this is not evidence of lack of efficacy (a negative study) but represents a failed study.

Study HGAJ was an uncontrolled comparison study of olanzapine and haloperidol. In this study olanzapine out-performs haloperidol; however, study design problems prevent this reviewer from making a positive statement about a potential clinical superiority of olanzapine over haloperidol. On the other hand, study HGAJ takes nothing away from the positive efficacy results of studies HGAD and HGAP.

Studies HGAD and HGAP (see sections 7.2.1 and 7.2.2 of this review) are well designed and offer sufficient data to support the claim that olanzapine is effective in the treatment of psychotic symptoms associated with schizophrenia with a minimum effective dose of 10 mg/day.

The relapse prevention analysis in the extension studies appear to show that the relapse rate is lower in olanzapine treatment groups over placebo. The extension studies do not, however, offer any data on the effectiveness of long-term olanzapine treatment versus short term olanzapine treatment (see section 7.3.3 of this review). Generally, clinical evidence supports the chronic use of antipsychotic

medication for the prevention of relapse in schizophrenia. The data provided do offer evidence that olanzapine's effectiveness does not wane over-time (i.e. therapeutic tolerance does not seem to occur) and therefore shows no evidence that olanzapine's effects are contrary to this general principal.

8.0 Integrated Review of Safety

8.1 Background and Methodology for Safety Review

The basic approach to examining the safety of olanzapine in the treatment of psychotic symptoms associated with schizophrenia included: 1) an examination of the entire (primary and secondary databases [Nolz=3139]) database for deaths (**Section 8.1.1**), dropouts (**Section 8.1.2**), and serious adverse events, (**Section 8.1.3**); these comprise the adverse events at the more serious end of the nonserious/serious continuum; and 2) within selected subsets of the primary safety database (Nolz=2500), an evaluation of the routinely collected safety data in order to describe the common adverse event profile for olanzapine in a schizophrenic population. Specific search stratagies were also employed to investigate potential treatment emergent hostility and emergent suicidality, **(Section 8.1.4)**. The evaluation of routinely collected safety data (adverse events, laboratory findings, vital signs, and ECG data) is provided in **Sections 8.1.5-8.1.8**. **Section 8.1.9** reviews opthalmologic, chest X-ray, and EEG evalautions of patient samples from the primary integrated database. Data regarding withdrawal phenomena and abuse potential are addressed in **Section 8.1.10**. Human reproduction experience is summarized in **Section 8.1.11**. Data pertinent to olanzapine overdoses is discussed in **Section 8.1.12**.

An analysis of the relationship between treatment-emergent adverse event occurrence and various demographic variables is presented in **section 8.1.5.4**. Similar analyses for changes in treatment-emergent high or low laboratory values in **section 8.1.6.4** and for vital signs and weight is found in **section 8.1.7.4**. These analyses were performed to examine the consistency of treatment effects over the strata of gender (male, female), racial origin (African descent, Caucasian, other), and age (less than 50 years of age, at least 50 years of age). These analyses were only performed when there were adequate numbers of patients for the analysis (a minimum of 10% of the total sample in each of the subgroup strata).

Important findings from the above review are then organized into a review of systems, where the findings are discussed by organ system (**Section 8.2**). This is then followed by a summary of the key adverse findings (**Section 8.3**).

The following safety review is based on the experience gleaned from the exposure of all patients (both primary and secondary databases) to olanzapine except that only serious adverse events adverse, dropouts due to adverse events, and deaths were from the secondary database.

The Primary Safety Database has a treatment group distribution, in terms of both number of patients (N) and exposure in patient-

years, as follows:

Drug	N	Patient-years
Olanzapine	2500	1122.2
Placebo	246	27.1
Haloperidol	810	193.0

Please note that, throughout the safety section, the acute, placebo-controlled study pool consists of the pool of the acute phases of studies HGAD and HGAP, minus the 1mg dose group from HGAP since this very low dose is not in the recommended dose range for olanzapine and is felt to have low pharmacodynamic activity.

The sponsor provided Case Report Forms for all deaths, discontinuations due to adverse events, and serious, unexpected adverse events (in CANDA form). Patient summaries were provided for all serious adverse events, all potentially clinically significant adverse events (identified by the algorithm described in volume 1.218, pages 288-289), and for all potentially clinically significant changes in laboratory values, vital sign measurements, and ECG records (by pre-defined criteria). Since these summaries were used to review most individual patient data, it was considered important to verify concordance between the CRF's and the patient summaries. Twenty CRF/Patient Summary pairs, selected at random, were examined and found to be in agreement.

8.1.1 Deaths

Among all patients (primary and secondary databases) exposed to olanzapine (N=3139), there were 22 deaths that occured during or within thirty days of study discontinuation. The descriptions of these cases follow in **Table 8.1.1.1** in **Appendix 8.0** and are discussed in the review of systems subsections that are pertinent to the cause of death (under section **8.2**). In the combined primary and secondary safety databases there were three deaths in the haloperidol treatment group and two in the placebo group within thirty days of study discontinuation. The reporting cut-off date for all deaths was June 30, 1995.

Twenty of these olanzapine exposed deaths occured in the primary database patient population (N=2500). Three deaths occurred in the haloperidol group and two in the placebo treatment group.

An analysis of crude mortality and exposure adjusted mortality was performed by the sponsor for the deaths that occurred in the primary integrated safety database [(N=2500) **Table 8.1.1.2**

below]. Five of 20 total deaths in olanzapine-treated patients across studies and 1 of 2 total deaths in placebo-treated patients across studies were from study HGAO in patients with primary degenerative dementia of the Alzheimer's type (median age of all patients from study HGAO who died, 83.5 years. Study HGAO did not include a haloperidol treatment group.

Table 8.1.1.2. Mortality Rates: Primary Integrated Database

Therapy	Deaths (N)	Crude Mortality (%)	Mortality/100 Patient-Years of Exposure
Olanzapine	20	0.008	1.8
Haloperidol	3	0.0037	1.6
Placebo	2	0.0085	7.4

In this reviewer's judgement, two deaths were possibly connected to olanzapine; all other deaths were not felt to be causally related to olanzapine. These 2 cases were:

HGAO 012-1208-This case of death subsequent to aspiration pneumonia will be discussed in the respiratory subsection of the review of systems section (**8.2.7**).

HGAO 006-0615-This case of death subsequent to aspiration pneumonia will be discussed also in the respiratory subsection of the review of systems section (**8.2.7**).

The following table enumerates the causes of death in all patients exposed to olanzepine that occurred during or within 30 days of the termination of treatment. These deaths were not judged by this reviewer to be related to olanzapine treatment.

There was one death (**HGBT 241-2409**) during or within 30 days of treatment termination in the secondary safety database that was judged not to be causally related to olanzapine treatment. There was one death during or within 30 days of treatment termination unrelated to olanzapine use reported after the February 14, 1995 cut-off date **(HGAP 005-1215)** that is not included in the mortality rate calculations but is included in the discussion of deaths in the following sections. These patients are listed in **Table 8.1.1.1** in **Appendix 8.0** and discussed the review of systems section.

Cause of Death	Treatment Group (N=total patients in group)		
	Olanzapine N=3139	Haloperidol N=836	Placebo N=277
Suicide	12	2	1
Cardiac Arrest	3	1	1
Respiratory Disorder/ Infection	2	0	0
Congestive Heart Failure	2	0	0
CVA	1	0	0
Accidental Injury	1	0	0

8.1.2 Assessment of Dropouts

8.1.2.1 Overall Pattern of Dropouts

The table below provides an enumeration of subjects who prematurely discontinued treatment in the olanzapine integrated clinical trial data base, categorized on the basis of the investigator's judgement regarding the single most important reason for withdrawal. **Table 8.1.2.1** enumerates the patient disposition for all patients treated with olanzapine in the primary safety database. **Table 8.1.2.2** show the patient disposition data for patients in placebo controlled acute studies respectively.

In placebo controlled studies patients, placebo patients dropped out more often than the olanzapine treatment groups for lack of efficacy; conversely, patients in the olanzapine treament group completed the study significantly more often than the placebo group.

Table 8.1.2.1 Olanzapine Treated Patients' Disposition: Primary Integrated Database	
	Olanzapine (N=2500)
Reason for Discontinuation	n (%)
Protocol Complete	118 (5)
Satisfactory Response	24 (1)
Adverse Event	372 (15)
Lack of Efficacy	651 (26)
Lost to Follow-up	71 (3)
Patient Decision	278 (11)
Criteria not met / Compliance	235 (9)
Sponsor Decision	37 (1)
Ongoing	736 (29)

Table 8.1.2.2 Patient Disposition Placebo-Controlled Integrated Database Acute Phase

Reason for Discontinuation	Olz (N=248*) n (%)	Placebo (N=118) n (%)	p-Value*
Reporting Interval Complete	106 (42.7)	32 (27.1)	.004
Adverse Event	12 (4.8)	7 (5.9)	.659
Lack of Efficacy	92 (37.1)	69 (58.5)	<.001
Lost to Follow-up	6 (2.4)	3 (2.5)	.943
Patient Decision	22 (8.9)	3 (2.5)	.025
Criteria not met / Compliance	10 (4.0)	4 (3.4)	.765

Patients included in the reasons discontinued, Reporting Interval Complete and Lack of Efficacy, may have continued into the next reporting interval or discontinued from the study.
* Frequencies are analyzed using a Chi-Square test.
+ Patients from studies HGAD and HGAP minus the 50 patients taking olanzapine 1 mg.

8.1.2.2 Adverse Events Associated with Dropout

When a patient discontinued the study, the investigator chose the most important reason for discontinuation. Investigators were encouraged to choose the reason adverse event if the choice were between an adverse event and another reason.

Fifteen percent (372/2500) of the olanzapine treated patients in the primary database dropped out with an associated adverse event. In the acute, placebo-controlled study pool, 4.8% (12/248) of olanzapine and 5.9% (7/118) of placebo patients

prematurely discontinued due to adverse events.

Table 8.1.2.2.1 lists adverse events that led to premature discontinuation of treatment at an incidence of at least 1% in the olanzapine group in the acute, placebo-controlled studies. These were defined as all adverse events that were treatment emergent and followed by the action "drug withdrawn" in the CRF.

Table 8.1.2.2.1 Adverse Events Reported as Reason for Discontinuation Placebo-Controlled Integrated Database Acute Phase

Event Classification	Olanzapine (N=248) n (%)	Placebo (N=118) n (%)	Fisher's Exact p-Value
SGPT increased	6 (2.4)	0 (0.0)	.183
Schizophrenic reaction	2 (0.8)	1 (0.8)	1.000
Headache	1 (0.4)	0 (0.0)	1.000
Leukopenia	1 (0.4)	0 (0.0)	1.000
Personality disorder	1 (0.4)	0 (0.0)	1.000
Agitation	1 (0.4)	3 (0.0)	0.100
Total Patients Discontinued	12 (4.8)	7* (5.9)	---

*Three other placebo treated patients were discontinued for akathisia, paranoid reaction, and suicide attempt.

An enumeration of adverse events leading to dropout in the primary integrated database for olanzapine patients is found in table 8.1.2.2.2 in appendix 8.0

Dropouts for clinically important adverse events will be discussed in the appropriate subsections of the Review of Systems (8.2).

8.1.3 Other Serious Adverse Events

The FDA and the sponsor defined serious adverse events as fatal, life threatening, permanently disabling, congenital anomalies, overdoses, cancers, or requiring hospitalization. The cut-off dates for serious adverse events in this submission encompasses those having an onset date on or before the submission cutoff date of 14 February 1995 and reported to the sponsor as of June 30, 1995.

The number of patients who experienced at least one adverse event is as follows:

Table 8.1.3 Patients with at least one serious adverse event	Olanzapine Total N=3139	Olanzapine Primary Integrated N=2500	Haloperidol N=810	Placebo n=236
Number Patients	568	542	145	26
Percent	18	22	18	11
Events per Patient-year		0.48	0.75	0.96

In the line listing for serious adverse events, the sponsor listed all adverse events occurring at the time of a serious event as serious; thus the listing of serious adverse events is relatively long yet few are truly serious. For all adverse events classified by the sponsor as serious, the patient narrative summary was reviewed individually to judge whether the event was drug related. Adverse events which were felt to be serious by the undersigned, based on FDA criteria, are discussed in the relevant subsections of the Review of Systems section (8.2).

8.1.4 Other Search Strategies

8.1.4.1 Search for Emergence of Suicidality

The MADRS rating scale was administered only to patients in study HGAJ. Data for the MADRS suicidal thoughts item (item 10)[1] were analyzed for patients treated with olanzapine or haloperidol in two databases for study HGAJ: the acute phase database and the double-blind extension phase database (all data, acute and extension phase, for patients who entered the double-blind extension phase).

In the first analysis, the focus was on de novo, substantial emergent suicidality (change in MADRS item 10 score from 0-2 at baseline to a score of 5-6 at any time). **Table 8.1.4.1** shows the results for the acute phase, and **Table 8.1.4.2** shows the results for the double-blind extension phase. No statistically significant differences were found.

Table 8.1.4.1. MADRS Suicidal Thoughts Item

[1]The MADRS item 10 is scored on a scale of 0 to 6, where 0 = "Enjoys life or takes it as it comes"; 2 = "Weary of life. Only fleeting suicidal thoughts"; 4 = "Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention"; 6 = "Explicit plans for suicide when there is an opportunity. Active preparations for suicide."

Incidence of Scores 5-6 at Any Time During Therapy Given Baseline 0-2 F1D-MC-HGAJ Acute Phase

Olz			Hal			Fisher's Exact
N	n	%	N	n	%	P-value
983	3	0.3%	407	1	0.2%	1.00

Table 8.1.4.2 MADRS Suicidal Thoughts Item
Incidence of Scores 5-6 at Any Time During Therapy Given Baseline 0- 2 F1D-MC-HGAJ Double-Blind Extension

Olz			Hal			Fisher's Exact
N	n	%	N	n	%	P-value
674	4	0.6%	211	2	0.9%	.633

For the entire Primary Safety Database, the incidence of completed suicide across treatment groups was: olanzapine 0.4% (9/2500), placebo 0.4% (1/236), and haloperidol 0.1% (1/810).

Within the acute, placebo-controlled study pool, the sponsor calculated the incidence of any adverse events suggesting the emergence of self-directed aggression (defined in detail in volume 1.219, pages 128-131, of the original NDA submission): olanzapine 4.0% (10/248) and placebo 3.4% (4/118); the difference is not statistically significant (p=0.967, Cochran Mantel-Haenszel).

From these analyses, it does not appear that olanzapine is related to the emergence of suicidality or self-directed aggression.

8.1.4.2 Search for Emergent Hostility

BPRS hostility item (item 10)[2] data were analyzed for patients

[2]Item 10 of the BPRS rates hostility on a scale of 1 to 7 where 1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate-severe, 6 = severe, and 7 = extreme.

treated with olanzapine (Olz), haloperidol (Hal), or placebo in studies included in four databases: the placebo-controlled integrated database (acute phase data), the active-controlled integrated database (acute phase data), the placebo-controlled long-term extension database (study HGAD double-blind extension only), and the active-controlled long-term integrated database (pooled double-blind extension data from studies HGAD, E003, and HGAJ).

The first analyses focused on any clinically significant increase (≥2 points) in the BPRS hostility item score to a clinically significant level (≥5 points) at any time during therapy, likely to represent the clinical situation of most concern. The denominator was restricted to patients with the potential to increase 2 points (baseline score ≤5). No statistically significant differences were found with this analysis.

The next analyses focused on clinically significant change in the BPRS hostility item score from a low level (≤3) to a clinically significant level (≥5) at any time during therapy, in essence, de novo, substantial emergent hostility. The denominator was restricted to patients with a baseline score ≤3. No statistically significant differences were found.

Next, all worsening in the BPRS hostility item scored at any time during therapy was considered. A worsening was defined as a change of ≥1 from baseline in BPRS hostility item. The denominator was restricted to patients with the potential to worsen (baseline score <7). No statistically significant differences were found.

Finally, the emergence of specific adverse events which suggested externally-directed aggression was examined within the acute, placebo-controlled study pool; such events are defined in detail in volume 1.219, pages 128-131, of the original NDA submission. The incidence of any such events was: olanzapine 14.1% (35/248) and placebo 13.6% (16/118); this difference is not statistically significant (p=0.755, Cochran Mantel-Haenszel).

Based on these analyses, it does not appear that olanzapine is related to the emergence of hostility or externally-directed aggression.

8.1.5 Adverse Event Incidence Tables

8.1.5.1 Establishing the Appropriateness of Adverse Event Categorization and Preferred Terms

Treatment-emergent adverse events are defined as events that first occurred or, if present at baseline, worsened during double-blind therapy. Adverse events were elicited by open-ended, nondirected questioning of the patient, clinical

observation, and source document review. In study HGAJ, the Association for Methodology and Documentation in Psychiatry (AMDP-5) scale was used to elicit adverse events. Formal rating scales were not used to solicit adverse events in the other studies included in the integrated primary safety database. The investigator recorded the adverse event in their own descriptive term following which the adverse events were coded as Coding Symbol and Thesaurus for Adverse Event Terminology (COSTART) classification terms.

The listing of investigator terms were compared with their COSTART assigned terms and the coding of investigator terms was appropriate for the most part. One COSTART term subsumed a peculiar investigator term: personality disorder was the COSTART classification term used to code nonaggressive objectionable behavior.

8.1.5.2 Selection of the Key Adverse Event Table for Characterizing the Adverse Event Profile

To examine the adverse event profile of olanzapine, the acute phases of studies HGAP and HGAD were pooled. HGAP is a fixed dose study whereas HGAD was a fixed dose range study; this is a minor difference and this pooling is felt to be otherwise reasonable because they are both placebo controlled studies of patients with schizophrenia of 6-weeks duration.

Table 8.1.5.2.1 in **Appendix 8.0** shows the adverse events reported by at least 1% of olanzapine-treated patients in the acute, placebo-controlled pool.

Following this table is **Table 8.1.5.2.2**, a narrative listing of COSTART terms for other adverse events experienced by patients treated with olanzepine at any dose during any phase of a trial within the primary database (N=2500). Nnote that events mentioned in the 1% table are not mentioned again in the narrative listing. Events are classified within body system categories using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

8.1.5.3 Common and Drug-related Adverse Events

As an indication of which events were common and likely to be olanzapine related, those adverse events with an incidence among olanzapine patients of ≥5% and an incidence at least twice that of the placebo patients were selected from the acute, placebo-controlled clinical trials database shown above: these are displayed in **Table 8.1.5.3.1** below.

Table 8.1.5.3.1. Common and Drug-related Treatment-Emergent Adverse Events Placebo-Controlled Integrated Database Acute Phase (Events Ordered by Body System and by Decreasing Frequency Within the Olanzapine Treatment Group).

Body System/Adverse Events	Percentage of Patients Reporting Event	
	Olanzapine (N=248)	Placebo (N=118)
Cardiovascular System		
Postural hypotension	5	2
Digestive System		
Constipation	9	3
Metabolic and Nutritional Disorders		
SGPT increased	8	3
Weight gain	6	1
Nervous System		
Dizziness	11	4
Akathisia	5	1

The term personality disorder, used to subsume non-aggressive oppositional behavior, is not included in the above table though it was statistically common and drug related by the above criteria. This term subsumes several behaviors that are not reasonably comparable.

8.1.5.4 Additional Analyses and Explorations

8.1.5.4.1 Dose Relatedness

Dose-relatedness of [redacted]rse events was assessed using data from clinical trials HGAD [redacted] E003 which had fixed dosage ranges. **Tables 8.1.5.4.1.1** and **8.1.5.4.1.2** enumerate the treatment-emergent adverse events in which there was a statistically significantly increasing dose response across the active drug groups (i.e. excluding the placebo group) for these two clinical trials.

Table 8.1.5.4.1.1 Dose-dependent adverse events in a fixed dosage range placebo-controlled clinical trial HGAD

	Percentage of Patients Reporting Event			
Adverse Event	Olz-L (N=65)	Olz-M (N=64)	Olz-H (N=69)	p-Value a
Asthenia	7.7	9.4	20.3	.027
Dry Mouth	3.10	4.7	13.0	.024
Nausea	0	1.6	8.7	.006
Somnolence	20.0	29.7	39.1	.016
Tremor	0	4.7	7.2	.034
Fungal dermatitis	0	0	4.3	.038

Abbreviations: Olz-L = olanzapine 5.0 ± 2.5 mg/day; Olz-M = olanzapine 10.0 ± 2.5 mg/day; Olz-H = olanzapine 15.0 ± 2.5 mg/day.
a Cochran-Mantel-Haenszel correlation p-value (based on therapy scores at 7.5, 12.5, and 17.5 mg).

Table 8.1.5.4.1.2 Dose-dependent adverse events in a fixed dosage range clinical trial E003.

	Percentage of Patients Reporting Event			
Adverse Event	Olz-L (N=87)	Olz-M (N=86)	Olz-H (N=89)	p-Value a
Eosinophilia	0	0	3.4	.035
Somnolence	1.1	4.7	9.0	.017

Abbreviations: Olz-L = olanzapine 5.0 ± 2.5 mg/day; Olz-M = olanzapine 10.0 ± 2.5 mg/day; Olz-H = olanzapine 15.0 ± 2.5 mg/day.
aCochran-Mantel-Haenszel correlation p-value (based on therapy scores at 7.5, 12.5, 17.5 mg).

A dose-response for somnolence was seen in both studies, although the incidence was considerably less in E003. Fungal dermatitis and eosinphilia are most likely statistically significant due to the large number of multiple comparisons.

8.1.5.4.2 Drug-Demographic Interactions

For the drug-demographic interaction analyses, comparisons were made between the olanzapine and placebo groups based on data from the short-term, placebo-controlled study pool.

Table 8.1.5.4.2.1 lists statistically significant differences in the incidence of treatment-emergent adverse events by gender. Incidence of treatment-emergent adverse events by gender is presented in Table 8.1.5.4.4 in appendix 8.0. These tables also present Fisher's Exact test within-stratum results comparing the incidence of treatment-emergent adverse events. Three events were identified as being statistically different between sexes.

back pain, abdominal pain, and hypotension. After considering adjustment for multiple comparisons, only back pain would likely demonstrate a difference by sex, suggesting an increased risk of back pain in males. The clinical significance of this finding is unknown.

Table 8.1.5.4.2.1 Breslow-Day Test Results for Homogeneity of Odds Ratios for Selected Treatment-Emergent Adverse Events by Gender Placebo-Controlled Integrated Database

Event Classification	p-Value[a]
Abdominal pain	.038
Back pain	.003
Hypotension	.035

a Breslow-Day p-value comparing treatment incidence while controlling for gender differences.

8.1.6 Laboratory Findings

8.1.6.1 Extent of Laboratory Testing in the Over-all Development Program

Laboratory testing in the primary integrated database consisted of clinical chemistry, hematology, and urinalysis. **Table 8.1.6.1.1** in **Appendix 8.0** lists the specific laboratory tests monitored in the olanzapine primary integrated database. These laboratory analyses were performed weekly during the acute phase and then weekly for the first six weeks of the extension phases and then monthly through the end of the first year, and then every-other-month thereafter. This battery of tests is adequate to study the effect of olanzapine on common laboratory variables.

8.1.6.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

As for the evaluation of treatment-emergent adverse events, the database of primary interest in examining laboratory data was the pool of the two acute, placebo-controlled studies, HGAD and HGAP. A central contract laboratory

) assayed all the samples for both studies. This pooling is therefore felt to be reasonable. The poolability of all studies in the Primary Safety Database is more questionable, since central contract laboratori s for each participating country in study E003 assayed all the sa nples for that country. In addition, for study E003, six enzyme analyt s (AST/SGOT, ALT/SGPT, GGT, creatine phosphokinase (CPK), alkaline phosphatase, prolactin) were analyzed at different temperatures depending on the central

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contract laboratories used for each participating country.

Dropouts were examined across the entire Primary and Secondary Safety Databases.

8.1.6.3 Standard Analyses and Exploration of Laboratory Data

Data are presented for clinical chemistry, hematology, and urinalysis measures in **Appendix 8.0** and important findings will be discussed in the appropriate Review of Systems sections (**8.2**). The specific approaches to this data are described below.

Results of the analyses of mean change from baseline (Visits 1 and 2) to endpoint (the patient's last visit during the 6-week acute phase) are presented for each variable.

Analyses of the proportions of patients with potentially clinically significant changes in lab parameters, based on specific criteria for each variable, at any time during the acute phase of the primary integrated database were performed.

A review of patients who dropped out due to abnormal laboratory results was performed for the pool of all studies in the primary integrated database(Nolz=2500).

8.1.6.3.1 Analyses focused on measures of central tendency

A summary of mean baseline-to-endpoint change for each clinical chemistry analyte is presented in **Appendix 8.0** in **Table 8.1.6.3.1.1** by group. Measures of mean change from baseline of albumin, AST, ALT, alkaline phosphatase, GGT, calcium phosphorus, uric acid, total bilirubin, chloride, prolactin, and cholesterol showed significant differences when compared to placebo in the integrated placebo controlled database ($p<0.10$). The mean changes in albumin, cholesterol, total bilirubin, chloride, calcium phosphorus, and uric acid were not felt to be clinically significant. The mean changes in AST, ALT, GGT, alk phos, and prolactin in-and-of themselves are not clinically significant but these changes are discussed in the context of outlying patients, potentially clinically significant lab values, and dropouts in the review of systems section.

A summary of mean baseline-to-endpoint change for each hematology analyte is presented in **Appendix 8.0** in **Table 8.1.6.3.1.2** by analyte. Significant differences in HCT, HGB, and eosinophil counts were observed when compared to placebo; however none of these differences were clinically significant.

A summary of baseline-to-endpoint change for urinary pH and urinary specific gravity is presented in **Table 8.1.6.3.1.3** by analyte. Statistically significant differences in urine specific gravity and pH were present when compared to placebo but neither

of these differences were clinically significant.

Results felt to be clinically important will be discussed further in the review of systems section **8.2**.

8.1.6.3.2 Analyses Focused on Outliers

Tables 8.1.6.3.2.1, 8.1.6.3.2.2, and **8.1.6.3.2.3** depict the high and low criteria for determining potentially clinically significant (PCS) changes in clinical chemistry, hematology, and urinalysis analytes, respectively. Note that, for all chemistry and hematology variables, a PCS increase is defined as a change from a baseline value less than the high criteria to a value greater than the high criteria at either endpoint or for two consecutive measures during therapy. A PCS decrease is defined analogously. For urinalysis analytes, a PCS change was defined as an increase from baseline of at 2 at either endpoint or two consecutive measures and an absolute value of at least 3; the denominator was the number of patients who did not meet the absolute limit at baseline.

These analyses were based on the acute, placebo-controlled study pool. The proportions of patients with potentially clinically significant changes are shown in **Tables 8.1.6.3.2.4, 8.1.6.3.2.5,** and **8.1.6.3.2.6**, for chemistry, hematology, and urinalysis analytes, respectively; where no olanzapine patients met these criteria, the lab parameter is not listed. Important results of these exploratory analyses will be discussed in the review of systems section **8.2**. There were no statistically significant differences between olanzapine and placebo in these comparisons.

8.1.6.3.3 Dropouts for Laboratory Abnormalities

Forty-four of the 2500 (1.8%) Primary Safety Database olanzapine-treated patients discontinued because of abnormal chemistry analytes. The most frequent abnormal analytes reported as reasons for discontinuation were CPK increased (15 patients) and SGPT increased (15 patients). The proportions of olanzapine patients dropping out for an elevated liver transaminase (AST, ALT, or GGT) or increased CPK was higher than those for the placebo and haloperidol groups, but not to a statistically significant degree (α=0.10):

	Olanzapine	Placebo	Haloperidol
↑ Transaminase	0.8%	0.0%	0.5%
↑ CPK	0.6%	0.0%	0.1%

Other clinical chemistry events reported as reason for discontinuation were bilirubinemia (2 patients), increased BUN or creatinine (2 patients), hypoglycemia (1 patient), hyponatremia (1 patient), "elevated liver function tests" (4 patients) and increased GGT (4 patients). All case summaries of dropouts due

to abnormal laboratories were reviewed, and these cases will be discussed in the appropriate sections of the review of systems sections (8.2).

Also, nine patients in Secondary Database studies dropped out due to elevated liver enzymes.

Elevated liver enzymes and bilirubinemia, as well as increased CPK,will be discussed further in sections **8.2.2.2.1** and **8.2.5.3.3**, respectively.

Seven of 2500 (0.3%) of olanzapine-treated patients discontinued because of treatment-emergent hematology analytes. The most frequent adverse event associated with hematology analytes reported as a reason for discontinuation was leukopenia (5 patients). The proportions of patients dropping out for leukopenia were: olaznapine 0.2% (5/2500), placebo 0.0% (0/236), and haloperidol 0.2% (2/810). Additionally, anemia (1 patient) and thrombocytopenia (1 patient) were reported as leading to discontinuation. Leukopenia will be discussed further in section **8.2.3.2.1**.

There were no discontinuations because of abnormal urinalysis analytes.

8.1.6.4 Additional Analyses and Explorations

8.1.6.4.1 Drug-Demographic Interactions

Analyses of these laboratory measures were performed to examine the consistency of treatment effects over the strata of gender (male, female), racial origin (African descent, Caucasian, other), and age (less than 50 years of age, at least 50 years of age). These analyses were performed by applying Lilly reference ranges (listed in volume 1.220, pages 272-275, of the original NDA submission) within the acute, placebo-controlled study pool.

Only for increased CPK was there significant difference by gender (p=0.028, Breslow-Day Test for Homogeneity of Odds Ratios), with males apparently at higher risk for this abnormality. The clinical significance of this finding can only be speculated: it may be related to greater muscle mass and activity among males versus females.

8.1.7 Vital Signs

8.1.7.1 Extent of Vital Sign Testing in the Development Program

Vital signs, including blood pressure, pulse, temperature, and weight, were measured at every visit for all patients in the olanzapine development program. Also, for most of these patients, orthostatic change in systolic blood pressure was

determined (supine X5 minutes to standing X2 minutes).

8.1.7.2 Selection of studies and analyses for overall drug-control comparisons

Analyses of mean change from baseline and of those patients with potentially clinically significant (PCS) changes were focused on the acute, placebo-controlled study pool. Dropouts due to vital sign abnormalities were examined across the entire Primary Safety Database as well as the Secondary Safety Database. These pools were felt to be reasonable for the purposes stated.

8.1.7.3 Standard Analyses and Explorations of Vital Signs

Mean change in blood pressure, pulse, temperature, weight, and orthostatic change in systolic blood pressure from baseline (Visits 1 and 2) to endpoint (the last visit of the 6-week acute phase) were compared betweeon olanzapine and placebo. Also, analyses of the proportions of patients with potentially clinically significant change in vital signs, using established criteria, at any time during the acute phase of the placebo controlled studies were examined. Finally, dropouts due to vital sign abnormalities were assessed for the whole safety database (N=3139 olanzapine patients).

8.1.7.3.1 Analyses Focused on Central Tendency

Analyses of the mean change from baseline of vital signs and weight are presented in **Table 8.1.7.3.1** in **Appendix 8.0**. There was a statistically significant difference ($p<0.001$) in weight change, with olanzapine patients gaining an average of 2.80 kg and placebo patients losing an average of 0.41 kg. There were no other significant differences between olanzapine and placebo with respect to vital sign changes. However, the change in mean standing pulse was about three-fold higher among olanzapine versus placebo patients (+2.70 bpm vs. +0.87).

8.1.7.3.2 Analyses Focused on Outliers

Criteria used to detect PCS changes in vital signs and weight are listed in **Table 8.1.7.3.2.1**.

The proportions of patients in the acute, placebo controlled database with PCS changes in these variables at any time while on therapy are shown in **Table 8.1.7.3.2.2**. It is notable that 5.5% (13/237) of olanzapine versus 1.8% (2/111) of placebo patients experienced a ≥30 mmHg change in systolic blood pressure with postural change (supine to standing); this difference was not statistically significant ($\alpha=0.10$). Also, 29.3% (70/239) of olanzapine and 2.7% (3/113) of placebo patients gained ≥7% of their baseline weight during treatment ($p=0.001$). Orthostatic

hypotension and weight gain will be further discussed under sections **8.2.1.2.1** and **8.2.4.2.1**, respectively.

It is interesting to note that tachycardia was reported as an adverse event in 4.4% (11/248) of olanzapine and only 0.8% (1/118) of placebo patients (p=0.113, Fisher's exact test). Based on the outlier data, however, it appears that most of these patients did not experience a marked increase in pulse. Tachycardia may represent a compensatory response to postural hypotension and will be further discussed in section **8.2.1.2.2**.

8.1.7.3.3 Drop outs for Vital Sign Abnormalities

Twelve olanzapine-treated patients in the Primary Safety Database discontinued because of vital sign and weight changes. The adverse event most frequently reported as a reason for discontinuation was weight gain (7 patients). Other adverse events leading to dropout included hypertension (4 patients) and fever (1 patient). No placebo or haloperidol patients dropped out due to vital sign changes.

Four patients dropped out from the Secondary Safety Database due to postural hypotension. Additionally, two other patients dropped out after syncope associated with hypotension.

8.1.7.4 Additional Explorations

Breslow-Day tests were performed to detect significant differences in vital sign and weight changes between sexes. Change from baseline to endpoint with respect to vital signs and weight was consistent between males and females with respect to comparisons between olanzapine and placebo.

Similarly, the effect of racial origin on vital signs and weight indicated a significant effect with respect to supine pulse: olanzapine patients of African descent had a mean increase of 4.73 bpm compared to racially similar placebo patients, who had a 3.04 bpm decrease in supine pulse (p=0.015); Caucasians and patients of other racial origins had less pronounced, statistically insignificant olanzapine/placebo differences.

8.1.8 Electrocardiograms (ECGs)

8.1.8.1 Extent of ECG Testing in the Development Program

Electrocardiograms were performed during the screening of each of the clinical trials, at the end of the acute treatment phase of the study, and at six month intervals during the extension phase. If patients elected to drop out of the study an ECG was performed at the exit visit. This was a sufficient number of measurements

to assess the effect of olanzapine on ECG.

8.1.8.2 Selection of Studies and Analyses for Over-all Drug-control Comparisons

Analyses of ECG data were performed using the acute, placebo-controlled study pool and included an analysis of baseline-to-endpoint change for each variable and a categorical analysis of potentially clinically significant (PCS) changes in ECG intervals. Dropouts due to ECG findings were examined across the entire Primary Safety Database; there were no dropouts for this reason in the Secondary Safety Database.

8.1.8.3.1 Analyses focused on central tendency

Analysis of the mean change from baseline to endpoint was performed in the acute, placebo-controlled database for heartrate and PR, QRS, QT, and Qtc intervals. Results of these comparisons may be found in **Table 8.1.8.3.1**. The only parameter for which statistical significance was even approached was heartrate: olanzapine= +2.44 bpm vs. placebo +0.06 bpm (p=0.121). This is consistent with findings from the vital sign analyses.

8.1.8.3.2 Analyses focused on Outliers

The criteria used to establish potentially clinically significant changes in ECG intervals and heart rate are given for each measure in **Table 8.1.8.3.2.1** below.

Table 8.1.8.3.2.1 Criteria for Identifying Patients with Potentially Clinically Significant Change in ECG Intervals and Heart Rate

Interval	Low	High
PR	--	200 msec
QRS	--	100 msec
QT	--	450 msec
QTc	--	430 msec
Heart rate	40 bpm	120 bpm

The proportions of patients who met these criteria at any time during the acute phases of the placebo-controlled studies are shown in **Table 8.1.8.3.2.2** in **Appendix 8.0**. There were no statistically significant differences (α=0.10).

8.1.8.3.3 Dropouts due to ECG Abnormalities

In the Primary Safety Database (2500 olanzapine patients), only two patients dropped out due to an ECG abnormality: bradycardia

(1 patient) and ventricular arrhythmia (PVC's) (1 patient). No placebo or haloperidol patients dropped out for this reason. These dropouts will be discussed under section **8.2.1.3.3**.

8.1.8.4 Additional Analyses and explorations

None were performed.

8.1.9 Special Examinations

8.1.9.1 Ophthalmologic Exams

In study HGAD, ophthalmology examinations were performed at baseline, at visits 9, 18, 32, and annually thereafter, as well as at the discontinuation visit. In study HGAJ, ophthalmology examinations were done at baseline, at visits 9, 19, and 26 and at the time of discontinuation. For both studies, in addition to determining current eye complaints and historical eye disorders, the examination included tonometric measurements, visual acuity (both near and far) tests, visual field tests, and physical condition of the eyes (external eye, slit lamp, and fundoscopic). Analyses were done combining data across the acute and double-blind extension phases rather than separately.

Significant findings are reported in the review of systems special senses subsection (**8.2.9.3.4**).

8.1.9.2 Chest X-Rays

For studies HGAD, E003, HGAP, and HGAJ, to include the long-term extension phases, chest x-rays were to be performed at baseline[3] and discontinuation visits. Patients who crossed over from double-blind placebo or haloperidol to open-label olanzapine were treated as olanzapine-treated patients in this analysis.

The results of these examinations are presented in section **8.2.7.3.4**.

8.1.9.3 Electroencephalograms

Two studies, JE-2001 and HGAP, included addendum studies involving baseline and on-drug EEG's. EEG data in the former study was collected before and after 8 weeks of open-label olanzapine therapy in 27 schizophrenic patients and the latter study collected data before and after randomization of 7 schizophrenic patients to double-blind treatment with either olanzapine 1.0 or 10.0 mg/day or placebo, for a duration of 4-6 weeks of therapy; only 4 of the patients from the latter study had both baseline and treatment assessments, however. In

[3]If no x-ray had been performed within the last 6 months.

summary, for the total of 31 patients with comparative EEG data, only two demonstrated deterioration with olanzapine therapy (**JE-2001 29-4** and **HGAP 4-1156**): both had normal baseline assessments with minimally slow background rhythms post-baseline, possibly related to an effect on level of alertness. None of these 31 patients showed evidence of epileptiform activity (see also section **8.2.6.2.4**).

8.1.9.4 Studies Examining Adaptation to Somnolence

There was one main study and two supporting studies of adaptation to somnolence. F1D-EW-HGCE was a double-blind, active-controlled and placebo-controlled, crossover, single-center, cognition and psychomotor performance pharmacodynamic study; healthy elderly male and female subjects (N=16); olanzapine dose (3.0 mg/day, po, maximum of 4 days), haloperidol dose (3.0 mg/day, po, maximum of 4 days), multiple dose study. Subjective level of alertness was evaluated after dosing on days one and four only. This study was performed in a very limited number of normal volunteers after only 4 days at doses much lower than the least effective therapeutic dose. This study did not support the labeling claim of adaptation to somnolence. Study E002 was a single-blind, 2-center, placebo-controlled, drug interaction study; healthy male subjects (N=8); placebo or biperiden dose (4.0 mg x 1 day, po), washout period, olanzapine dose (10.0 mg/day x 7 days, po), placebo or biperiden dose (4.0 mg x 1 day, po, on last day of olanzapine dosing). Study HGAN was an open-label, single-center, crossover, pharmacodynamic and drug interaction study; healthy nonalcoholic male subjects (N=15); olanzapine dose (2.5 mg/day x 2 days, 5.0 mg/day x 2 days, 10.0 mg/day x 7 days, po), placebo or EtOH dose (45 mL/70 kg, po) participated. Likewise, these studies were performed on a very limited number of normal subjects and subjects did not take drug long enough to evaluate adaptation to somnolence.

8.1.10 Withdrawal and Abuse Potential

Olanzapine has been administered at doses ranging from 1 mg to 20 mg per day for periods over one year; 200 patients have been treated for over one year with modal doses ≥15 mg/day. In these clinical trials, the dose of olanzapine was abruptly stopped, and there was no attempt to gradually decrease the dose. Evaluation of the olanzapine clinical trial database indicated no evidence of withdrawal signs or symptoms associated with stopping olanzapine. However, there was no systematic attempt to follow up patients to observe the signs and symptoms of withdrawal.

The sponsor does not propose that olanzapine is a controlled substance. In prospective animal studies designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential for abuse or physical dependence in rats administered oral doses up to 112

times the maximum daily human dose (20 mg) and rhesus monkeys administered oral doses up to 28 times the maximum daily human dose. Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence.

8.1.11 Human Reproduction Studies

There are no adequate and well-controlled studies in pregnant females. During clinical trials with olanzapine, 7 pregnancies were reported as of February 14, 1995. Two pregnancies produced apparently normal infants, one produced an infant that died two hours after birth from a cardiovascular defect, three ended in therapeutic abortions, and one ended by spontaneous abortion. Since human experience is limited, this drug should be used in pregnancy only if clearly needed.

8.1.12 Overdose Experience

The COSTART classification terms "overdose," "accidental overdose," and "intentional overdose" were used by the sponsor to identify patients who had ingested an olanzapine overdose. From this review, 67 patients were identified who had taken an overdose of olanzapine: 64 patients were from the Primary Safety Database and 3 patients were from Secondary Safety Database.

There was one death (patient **051-0319**): this death is questionably related to an olanzapine overdose and is discussed in detail in section **8.2.11.3**.

In these cases, overdose ingestions of 25mg to 300mg were taken. The largest overdose was by patient **HGAJ 027-0335,** who reported to his wife that he had taken 300 mg of olanzapine. He was taken to the emergency room, where he was found to be drowsy and had slurred speech; he had no other symptoms.

In the limited number of patients who were evaluated in hospitals, there were no trends toward any of the following: cardiac arrhythmia, conduction abnormality, prolongation of corrected QT interval or PR interval, or extrasystoles. There were also no data indicating abnormal hematology or clinical chemistry results or hepatic or renal dysfunction, and vital signs were usually within normal limits after overdoses.

The next highest single medicine overdose was 100mg (patient **HGAJ 003-0798**) who experienced no acute adverse events or laboratory abnormalities. Patient **HGAJ 324-2947** took an overdose of 60mg of olanzapine, 17mg of lorazepam, and 50mg of temazepam. He suffered ataxia and somnolence and had a serum prolactin of 1.743 nmole/L. Patients who took multiple-dose overdoses of 25mg/day to 45mg/day (patient **HGAJ 881-7095** took olanzapine 45mg for one month) evinced no lab abnormalities and no acute adverse events.

Olanzapine was used in overdose alone and in combination with other drugs. The drugs taken along with olanzapine included alcohol, acetaminophen, lorazepam, diazepam, chloral hydrate, tricyclic antidepressants, and other antipsychotics. Overdoses where benzodiazepines were taken exhibit somnolence and ataxia at levels of impairment that do not reflect a synergistic effect from olanzapine.

Charcoal reduced the oral bioavailability of olanzapine by about 50%. Thus, charcoal may be useful in the treatment of overdoses.

In conclusion, olanzapine has been taken in overdose by 67 patients, both as a single agent and in combination with other drugs. The highest reported overdose was 300 mg, and the patient experienced no serious or persistent sequelae. In the limited number of patients hospitalized because of overdose, no clear set of clinical or laboratory findings was characteristic of the patients. Olanzapine appears to be moderately safe in overdoses up to 300mg.

8.2 Review of Systems

8.2.1 Cardiovascular

8.2.1.1 Adequacy of Assessment

As mentioned previously, for studies in the primary safety database, vital signs were performed at each visit and consisted of blood pressure, heartrate, body weight, temperature; also, for the large, controlled studies HGAD, HGAP, HGAJ, E003, and HGAO, postural changes in blood pressure and heartrate were evaluated by measurements after lying for 5 minutes and standing for 2 minutes. ECGs were performed for patients in the placebo-controlled integrated databases, study HGAO (geriatric patients), and the subset of geriatric patients in study HGAJ. ECGs were performed at Visit 1 and at the end of acute treatment, at 6 months, and at any time the subject discontinued after randomization in study HGAP and HGAD. In studies HGAO and HGAJ ECGs were performed at baseline and at the end of the acute treatment and at the last patient visit in the open-label extension.

Overall, these evaluations were felt to be adequate to assess the effect of olanzapine on the cardiavascular system.

8.2.1.2 Events Likely to be Related to Olanzapine

8.2.1.2.1 Postural Hypotension

In the pool of the acute phases of the two placebo controlled studies, HGAD and HGAP (excluding 1.0mg dose group), a potentially clinically significant (PCS) postural change in systolic blood pressure (i.e. ≥30 mmHg decrease in systolic BP supine to standing) was a common and drug-related vital sign measurement, occurring in 5.9% (13/237) of olanzapine and 1.8% (2/111) of placebo patients. (Postural hypotension was reported as a treatment-emergent adverse event in 5.2% of olanzapine and 1.7% of placebo patients in this pool.) Among olanzapine patients, all such changes were transient, none dropped for this reason, and none experienced clinical events attributable to an orthostatic drop in SBP.

However, examination of this pool for adverse events that may be related to orthostasis, specifically dizziness and syncope revealed that there was a statistically significant difference between olanzapine and placebo patients for dizziness: olanzapine 10.9% (27/248) vs. placebo 4.2% (5/118) (p=0.046, 2-tailed Fishers exact test).

Among the 13 olanzapine patients meeting criteria for PCS orthostasis, the mean of the maximum differences between supine and standing SBP was 35 mmHg; the maximum postural difference

was 46 mmHg (patient **HGAD 10-1452**).

In the human pharmacology studies, where vital signs were monitored more closely, the sponsor does indicate that postural hypotension occurred early or with the first dose of olanzapine and the effect was more prominent with doses ≥10mg or when olanzapine was combined with ethanol. In those studies, adaptation to this effect was seen as olanzapine reached steady-state concentrations, being most severe as peak plasma concentrations were attained. Adaptation appeared to develop as a result of a compensatory tachycardia, usually in the range 100-140 bpm.

Considering mean changes from baseline to endpoint in orthostatic SBP difference from the placebo controlled clinical studies, mean change for olanzapine (N=237) was -0.83 (SD=12.99) and for placebo (N=112) +0.50 (SD=11.67); the intergroup difference is not significant. Thus, on the whole, changes in orthostatic SBP are not appreciable.

Across the entire Primary Safety Database (N-olanzapine=2500 or 1122.2 patient-years of exposure), there were no serious adverse events related to orthostatic hypotension among olanzapine patients. There were 15 cases syncope in olanzapine exposed patients; 6 occurred in the acute phase of the study in patients taking olanzapine; one occurred in the 1 mg/day treatment group of study E003 (105-1054). The other nine cases occurred in the extension phases of the protocol. Thus in the acute phases of controlled studies there were 5/1796 (0.28%) cases of syncope (the 1 mg/day group was excluded from safety evaluation statistical calculations) versus 2/810 (0.25%) cases in the active control group (one in each group dropped out). This was not a statistically significant difference by the Fisher's exact test. Subject HGAP 003-1111 dropped out due to syncope in the extension phase of the protocol.

In the secondary database, four normal volunteers experienced symptomatic postural hypotension and dropped out following olanzapine doses of 4mg (**P100 S-III-L**, **P200 M-C**, and **P200 M-F**) and 6mg (**P100 S-IV-1**). Also, two other normal volunteers (**HGCD 1-1** and **HGCD 1-9**) dropped out after experiencing syncope and hypotension following a 10mg dose of olanzapine. None were considered serious adverse events.

8.2.1.2.2 Tachycardia

Tachycardia was reported as a <u>treatment-emergent adverse event</u> in 4.4% (11/248) of olanzapine vs. 0.8% (1/118) of placebo patients in the acute phase of the placebo controlled study pool (p=0.09, 2-tailed Fishers exact test). However, when one focuses on those patients meeting the criteria for a potentially clinically significant <u>increase in pulse measurement</u> (i.e. >120 and an

increase ≥15 bpm), 3.9% (9/232) of olanzapine and 3.7% (4/109) of placebo patients met criteria for standing tachycardia; only 0.4% (1/239)of olanzapine and 0% of placebo patients met criteria for supine tachycardia.

Considering mean changes from baseline to endpoint in heartrate, the mean change for olanzapine (N=237) with regard to standing pulse was +2.70 bpm (SD=15.70) and for placebo (N=111) +0.87 bpm (SD=13.81); the intergroup difference is of borderline statistical significance (p=0.125). For supine pulse, the mean change in the olanzapine group was +1.65 bpm (SD=14.18) versus +0.80 bpm (SD=14.27) for placebo; this difference is not significant (p=0.560).

In the fixed dose range study HGAD, examination of the mean changes in standing and supine heartrates by dose group revealed no evidence to support a dose relationship. Also, the incidence of tachycardia as a reported treatment-emergent adverse event by dose group in this study did not suggest dose-dependency.

No patients in the Primary or Secondary Databases dropped out due to tachycardia.

The extent to which these cases of tachycardia are attributable to orthostatic hypotension can not be inferred from the analyses which have been done to date but it is felt to be likely that many could be explained on that basis.

Thus, while it appears that olanzapine is associated with an increase in heart rate, changes were generally not clinically significant and some may be explainable on the basis of postural hypotension.

8.2.1.3 Events Unlikely to be Related to Olanzapine

8.2.1.3.1 Deaths

In the primary safety database, there were five olanzapine treated patients who had cardiac related death. The first was patient **HGAJ 752-6057**, a 63 year old male whose cause of death was reported as a coronary artery disorder, myocardial infarct, pulmonary edema, and cerebral edema. Death occurred after study participation but within 30 days of study discontinuation. This death was not connected with the use of olanzapine.

The second was patient **HGAJ 035-0206**, a 37 year old male whose cause of death was cardiac arrest secondary to arterial thrombosis. This patient was diagnosed with severe atherosclerotic occlusion of the cardiac arteries, including total blockage of the right descending artery with a thrombus overlying plaque, that led to coronary thrombosis and death. The

patient's father died at age 39 of a similar medical condition. This was therefore a family related pathologic condition, the process of which began long before the olanzapine trial; olanzapine could not be implicated in this patient's death.

The third patient **(HGAO 020-2003)** was an 88 year old male with advanced dementia of the Alzheimer's type who was reported to have died from congestive heart failure. This patient developed a productive cough, decreased his oral intake, and became dehydrated. After rehydration, the patient became lethargic and died. No autopsy was performed and the cause of death was listed as congestive heart failure. Death occurred 20 days after the end of study participation. This was not related to the olanzapine clinical trial.

Patient **HGAP 005-1215** who was a 63 year old male with schizophrenia, diabetes mellitis, and who had been hospitalized with a prolonged pneumonia. This patient's death was not be attributed to olanzapine.

Patient **HGAO 22-2210** was an 88 year old female who experienced dyspnea, hypotension, and fever, with a chest X-ray revealing bilateral infiltrates consistent with congestive heart failure, after taking olanzapine (3 mg/day) for 37 days. She subsequently died of CHF. There was a past history of atherosclerotic heart disease, myocardial infarction, and cardiac valvular disease. It is unlikely that olanzapine played an important role in this death.

Additionally, there was one death in an ongoing Secondary Database study **(HGBT 241-2409)**. A 71 year old male received olanzapine up to 7.5 mg/day for a total of about 6 weeks. He experienced dehydration, fever, delirium, and heart failure following elective hip replacement surgery and olanzapine was stopped. Subsequently, full-blown sepsis and multiple organ failure developed and he died one week after olanzapine discontinuation. Past medical history was remarkable for heart failure, myocardial infarction, CABG, and Parkinson's disease. Olanzapine was unlikely to play a role in this death.

8.2.1.3.2 Other Serious Adverse Events

Among olanzapine-treated patients, there were two patients who suffered a cerebrovascular accident **(HGAJ 007-0907; HGAO 007-0714)**, one who suffered a myocardial infarction **(HGAO 004-0407)**, and one with myocardial ischemia **(HGAO 16-1603)**. These events were coded as serious, but are not likely to be related to olanzapine.

8.2.1.3.3 Dropouts due to Adverse Events

Across the entire Primary Safety Database, four olanzapine-

treated patients (and no placebo patients) prematurely discontinued study participation due to hypertension; the difference in incidence between olanzapine and placebo is not statistically significant (p= 1.000, 2-tailed Fishers exact test).

Additionally, two olanzapine patients dropped out due to an ECG abnormality, one for bradycardia (**HGAJ 992-7774**: a 60 y.o. female who had an asymptomatic heartrate of 50 bpm on Day 57 of therapy and an associated QT interval of 460 msec;) and another for a ventricular arrhythmia (**HGAJ 996-7876**: a 29 y.o. obese female with an incomplete RBBB at baseline who manifested ventricular bigeminy, trigeminy, and quadrigeminy on day 296 of therapy with preceding transient low blood pressure and pulse rates). These abnormalities are not likely to be causally related to olanzapine.

QT interval prolongation has been associated with antipsychotic drugs. No patient in either the Primary or Secondary Database dropped out due to QT interval prolongation. In the placebo-controlled, acute phase studies, the mean change from baseline to endpoint for both QT and QTc was not significantly different between olanzapine and placebo (QT: olanzapine=-4.81 vs. placebo=-1.84 msec, p=0.310; QTc: olanzapine=+1.32 vs. placebo=-1.09 msec, p=0.297). In this pool, no olanzapine patients had a QT>450 msec at any time; only two olanzapine patients had a QTc>450 msec: **HGAD 11-1509** (464 msec) and **HGAD 13-1634** (481 msec). Neither patient dropped out due to any cardiovascular event or ECG finding and neither had any symptoms referable to the cardiovascular system. Thus, QT interval prolongation does not appear to be associated with olanzapine.

8.2.1.4 Summary and Conclusions

Clinical data suggests that olanzapine is associated with measurable postural hypotension, consistent with its α-1 receptor antagonism.

Additionally, it appears to be related to the occurrence of tachycardia, which may be secondary to postural hypotension in many patients. Neither event has been associated with any hazardous clinical effects in the primary or secondary databases. However, labeling should clearly reflect these findings.

No other findings relevant to the cardiovascular system were reasonably attributable to olanzapine exposure.

8.2.2 Gastrointestinal

8.2.2.1 Adequacy of Assessment

All patients in the Primary safety Database were monitored for

liver transaminases (AST, ALT, and GGT), alkaline phosphatase, and total bilirubin as well as adverse events at each study visit. These assessments are felt to be adequate to gauge the effects of olanzapine on the gastrointestinal system.

8.2.2.2 Events Considered Likely to be Drug Related

8.2.2.2.1 Liver Injury

Examination of the mean changes from baseline to endpoint for liver function tests does suggest a tendency for olanzapine to be associated with elevations in AST, ALT, and GGT. In the placebo controlled, acute phase studies, mean changes for AST were: olanzapine +4.65 vs. placebo -0.09 U/L ($p=0.087$). Those for ALT were: olanzapine +13.13 vs. -0.53 U/L ($p=0.062$). Likewise, there was a significant differerence in the mean changes for serum gamma-glutamyl transpeptidase (GGT): olanzapine +4.08 vs. placebo -4.12 U/L ($p<0.001$).

To further assess these findings, the proportions of patients meeting established criteria for a potentially clinically significant change (PCSC)[1] for these measures were examined in this study pool. Considering the number of unique patients who met PCSC criteria for at least one of these parameters, the difference is considered borderline significant ($\alpha=0.10$): olanzapine 2.9% (7/243) and placebo 0.0% (0/115) ($p=0.102$).

The patient summaries for the seven olanzapine patients[2] with PCSC LFT values were examined to characterize these findings. Five had peak transaminase levels less than 8X the upper limit of normal (ULN); the remaining two had maximum levels 11X and 20X ULN. None of these patients experienced jaundice or are known to have progressed to liver necrosis or liver failure. Only one patient (**HGAD 15-1704**) had symptoms possibly related to liver injury (nausea and diarrhea). Three had LFT's which normalized even with continued drug exposure and two had values which decreased after olanzapine discontinuation. These findings did not appear to be dose related in this small sample.

In the larger Primary Safety Database (N-olanzapine=2500), a total of 74 olanzapine, 1 placebo, and 7 haloperidol patients met criteria for a PCSC in liver enzymes (AST, ALT, or GGT). Comparison of exposure adjusted rates did reveal a substantially

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PCSC= change from a value ≤ high limit at all baseline visits to a value > limit at endpoint or at two consecutive visits during therapy. Limits were: AST>150 U/L, ALT >165 U/L, and GGT>135 U/L (female) or 195 U/L (males).

HGAP 4-1159; HGAD 9-1404, 11-1526, 15-1701, 15-1704, 19-1870, 20-1951.

higher rate for olanzapine: olanzapine= 6.6/100 PEY, placebo= 3.7/100 PEY, and haloperidol= 3.6/100 PEY. Again, however, none of these patients had jaundice, adverse events attributable to liver dysfunction, or progressed to liver necrosis or failure. One patient (**E003 751-7501**) apparently died about one year after study discontinuation and liver autolysis was evident on liver autopsy. Liver function tests several months after olanzapine discontinuation were reportedly normal. This finding is probably unrelated to olanzapine treatment.

Using this database, the sponsor conducted an evaluation of the 50 olanzapine patients who had baseline ALT values ≤90 IU/L and who experienced treatment-emergent values >200 IU/L to ascertain the pattern of elevation at last measurement: 34/50 had a transient pattern (i.e. the last value was below the upper limit of the Lilly reference range while still on drug; 8 had a falling pattern (decreased ≥10% but not below reference range,; 3 had a plateau (±10% of peak value); and 5 had a rising pattern (last value was peak and ≥10% over prior values). Additionally, analysis of time to a value >200 IU/L revealed that 39/50 occurred on or before day 42 of therapy.

Three olanzapine patients in the Primary Database did meet criteria for a PCSC in total bilirubin but did not meet criteria for PCSC in liver enzymes. **HGAJ 322-3011** was diagnosed with a toxic hepatitis after 253 days of treatment which resolved with continued olanzapine treatment. **E003 102-1154** and **E003 906-9112** had hyperbilirubinemia without jaundice and did not experience a serious adverse event or drop out for an adverse experience.

The incidence of dropout due to elevated transaminases in the Primary Database did not vary to a statistically significant degree between treatment groups (α=0.10), although it was highest in the olanzapine group: olanzapine 0.9% (23/2500), placebo 0.0% (0/236), and haloperidol 0.5% (4/810).

Within the Secondary Safety Database (N-olanzapine=639), 9 olanzapine subjects prematurely discontinued treatment due to elevated liver enzymes. Two of these were attributed to hepatitis C infections and some of the other subjects were suspected by the sponsor as having chronic liver dysfunction based on data from other clinical trials for which these subjects were considered. None of these subjects experienced symptoms or known progression of liver injury.

8.2.2.2.2 Constipation

Within the acute, placebo controlled study pool, constipation was reported as a treatment-emergent adverse event by 9.3% (23/248) olanzapine and 3.4% (4/118) placebo patients (p=0.053, Fisher's exact test). This may be related to the antimuscarinic activity of olanzapine. This event was not identified as being dose-

related when events from fixed dose range studies were examined. None of these patients dropped out for this event.

In the larger Primary Safety Database, constipation was reported by 5.8% (145/2500) of olanzapine, 3.4% (8/236) of placebo, and 4.1% (33/810) haloperidol patients. None of these patients dropped out for this reason. One patient, **HGAJ 328-3070**, experienced a paralytic ileus after about 6 months of olanzapine treatment; however, this occurred in the context of a pyelonephritis and may not be related to olanzapine per se. No other patients experienced serious adverse sequelae possibly related to constipation, such as toxic megacolon.

8.2.2.3 Events Considered Unlikely to be Drug Related

8.2.2.3.1 Deaths

There were no deaths that were attributed to a gastrointestinal adverse event in the total safety database.

8.2.2.3.2 Other Serious Adverse Events

There was only one gastrointestinal adverse event among olanzapine treated patients that was classified as serious: acute appendicitis (**HGAJ 54-1149**). This was felt to be unlikely related to olanzapine treatment.

8.2.2.3.3 Dropouts due to Adverse Events

Adverse events leading to dropout among olanzapine patients were: abdominal pain (**HGAP 10-1454**), abnormal stool (**HGAJ 59-1123**), diarrhea (**HGAO 9-904** and **24-2402**), and flatulence (**HGAD 10-1457**). None of these events were deemed to be related to olanzapine therapy.

8.2.2.4 Summary and Conclusions

There were only two adverse events of clinical importance which were felt to be related to olanzapine in the total safety database: elevated liver transaminases and constipation.

Significantly increased liver enzymes (i.e. those meeting PCSC criteria) were reported in approximately 3% (74/2500) of the olanzapine patients in the Primary Safety Database versus 0.4% (1/236) for placebo and 0.9% (7/810) for haloperidol. Exposure adjusted rates (per 100 patient-years) were about twice as high for olanzapine patients: olanzapine= 6.6, placebo= 3.7, and haloperidol= 3.6. Most of these abnormalities, however, appear to be transient (i.e. decreasing even with continued treatment), none were associated with important clinical symptoms such as jaundice, and none progressed to liver necrosis or liver failure. Most of these abnormalities emerged during the first 6 weeks of

olanzapine therapy. Although several patients did drop out due to concern over elevated liver enzymes, the dropout rates for elevated LFT's were not substantially different across treatment groups in the primary safety database.

Constipation was reported by a statistically significant higher percentage of olanzapine versus placebo patients in the placebo controlled, acute phase studies: 9.3% (23/248) for olanzapine and 3.4% (4/118) for placebo. In the larger Primary Safety Database, the olanzapine reporting rate (5.8% or 145/2500) was numerically higher than the placebo rate (3.4% or 8/236) (p=0.139 Fisher's exact test). But even in this larger sample, no patients dropped out for this reason and only one had serious adverse event possibly, but probably not, related to olanzapine (paralytic ileus). This adverse event may be due to the muscarinic blocking activity of olanzapine.

8.2.3 Hematologic and Lymphatic

8.2.3.1 Adequacy of Assessment

The sponsor conducted red blood cell (RBC) counts, white blood cell (WBC) counts, analysis of segmented neutrophils and eosinophils as percentages of the WBC count (as opposed to absolute counts), and platelet counts on approximately 2400 patients during both acute and extended treatment with olanzapine in the Primary Safety Database. Collection of hematology laboratory data was done at each visit during the acute study phases and at intervals during extension treatment. Additionally, adverse events were monitored at each visit. These assessments were felt to be adequate to evaluate the hematologic effects of olanzapine.

8.2.3.2 Events Considered Likely to be Drug Related

8.2.3.2.1 Leukopenia

The mean change from baseline to endpoint in WBC and neutrophil counts in the pool of the acute phases of the placebo controlled studies revealed a numerical but not statistically significant differences between olanzapine and placebo (units =1,000 cells/cmm):

	Olanzapine	Placebo	p-value
Mean Δ in WBC count	-.360	-.220	0.281
Mean Δ in neutrophil count	-.280	-.100	0.249

No patients in this pool met criteria for a potentially clinically significant (PCS) decrease in WBC count or neutrophil count, defined as: a change from a baseline value ≥ the low limit at all baseline visits to a value less than the low limit at

endpoint or for two consecutive visits during therapy. The low limit for WBC= 2,800/cmm and for neutrophils= 15% of the WBC count.

To identify patients of concern in a larger database, the sponsor examined the entire Primary Safety Database using slightly more inclusive criteria: 1) given a baseline WBC count ≥3,000/cmm, those patients with a WBC count <3,000/cmm at any time during treatment and 2) given a baseline neutrophil count ≥1,500/cmm, those patients with a neutrophil count <1,500/cmm at any time on drug. Using these criteria, the incidence of low WBC's and neutrophils is shown below:

	Olanzapine	Placebo	Haloperidol
↓ WBC	1.0% (23/2412)	0.0% (0/229)	1.3% (10/775)
↓neutrophils	2.1% (51/2394)	1.3% (3/228)	2.6% (20/771)

For both parameters, the olanzapine incidence was numerically higher than placebo, but not to a statistically significant degree (p=0.256 (WBC) and 0.623 (neutrophils)); olanzapine rates were slightly lower than haloperidol rates. The sponsor calculated exposure adjusted rates (per 100 patient-years) for these patients, which are shown below. The olanzapine rates are slightly lower than the corresponding haloperidol rates. However, if these events occur relatively early in treatment as will be suggested shortly, these rates will be biased to favor olanzapine.

	Olanzapine	Placebo	Haloperidol
↓ WBC	2.07	0.0	5.20
↓neutrophils	4.63	11.15	10.42

The sponsor analyzed these patients to evaluate the pattern of leukocyte and neutrophil decline. Among the 23 olanzapine patients with WBC <3,000/cmm, 15 were classified as transient (i.e. last value was above the lower limit of the Lilly reference range while still on drug); among the 51 olanzapine patients with neutrophils <1,500/cmm, 38 were felt to be transient by this criterion.

Also, the sponsor analyzed time to first WBC count <3,000/cmm and to first neutrophil count <1,500/cmm among patients in this database. These decreases tended to occur early in all treatment groups. In the olanzapine patients, 65% (15/23) of the decreases in WBC and 67% (34/51) of the decreases in neutrophils occurred within the first 6 weeks of olanzapine treatment.

To focus on those patients with more severe abnormalities, the

incidence of WBC< 2,000/cmm or neutrophils< 1,000/cmm in the total Primary Database are shown below. Again, olanzapine rates were higher than placebo rates but were not significantly different from placebo rates (p=1.000).

	Olanzapine	Placebo	Haloperidol
↓ WBC	0.04% (1/2412)	0.0% (0/229)	0.1% (1/775)
↓neutrophils	0.2% (5/2394)	0.0% (0/228)	0.1% (1/771)

The olanzapine patient with the low WBC count also had a low neutrophil count and will be described below, along with the other four patients with significant neutropenia. The corresponding exposure adjusted rates (per 100 patient-years) for the active drugs are higher than placebo but the olanzapine rates did not exceed the haloperidol rates:

	Olanzapine	Placebo	Haloperidol
↓ WBC	0.09	0.0	0.52
↓neutrophils	0.45	0.00	0.52

These five olanzapine patients with significant leukopenia and/or neutropenia will be briefly discussed below.

E003 603-6062: 29 y.o. white female who experienced a decline in both WBC and neutrophil counts from baseline, with minimum counts on day 13 of olanzapine therapy (17.5 mg/day) of 1,400 WBC/cmm and 440 neutrophils/cmm. A repeat count on day 15 indicated normalized counts. On day 15, the patient elected to discontinue study participation. There were no symptoms of infection. The investigator suspected that the low counts were due to laboratory error since blood specimens were clotted and repeat testing was normal.

HGAJ 3-473: 36 y.o. female of African descent experienced a neutrophil count of 670/cmm after about 260 days of olanzapine treatment (20 mg/day); the WBC count was about 4,000/cmm, the minimum WBC count for this patient during treatment. Olanzapine was continued and the neutrophil count rebounded to >2,000/cmm within two months and remained >1,500/cmm thereafter. No adverse events were experienced and the patient continued treatment indefinitely.

HGAJ 333-3287: 31 y.o. male manifested a neutrophil count of about 920/cmm with a borderline low WBC count (3,000/cmm) on day 200 of olanzapine treatment (5 mg/day). Olanzapine was continued for another 200 days prior to the cutoff date with a plateau of the neutrophil count just below 1,000/cmm and WBC counts between 2,000-3,000/cmm. The patient was asymptomatic and

continued therapy after the cutoff date.

HGAJ 722-5560: 19 y.o. white female had a neutrophil count of 790/cmm with a WBC count of 3,100/cmm on day 160 of olanzapine treatment (15 mg/day). Subsequent neutrophil counts increased over the next 200 days of treatment but remained in the range 1,500-2,000/cmm; WBC's increased and stayed between 4,000-5,000/cmm. There were no symptoms associated with the decreased neutrophil counts and the patient continued treatment beyond the data cutoff date.

HGAJ 814-6389: 34 y.o. white male who had a neutropenia (930/cmm) after about 80 days of olanzapine therapy (15 mg/day); leukocyte count was 2,910/cmm. Treatment was continued and the neutrophil count rapidly rose to >4,000/cmm and remained >3,000/cmm for the next 300 days of treatment. Total WBC count also rose and remained >6,000/cmm subsequently. There were no adverse events associated with this transient neutropenia.

In the Primary Safety Database, 6 olanzapine, 2 haloperidol, and no placebo patients dropped out due to leukopenia. There was no substantial difference in dropout rates: 0.2% (6/2500), 0.2% (2/810), and 0% (0/236), respectively. Among the 6 olanzapine dropouts, all had a leukocyte count ≥2,600/cmm and none developed associated symptoms of infection.

The sponsor also conducted a search to identify patients in the olanzapine clinical trials who had a history of decreases in leukocyte or neutrophil counts associated with prior clozapine treatment. Twenty-six such patients who received olanzapine in these studies were located: on olanzapine, 25/26 had a final WBC count ≥3,000/cmm and a neutrophil count ≥2,000/cmm; the remaining patient had a neutrophil count of 1,500/cmm, which was actually higher than his baseline count (1,300/cmm). Thus, they conclude that there is no evidence to indicate that patients with clozapine associated neutropenia are at risk for recurrence with olanzapine.

In the Secondary Safety Database (N-olanzapine=639), there were no deaths, serious adverse events, or adverse dropouts due to WBC abnormalities.

It is notable that olanzapine has been linked to significant leukopenia in animal studies when administered at doses much higher than the equivalent recommended human dose.

8.2.3.3 Events Considered Unlikely to be Drug Related

8.2.3.3.1 Deaths

There were no deaths involving a hematologic adverse event.

8.2.3.3.2 Other Serious Adverse Events

HGAJ 27-956: 45 y.o. female with lymphadenopathy at baseline which was determined to be secondary to wide-spread lymphoma after study entry. This could not be attributed to olanzapine exposure.

8.2.3.3.3 Dropouts due to Adverse Events

There were two dropouts due to hematologic abnormalities other than leukopenia:

HGAJ 58-605: 53 y.o. male experienced a declining platelet count beginning about one month after starting olanzapine. This decline continued with treatment over the next 5 months, with a minimum count of 63,000/cmm. The patient was discontinued because of the persistent decline but he had no symptoms of abnormal bleeding.

HGAO 23-2302: 84 y.o. male had an low hematocrit at baseline (34%) which decreased over the next 2 months (to 28%) during olanzapine treatment, with corresponding decreases in hemoglobin. There were no overt symptoms of anemia and it was decided to discontinue his study participation after 2 months.

These events were not felt to be related to olanzapine.

8.2.3.4 Summary and Conclusions

There was an appreciable incidence of leukopenia (1% with WBC <3,000/cmm) and neutropenia (2% with neutrophils <1,500/cmm) among olazanzapine treated patients in the Primary Safety Database (versus 0% and 1%, respectively, in the placebo group). Thus, it is felt to be possible that olanzapine is associated with decreases in WBC and neutrophil counts. Animal study findings of leukopenia support this view. However, the following comments qualify this conclusion:

1) most of these findings are transient;
2) few patients experienced WBC counts <2,000/cmm or neutrophil counts <1,000/cmm and none of these had associated clinical events such as infection or sepsis;
3) no cases of leukopenia are known to have progressed to agranulocytosis; and
4) few patients dropped out due to low WBC or neutrophil counts and none of these were associated with clinical symptoms.

Leukopenia tended to occur within the first 6 weeks of olanzapine treatment. Overall, this finding is felt to be clinically benign based on currently available data.

No other hematologic or lymphatic adverse events were felt to be

drug related.

8.2.4 Metabolic and Endocrine

8.2.4.1 Adequacy of Assessment Metabolic and Endocrine System

Body weight, glucose, albumin, protein, cholesterol, triglycerides, and prolactin (mostly by radioimmunoassay) were measured at every visit for patients in the primary integrated database. Glucose values were recorded as fasting or non-fasting as appropriate. This was adequate in the assessment of olanzapine's effect on the metabolic and endocrine system.

8.2.4.2 Adverse Events Likely to be Drug-related

8.2.4.2.1 Weight Gain

Weight gain was an adverse event that was common and drug-related in the acute, placebo-controlled study pool, being reported in 5.6% (14/248) of the olanzapine and 0.8% (1/118) of the placebo patients (p= 0.044, 2-tailed Fisher's exact test). Based on analysis of data from fixed dose range studies, this effect did not appear to be dose-related.

With respect to mean change from baseline to endpoint in this pool, olanzapine patients gained an average of 2.80 kg while placebo patients lost 0.41 kg (p< 0.001).

In analysis patients from this pool who gained greater than 7% of their baseline weight (the criteria for potentially clinically significant), 29.3% (70/239) of olanzapine treated patients and 2.7% (3/113) of placebo patients reached this threshold (p< 0.001).

Across the entire Primary Safety Database, there were 7 olanzapine dropouts due to weight gain (amount of weight gain and days on drug): **E003 304-3069** (+17kg after 198 days), **305-3089** (+20kg after 183 days), **751-7502** (+10kg after 98 days), **HGAJ 001-1663** (+8kg after 82 days), **020-0837** (+9kg after 124 days), **042-1464** (+8kg after 55 days), and **30 2825** (+13kg after 111 days). No placebo or haloperidol patients dropped out due to weight gain.

There was one patient listed as experiencing a serious adverse event associated with weight gain (**HGAJ 319-2915**, 9kg); this patient was hospitalized for an exacerbation of diabetes mellitus. This particular exacerbation might possibly be related to olanzapine treatment due to the drug's tendency to cause weight gain (which is associated with exacerbation of adult onset diabetes mellitus). The placebo rate of potentially clinically significant high glucose was greater (0.[illegible]%) than the olanzapine treatment group (0.4%) in the acute, placebo-controlled database.

Analysis of weight gain over time and depiction of the distribution of the amounts of weight gain were not provided by the sponsor.

8.2.4.2.2 Hyperprolactinemia

In the short-term, placebo controlled study pool, olanzapine patients manifested a mean increase in serum prolactin of 0.15 nmol/L versus an increase of 0.04 nmol/L in the placebo group (p=0.066).

Applying the Lilly reference range for prolactin (males: 0-0.6 and females: 0-0.8 nmol/L) to this study pool, 34.0% (66/194) of olanzapine and 13.1% (13/99) of the placebo patients had elevated prolactin levels during treatment (p< 0.001, Fisher's exact test).

Among high dose (15 ±2.5 mg/day) olanzapine patients in the acute phase of study HGAD, selected because prolactin levels were measured more frequently than in any other study, the mean prolactin concentration rose to a peak of 0.68 nmol/L (a 143% increase over the baseline) at Week 4 and then declined to 0.52 nmol/L (an 86% increase over baseline) at Week 6. From among these patients, the cohort who continued into long-term treatment were also examined: the peak mean level was 0.78 nmol/L (200% increase vs. baseline) at week 4; the mean fell to 0.40 nmol/L (54% increase over baseline) at week 24. Further, when the percentage of this cohort who met criterion for an elevated prolactin level were assessed over time, the highest percentage (~58%) occurred in the first 2 weeks with a gradual decline to 15-20% from about week 12 onward (see histograms in volume 1.219, page 221, of the NDA submission). Thus, there does seem to be a tendency for prolactin levels to decline substantially after a peak in the first 2-4 weeks of treatment.

In general, several clinical symptoms have been associated with elevated prolactin levels, e.g. hypogonadism, galactorrhea, amenorrhea, and impotence. In the Primary Safety Database, there were no statistically significant differences between olanzapine and control groups when the incidence of amenorrhea and impotence was compared in pairwise fashion (denominators were adjusted for gender):

	Olanzapine	Placebo	Haloperidol
Amenorrhea	0.7% (6/892)	0.0% (0/102)	0.7% (2/273)
Impotence	0.7% (11/1608)	0.0% (0/134)	1.3% (7/537)

In the Primary Safety Database, two olanzapine patients were diagnosed with breast cancer during treatment (**HGAJ 329-3157** after 17 days of drug and **305-2831** after 458 days); a causal link in the former case is highly unlikely given the brief drug

exposure prior to diagnosis. No placebo or haloperidol patients were so diagnosed; however, the olanzapine exposure was much greater than that for the placebo and haloperidol groups (1122.2 vs. 27.1 and 193.0 PEY's, respectively) and so this finding is not considered consequential.

In the Primary Safety Database, no olanzapine patients dropped out because of concern about hyperprolactinemia.

The clinical significance of changes in serum prolactin are not clearly known. Hyperprolactinemia may be of concern in patients with hormonally sensitive neoplasms (e.g. breast cancer) and it has been postulated by some that elevated prolactin levels are a risk factor for breast cancer.

8.2.4.3 Adverse Events Unlikely to be Drug-related

8.2.4.3.1 Deaths

There were no deaths attributed to a metabolic or endocrine adverse event in either the Primary or Secondary Safety Databases.

8.2.4.3.2 Other Serious Adverse Events

There were a number of endocrine/metabolic adverse events among olanzapine patients within the Primary Safety Database (n=2500) which were classified as serious:

Patient **HGAJ 044-1570**, a 47 y.o. male who was treated with olanzapine 10.0 mg/day for a total of 13 days, was diagnosed with pituitary adenoma. Because of an elevated baseline prolactin level (over 3000 ng/mL) reported on 28-JUL-94, a CT scan of the head was ordered on the patient which revealed a brain mass, probably pituitary in origin. The patient was discontinued by the investigator on 18-AUG-94. After the discontinuation, the patient was treated with medication and prolactin levels decreased to less than 1000 ng/mL. This condition was not felt to be related to olanzapine treatment.

Other serious adverse events were complications of pre-existing diabetes mellitus (**HGAJ 319-2915**), hospital treatment due to symptoms of newly diagnosed diabetes mellitus (**HGAJ 51-313** and **300-3003**; and **HGAP 1-1002**) and a case of pancreatitis (**HGAJ 43-1095**). A review of these cases did not suggest that any were causally linked to olanzapine therapy. Among the three patients with treatment-emergent diabetes mellitus, the wide range of durations of olanzapine exposure prior to onset (293, 9, and 116 days, respectively) suggest that olanzapine did not play a causal role in the development of this disorder.

8.2.4.3.3 Dropouts due to Adverse Events

There was one drop-out due to hypothyroidism (**HGAJ 337-3247**); this event was judged to be unlikely related to olanzapine treatment.

8.2.4.4 Summary and Conclusions

Weight gain was deemed to be a common, drug-related adverse event among olanzapine treated patients, occurring in 5.6% of those patients in the placebo-controlled, acute phase studies. Although data regarding the distribution of the amounts of weight gain in the olanzapine sample and the pattern of weight gain over time was not provided, it does seem that this effect at least begins within the first several weeks of therapy, since it was observed commonly in the acute (6 week) studies, and may reach substantial proportions in some patients: two of the seven olanzapine patients who dropped out due to weight gain had gained at least 35 lbs. compared to their baseline weights.

Serum prolactin levels in olanzapine patients tend to increase acutely and persist, albeit at a lower level, over time with therapy. No clear clinical correlates of hyperprolactinemia were observed.

8.2.5 Musculoskeletal System

8.2.5.1 Adequacy of Assessment

The assessment of the musculoskeletal system was performed by monitoring spontaneously reported adverse events. Beyond the regular assessment of serum creatine phosphokinase, which may be elevated in muscle disorders, no specific systematic laboratory measures were performed. This was adequate safety monitoring for the musculoskeletal system.

8.2.5.2 Events Likely to be Related to Olanzapine

There were no clinical events belonging to the musculoskeletal system which were felt to be related to olanzapine exposure.

8.2.5.3 Events Unlikely to be Related to Olanzapine

8.2.5.3.1 Deaths

There were no deaths in the Primary or Secondary Safety Databases which were attributed to muscular or skeletal adverse events.

8.2.5.3.2 Other Serious Adverse Events

There was one patient who was hospitalized due to back pain: **HGAJ 074-1361**. This adverse event was not judged to be related to olanzapine treatment.

8.2.5.3.3 Dropouts due to Adverse Events

There were two dropouts due to musculoskeletal events not previously described:

HGAO 17-1711: 77 y.o. female experienced a pathological fracture after treatment with olanzapine 1.0 mg/day for 8 days. This event was not felt to be due to olanzapine treatment given her brief exposure to a very low dose.

HGAJ 24-731: 41 y.o. male of African descent was diagnosed with a myopathy after receiving olanzapine 5 mg/day for 7 days. He was discovered to have a CPK= 2,960 U/L but apparently had no symptoms referable to the musculoskeletal system. A cardiac etiology was ruled out but further work-up (e.g. muscle biopsy) is not described.

Within the placebo-controlled, acute phase studies, there was no statistically significant difference (α= 0.10) between olanzapine and placebo with respect to the mean change from baseline to endpoint in mean CPK or in the proportion of patients with a potentially clinically significant (PCS) increase in CPK. In the larger Primary Safety Database, there was no significant difference between olanzapine and placebo in the incidence of dropout due to increased CPK or in the proportion of patients with a PCS increase in CPK. Among the 14 dropouts due to increased CPK in the Primary Database, none were associated with clinical symptoms. It was concluded that CPK elevation was unlikely to be a drug-related laboratory finding.

8.2.5.4 Summary and Conclusions

There were no adverse events in the musculoskeletal system judged likely to be related to olanzapine treatment.

8.2.6 Nervous System

8.2.6.1 Adequacy of Assessment of Nervous System

In addition to monitoring nervous system related adverse events, the sponsor monitored mental status via the BPRS and MADRS, extrapyramidal side effects via the Simpson-Angus Scale, akathisia via the Barnes Akisthisia Scale, and dyskinetic movements via the AIMS on each visit of the acute and extension phases of the Primary Safety Database studies. Also, emergent suicidality and hostility were evaluated using data from these scales. Also, EEG effects were evaluated in two addendum studies, JE-2001 and HGAP.

This was felt to be adequate to assess the effects of olanzapine on the nervous system.

8.2.6.2 Nervous System Events Considered to be Drug-related

8.2.6.2.1 Somnolence

In the placebo-controlled, acute phase study pool, somnolence was experienced as a treatment-emergent adverse event by 26.2% (65/248) of the olanzapine and 15.3% (18/118) of the placebo patients.

Dose-relatedness of nervous system related adverse events was assessed using data from olanzapine patients in clinical trials HGAD and E003, which had fixed dosage ranges: somnolence was identified as being significantly dose related in both studies, based on the Cochran-Mantel-Haenszel correlation p-values (α=0.05):

	% of Patients Reporting	
Dose Group	HGAD	E003
5.0±2.5 mg/day	20.0%	1.1%
10.0±2.5 mg/day	29.7%	4.7%
15.0±2.5 mg/day	39.1%	9.0%

No patients in this placebo controlled study pool dropped out due to somnolence. Few patients in the Primary Safety Database dropped out due to somnolence (0.4% or 9/2500).

8.2.6.2.2 Dizziness

In the placebo controlled, acute phase studies, dizziness was reported as an adverse event by 10.9% (27/248) of the olanzapine and 4.2% (5/118) of the placebo patients.

Dizziness was not identified as being dose related in studies HGAD or E003.

No patients in this study pool dropped out due to dizziness. In fact, only one olanzapine patient dropped out for this reason in the entire Primary Safety Database (N=2500). The extent to which this adverse experience is related to orthostatic hypotension is not clearly known.

8.2.6.2.3 Extrapyramidal Symptoms

Dopamine receptor antagonists are well known to be associated with extrapyramidal effects. According to an analysis done by the sponsor using data from the acute phases of the placebo controlled studies, 21.0% (52/248) olanzapine and 14.4% (17/118) of placebo patients reported any extrapyramidal event, defined by one or more of the following COSTART terms; also indicated are the event categories under which specific terms were subsumed for the subsequent analysis.

COSTART Terms	Event Category
dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis	Dystonia
akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor	Parkinsonism
akathisia, hyperkinesia	Akathisia
buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia	Dyskinesia
movement disorder, myoclonus, twitching	Residual Events

The percentages of patients in this study pool reporting each event category, as defined above, are displayed in **Table 8.2.6.2.3** below.

Table 8.2.6.2.3
Incidence of Extrapyramidal Treatment-Emergent Events in the Acute Phase of Placebo Controlled Studies

Event Category	Olanzapine (N=248)	Placebo (N=118)	p-values (Fisher's Exact)
Dystonia	2.0%	0.8%	0.669
Parkinsonism	11.7%	8.5%	0.469
Akathisia	7.3%	2.5%	0.091
Dyskinesia	0.8%	2.5%	0.334
Residual Events	3.2%	1.7%	0.511

With the exception of dyskinesia, all other categories of events occurred more frequently in the olanzapine group compared to the placebo group. However, only for the category "akathisia" was the difference in incidence statistically significant (α=0.10). If one excludes the cases of hyperkinesia, the difference is even more significant: olanzapine 5.2% (13/248) and placebo 0.8% (1/118) (p=0.043, Fisner's exact test).

In these studies, Barnes Akathisia Scale data was available for 242 olanzapine and 113 placebo patients. The mean changes from baseline to maximum global score were not significantly different between the groups (olanzapine +0.30, placebo +0.42; p=0.278), although this data suggests that the placebo patients experienced

slightly more severe akathisia as measured by this instrument. The baseline mean score was slightly higher in the drug group (olanzapine 0.64 and placebo 0.47).

Comparison of the two treatments with respect to the Simpson-Angus total score, which rates Parkinsonism, for mean change from baseline to maximum rating indicated no significant difference (olanzapine +0.74, placebo +0.45; p=0.989).

Likewise, in the comparing placebo versus olanzapine, there were no statistically significant differences in change from baseline to maximum AIMS total score between the two treatments (olanzapine +0.87, placebo +0.86; p=0.710).

There were very few premature discontinuations due to extrapyramidal events. Across the entire Primary Safety Database, only 8 olanzapine patients dropped out due to symptoms compatible with extrapyramidal effects: hypertonia (3 patients), akathisia (2), dystonia (1), myoclonus (1), and tremor (1). Two placebo patients discontinued treatment due to EPS, one each for akathisia and neck rigidity. The dropout rate for the olanzapine group was lower than that for placebo, 0.3% (8/2500) versus 0.8% (2/236), respectively; this difference is not significant (p=0.211, Fishers exact test).

Because extrapyramidal signs and symptoms may improve, worsen, or show no change with concomitant anticholinergic therapy (permissible by protocol at investigator's discretion), an analysis of concomitant therapy was conducted. There was no meaningful difference in the percentagse of patients using anticholinergic medication between olanzapine (17.7% or 44/248) and placebo (13.6% or 16/118) in the acute placebo controlled trials (p=0.366).

As will be discussed below, there were no clear cases of neuroleptic malignant syndrome identified from the Primary and Secondary Safety Databases.

8.2.6.2.4 Seizures

An association of seizures with neuroleptic treatment is well known. Twenty-three olanzapine-treated patients were reported to have events of coded as convulsion or grand mal convulsion in the total safety database. Of these, 22 were reported during the course of five studies (E003, HGAD, HGAJ, HGAO, and HGAP) included in the integrated primary safety database (N=2500 patients) and 1 was reported during the study (HGBC) included in the secondary safety database (N=639). Raw and exposure adjusted seizure rates for the Primary Safety Database are displayed in **Table 8.2.6.2.4** below. Pairwise comparisons of unadjusted incidence revealed no statistically significant differences (olanzapine vs. placebo p=0.252 and olanzapine vs. haloperidol

p=0.168).

Table 8.2.6.2.4 Incidence of Seizures in Primary Integrated Database		
Therapy	% (n/N)	Incidence /100 patient-years
Olanzapine	0.88% (22/2500)	1.96
Haloperidol	0.37 (3/810)	1.55
Placebo	0 (0/236)	0.00

The reports of each of the 22 patients in the primary database are categorized by confounding conditions below:

· Prior history of seizure activity-2
· Metabolic states of hyponatremia and hyperventilation-induced respiratory alkalosis-3
· History of or possible concurrent structural lesions-3
· CNS-acting medications-5
· Episodes possibly suggestive of other neuropsychiatric conditions associated with loss of consciousness or resembling seizure activity-3
· No specifically identifiable seizure-related conditions-6.

The one secondary database patient who experienced a seizure did so 30 hours after 1 dose of 10 mg of olanzapine. Follow-up EEG demonstrated abnormal activity and history was elicited for a past history of absence seizures. The connection of olanzapine with this event is uncertain.

A visual examination of the distribution of olanzapine doses at the time of seizure among the all 23 olanzapine patients revealed a broad distribution of doses and did not suggest a dose-related effect.

Also, as discussed in section 8.1.9.3, a total of 31 schizophrenic patients from two addendum studies, JE-2001 and HGAP, had baseline and treatment EEG data to assess the effect of olanzapine, in doses up to 15 mg/day for durations up to 8 weeks, on brain electrical activity. Although two of these patients showed a slowing of the background rhythm on drug compared to baseline, none of these patients showed evidence of epileptiform activity.

8.2.6.3 Nervous System Related Events Considered Unlikely to be Drug Related

8.2.6.3.1 Deaths

Most of the deaths that occurred in the olanzapine clinical trials program were due to suicide (12/23 olanzapine treated patients who died during or within 30 days of the study), a common event among schizophrenic patients. Completed suicide was the only nervous system related cause of death. To further explore whether or not olanzapine treatment could have contributed to emergent suicidal completion or ideation, the proportions of olanzapine and haloperidol patients with changes from baseline during therapy in the suicide item on the MADRS rating scale were examined in study HGAJ. The details of this analysis are reviewed in section **8.1.4.1**. Olanzapine treatment did not appear to be associated with either emergent suicidality when compared to haloperidol. Patient numbers and brief histories of these deaths may be found in **Table 8.1.1.1** in **Appendix 8.0**.

8.2.6.3.2 Other Serious Adverse Events

Elevated CPK is one sign of neuroleptic malignant syndrome (NMS), an uncommon, potentially life-threatening disorder comprised of a myriad of symptoms consisting of hyperthermia, extrapyramidal symptoms, autonomic dysfunction, altered mental state, and elevation of creatine phosphokinase (CPK). The syndrome has infrequently been observed in patients being treated with neuroleptic agents. For the evaluation of potential cases of NMS, treatment-emergent adverse events identified by the COSTART terms coma, CPK increased, fever, hypertonia, malignant hyperthermia, neuroleptic malignant syndrome, and stupor were reviewed in the Primary and Secondary Safety Databases for patients in all treatment groups.

This review revealed four olanzapine treated patients who represented possible cases of NMS:

HGAJ 049 0767

This 33-year-old male on 5.0 mg/day of olanzapine for 7 days was hospitalized for worsening of psychosis. The patient's admitting CPK concentration was 3785 U/L, and it continued to increase to a high concentration of 17,490 U/L during treatment. Evaluation revealed no changes on ECG, myoglobinuria, acute muscle injury, or cardiac ischemia, and no additional signs or symptoms suggestive of NMS. CPK concentrations decreased to normal range within 7 days following discontinuation of olanzapine. The patient also had a history of exfoliative dermatitis with an increase in CPK concentrations associated with carbamazepine therapy several years prior to these current elevations. This

patient failed to show disorientation, marked EPS, or fever; therefore, this did not represent a convincing case of NMS.

F1D-JE-202E 045 0003

This male patient of unknown age on olanzapine for 55 days developed micturition disorder, facial flushing, tremor, gait difficulties, and elevated CPK concentrations 2 days after stopping olanzapine. The patient improved with supportive care only. Concurrent medications included lormetazepam, etizolam, and triazolam. Although the group of symptoms reported by the patient deserve further assessment, key symptoms for the diagnosis of NMS are not reported, including fever, mental status changes, degree of CPK elevation, and possible autonomic dysfunction.

F1D-JE-2001 014 0001

This 58-year-old male had been previously hospitalized several months prior to the olanzapine study and treated with haloperidol and two anticholinergic medications for the symptoms of hallucinations, delusions, and extrapyramidal syndrome. To enter the olanzapine study the haloperidol washout was started, the anticholinergic medications were discontinued, and after 2 days the patient became stuporous so olanzapine was initiated. He was discontinued from olanzapine because of a temperature of 39°C and was treated with piperacillin and dantrolene. Chest x-ray identified pneumonia with a bacteriuria on urinalysis. The patient had experienced slight tremor and muscle rigidity before starting olanzapine therapy and these symptoms increased along with increased salivation and dysphagia. The patient was noted to have a slight tachycardia and hypotension, dysuria, weakness, malaise, and reportedly a decrease in consciousness. Laboratory data revealed a white blood cell count of 12.2 GI/L with a left shift and elevated CPK concentration of 1085 U/L.

This patient's symptomatology of stupor began prior to olanzapine therapy. Coupled with the abnormal chest x-ray demonstrating pneumonia and the bacteriuria identified on urinalysis, a diagnosis of NMS cannot be made.

F1D-MC-HGAJ 027 0954

This 42-year-old male on 5.0 to 10.0 mg/day of olanzapine for 8 days was discontinued from the study because of elevated temperature and CPK concentrations. Further assessment included the following studies: normal chest x-ray; ECG with normal sinus rhythm; negative blood, throat and urine cultures; white blood cell count of 12.7 GI/L; CPK concentrations from 59 to 1808 U/L. The patient did not demonstrate muscle rigidity or mental status changes. He was treated with gentamicin and amoxicillin for the elevated temperature. The patient's CPK concentration began to decrease approximately 6 days after olanzapine had been

discontinued. With the lack of significant EPS or mental status changes, the diagnosis of NMS can not be made.

Thus, there were no convincing cases of NMS identified among olanzapine patients.

Four olanzapine treated patients were identified as experiencing coma as a serious adverse event. The more likely etiologies of the comatose states were tricyclic antidepressant intentional overdose, pneumonia, seizure (with a prestudy history of seizure), and intentional diazepam overdose.

Other adverse events reported as serious, primarily because they lead to hospitalization, consisted of delusions, depression, emotional lability, hallucinations, hostility, manic reaction, paranoid reaction, psychosis, psychotic depression, and schizophrenic reaction. These were felt to represent manifestations of the condition under treatment as opposed to drug-induced adverse events.

8.2.6.3.3 Dropouts due to Nervous System Events

Dropouts due to nervous system related adverse events involved the following events: schizophrenic reaction (19 patients), depression (9), hostility (6), suicide attempt (3), agitation (2), paranoid reaction (2), and 1 report of each of the following events: delusions, drug dependence, emotional lability, intentional injury, intentional overdose, and psychotic depression. As stated above, these events were likely to represent symptoms of the underlying disease and not drug-induced events per se.

The suicidality analysis is described above. Analogous analyses for the emergence of hostility, using the hostility item of the BPRS, is described in section **8.1.4.2**: no association between increases in this rating and olanzapine treatment, as compared with placebo and haloperidol, was observed.

8.2.6.4 Summary and Conclusions

Somnolence, dizziness, extrapyramidal symptoms, and seizures are adverse experiences which are considered to be related to olanzapine treatment. Dizziness may, in large part, be secondary to postural hypotension related to olanzapine. With the exception of seizures, very few of the patients experiencing these adverse events discontinued treatment due to the event. The most common manifestations of extrapyramidal symptoms in the acute, placebo-controlled studies were Parkinsonism (11.7% of olanzapine patients versus 8.5% of placebo patients) and akathisia (7.3% of olanzapine patients versus 2.5 % of placebo patients). From a clinical point of view, these are small differences between the placebo and olanzapine groups, yet these

differences are most likely drug related.

No clear-cut cases of neuroleptic malignant syndrome were identified from among 3,139 olanzapine-exposed patients. Nonetheless, there were four cases suggestive of NMS; also, this patient population may not be completely representative of the target population and the possibility of NMS associated with olanzapine cannot be ruled out. Post-marketing surveillance data may provide a better estimate of this risk.

Emergent hostility and suicidality did not appear to be related to the use of olanzapine in schizophrenic patients.

8.2.7 Respiratory

8.2.7.1 Adequacy of Assessment of Respiratory System

The respiratory system was assessed by monitoring chest X-rays and monitoring for respiratory adverse events. The chest X-ray schedule and summary of results are presented in section **8.1.9**. This was considered an adequate assessment of olanzapine's potential effects on the respiratory system.

8.2.7.2 Respiratory Events Considered to be Drug-related.

8.2.7.2.1 Aspiration Pneumonia

There were two deaths involving aspiration pneumonia that could possibly be connected to olanzapine treatment. Both were cases of death due to aspiration pneumonia. Both of these patients were in HGAO and studied patients with senile dementia of the Alzheimer's type (DAT). Summaries of the two deaths follow:

HGAO C12-1208: 80 year-old white male with a diagnosis of dementia of Alzheimer's type, taking olanzapine 5 mg/day for 31 days. On 19-Nov-94 the patient developed the first notable signs of dysphagia and was prescribed reglan as an antiemetic but the dysphagia continued. By 12-Dec-94 the patient was unable to swallow and had evidence of food and mucus in the sinus cavities and lungs. The patient was discontinued from the study on 15-Dec-94 because of noncompliance. He was admitted to the hospital on 17-Dec-94 with the diagnosis of aspiration pneumonia. Since the patient had a living will the family declined to have a feeding tube placed and the patient was discharged to the nursing home. Lilly received notification on 4- Jan-95 that the patient had expired on 30-Dec-94.

HGAO 006-0615: 71 year old male Caucasian patient with a diagnosis of dementia of the Alzheimer's type taking olanzapine 5 mg/day for 116 days duration. He started having fever and chills on the evening of 15-Dec-94 and was admitted to the hospital with the possible diagnosis of pneumonia. Treatment included IV

fluids and antibiotics. The patient expired on 31-Dec-94. Cause of death was given as respiratory arrest, secondary to aspiration pneumonia. Autopsy was not performed.

Esophageal dysmotility and aspiration have been associated with antipsychotic use.[3] Aspiration pneumonia is also a common cause of morbidity and mortality in patients with advanced cases of dementia of the Alzheimer's type. Olanzapine and other antipsychotic medications should be used cautiously in patients at risk for aspiration pneumonia.

8.2.7.3 Respiratory Events Considered Unlikely to be Drug-related

8.2.7.3.1 Deaths

With the exception of the two cases of aspiration pneumonia outlined above, there were no deaths in the total safety database which were attributed to a pulmonary etiology.

8.2.7.3.2 Other Serious Adverse Events

Other serious respiratory events in olanzapine patients which were not felt to be causally related to olanzapine are: asthma (**HGAJ 27-1525, 45-1414, 49-1257, and 62-1075**), bronchitis (**HGAO 11-1110**), exacerbation of COPD (**HGAJ 1-875**), and pneumonia (**HGAJ 21-844, 43-642, 48-349, 62-1075, 997-7914, HGAO 11-1107,** and **HGAP 5-1215**).

To further explore the possibility that important respiratory events were related to olanzapine, the total incidence of treatment-emergent respiratory adverse events (by reported COSTART term) was examined in the Primary Safety Database is displayed in **Table 8.2.7.3.2** below.

Bazemore, P. H., Tonkonogy, J., Ananth, R.; Dysphagia in psychiatric patients: clinical and video fluoroscopic study. Dysphagia, 6:2-5, 1991.

Kruk, J., Sachdev, P., Singh, S.; Neuroleptic-induced respiratory dyskinesia. J Neuropsychiatry Clin Neurosci, 7:223-229, 1995

Table 8.2.7.3.2: Incidence of Treatment-Emergent Respiratory Adverse Events				
	Olanzapine (N=2500)	Placebo (N=236)	Haloperidol (N=810)	p-value* (Olz. vs. Plac.)
Asthma	0.8%	0.4%	0.2%	1.000
Dyspnea/Hypoxia	1.3%	1.3%	1.2%	1.000
Pneumonia	0.4%	0.0%	0.1%	0.614
Bronchitis	2.1%	0.0%	1.1%	0.013
Hemoptysis	0.1%	0.0%	0.0%	1.000
Cough Increased	5.2%	3.8%	1.7%	0.439

* Two-tailed Fisher's exact test.

It is notable that the incidence of bronchitis among olanzapine patients was significantly higher than among those in the placebo group; it was also significantly higher than haloperidol (p=0.073). When adjusted for exposure, the incidence rates (per 100 PEY's) are: olanzapine 4.7, placebo 0.0, and haloperidol 4.7. To further evaluate the possible role of olanzapine in the development of bronchitis, the time to onset of this event was examined for the 53 olanzapine patients with an event coded as bronchitis in the Primary Safety Database.[4] As shown in the display below, almost half of these occurred within the first 90 days of treatment.

Time interval (days)	Number of cases of bronchitis with time to onset in interval
1-90	24
91-180	8
181-270	12
271-360	3
>360	6

A more rigorous approach would entail the calculation of hazard rates, using patient-years of exposure as a denominator. However, since the data necessary to perform these calculations was not provided by the sponsor, the distribution of these cases by time to onset was simply inspected to discern any clustering. Since this preliminary approach did not suggest drug relatedness, more rigorous analysis was not pursued.

However, it must be remembered that the number of patients at risk for any adverse event was greatest during this period since it includes all 2500 patients in the Primary Safety Database; subsequent time periods have progressively fewer at-risk patients. The times to onset for the 24 cases occurring within the first 90 days of olanzapine therapy are depicted below:

Time interval (days)	Number of cases of bronchitis with time to onset in time interval
1-14	2
15-28	4
29-42	6
43-56	4
57-70	5
71-90	3

The distributions of these cases by time to onset suggest that these events represent the spontaneous occurrence of bronchitis in this sample as opposed to a drug induced adverse event.

8.2.7.3.3 Adverse Dropouts

There were two dropouts due to respiratory related adverse events in the total safety database which were not previously listed: **HGAJ 809-6545** (asthma) and **HGAJ 307-2847** (scleroemphysema). The latter patient was a 72 year old white female with a reportedly normal baseline chest x-ray who received haloperidol for 35 days, then was switched to olanzapine 10 mg/day for 31 days when she experienced dyspnea. A chest x-ray revealed scleroemphysema with a comment that this finding "might be the cause of an interstitial syndrome due to olanzapine." Olanzapine was stopped due to dyspnea and this x-ray abnormality. She was referred to a pulmonary specialist but no further information was provided by the sponsor. Although a causative role for olanzapine cannot be absolutely ruled out, it was felt to be unlikely due to the brief exposure to olanzapine relative to the time needed for symptomatic emphysema to develop and the lack of similar findings in other patients.

8.2.7.3.4 Chest X-Ray Examinations

For studies HGAD, E003, HGAP, and HGAJ, to include the long-term extension phases, chest x-rays were to be performed at baseline and discontinuation visits.

Among olanzapine-treated patients who had normal chest x-rays at baseline, 4.7% (29 of 619) had abnormal x-rays at any time during therapy; of these, six were felt to show no change from baseline, indicating that some baseline findings had not been noted pre-drug. Thus, the incidence of abnormal chest x-rays perhaps

should be adjusted downward to 3.8% (23/613). Among haloperidol-treated patients who had normal chest x-rays at baseline, the proportion having abnormal x-rays at any time during therapy was 1.9% (3 of 156)[olanzapine vs. haloperidol comparison: p=0.328, 2-tailed Fisher's exact test]. There were no placebo patients who had abnormal chest X-rays after normal chest X-rays at baseline. There was no clear pattern of chest x-ray abnormalities among olanzapine patients. These data, from 619 olanzapine patients with baseline and follow-up chest x-rays, do not suggest an excess risk of either pulmonary or interstitial inflammatory processes because of olanzapine treatment.

8.2.7.4 Summary and Conclusions

Aspiration pneumonia may possibly be related to the use of olanzapine; aspiration pneumonia is observed with the use of other antipsychotic drugs. There were two deaths in elderly Alzheimer's patients attributed to aspiration pneumonia: the relative contributions of olanzapine, age, disease, and other factors such as depressed levels of consciousness in these cases are difficult to estimate based on these rare cases. The overall incidence of treatment-emergent adverse events coded as pneumonia did not significantly differ across treatment groups in the Primary safety Database.

While bronchitis did occur significantly more often among olanzapine treated patients compared to placebo, this event is not felt to be drug related based on the distribution of times to event onset among the olanzapine patients. More likely, these cases represent the spontaneous occurrence of a common infection.

8.2.8 Dermatological System

8.2.8.1 Adequacy of Assessment of Dermatologic System

Beyond monitoring adverse events relevant to this body system, no special monitoring of the dermatologic organ system was performed. Nonetheless, this is felt to be adequate for the safety evaluation of olanzapine with respect to dermatologic effects.

8.2.8.2 Dermatologic Events Considered Likely to be Drug-related

There were no adverse events involving the skin which were felt to be clearly drug-related.

8.2.8.3 Dermatologic Events Considered Unlikely to be Drug-related

8.2.8.3.1 Deaths

There were no deaths related to dermatologic adverse events.

8.2.8.3.2 Other Serious Adverse Events

Cellulitis with a rash and edema resulted in hospitalization in one patient following about 5 weeks of treatment with olanzapine 20 mg/day (**HGAJ 74-1357**). Stasis dermatitis was diagnosed. These symptoms resolved despite continued treatment These events were not judged to be due to olanzapine treatment.

There were no other events in this body system deemed to be serious in the Primary or Secondary Safety Databases.

8.2.8.3.3 Dropouts due to Adverse Events

There was one dropout due to adverse events coded as an allergic reaction. Patient **HGAP 13-1602** was a 44 y.o. white female who developed a petechial rash with a fever (101.3) after receiving olanzapine 1 mg/day for 5 days. Additionally, thrombocytopenia and leukopenia were mentioned as associated findings: however, neither was markedly abnormal (WBC= 3,900/cmm with 2,800 neutrophils; platelets= 135,000/cmm) and follow-up lab studies indicated values fluctuating in this range months after study discontinuation. Olanzapine was stopped and these symptoms resolved within 2 weeks, with no sequelae.

To further evaluate the occurrence of similar events, the incidence of events coded as rash or vesiculobullous rash was examined in the placebo-controlled, acute phase study pool, based on the number of unique patients with an event coded as one of these events. The placebo incidence was higher than that for olanzapine (olanzapine 4.8% (12/248) and placebo 6.8% (8/118)). However, for vesiculobullous rash itself, the olanzapine incidence was twice that for placebo, although not statistically significant due to the small numerators (1.6% (4/248) vs. 0.8% (1/118), p= 1.000, Fisher's exact test).

Across the entire Primary Safety Database (N=2500), only 3 other olanzapine patients discontinued treatment due to rash (**HGAJ 1-809** and **810-6365**; **HGAP 10-1457**); no placebo or haloperidol patients did so. None of these patients are reported to have experienced associated fever, eosinophilia, or progression to more serious forms of skin reactions (e.g. toxic epidermal necrolysis) and the durations of drug exposure prior to onset raise some doubt about drug-relatedness (23, 70, and 65 days, respectively).

No olanzapine patients in the acute, placebo-controlled study pool experienced urticaria, another possible form of allergic skin reaction.

Only one olanzapine patient (**HGAP 11-1508**) discontinued treatment due to urticaria in the larger Primary Database. This occurred after 6 days of treatment with 1.0 mg/day. Olanzapine was stopped and the event resolved within 10 days. This event was conceivably drug-related but, if so, would likely be idiosyncratic in nature.

Photosensivity has been associated with antipsychotic drugs, particularly with chlorpromazine. There was one dropout due to photosensitivity among the olanzapine patients (N=2500) in the Primary Safety Database (**HGAJ 810-6365**). Within this sample, the incidence of adverse events coded as photosensitivity reactions was not significantly higher (α=0.10) in olanzapine patients compared to placebo or haloperidol patients (0.2% (4/2500), 0.0% (0/236), and 0.2% (2/810), respectively).

Other events which led to dropout in the Primary Database were acne, eczema, and herpes simplex, each reported in one olanzapine patient. These were felt to be unlikely related to olanzapine therapy.

There were no dropouts due to dermatologic events in the Secondary Safety Database.

8.2.8.4 Summary and Conclusions

Overall, these data suggest that any dematologic events which are causally related to olanzapine therapy, such as rash, urticaria, and photosensitivity, are probably rare and idiosyncratic; there is no evidence to suggest the common occurrence of skin events which are reasonably attributable to olanzapine therapy. No truly serious adverse events, such as Stevens-Johnson syndrome, were reported in these trials.

8.2.9 Special Senses

8.2.9.1 Adequacy of Assessment of Special Senses

Adverse events related to the special senses were documented at each visit during the trials in the olanzapine development program. Also, ophthalmologic exams were performed in studies HGAD and HGAJ according to the schedule noted in section **8.1.9**. No other special examinations of special senses were warranted. These assessments are felt to be adequate to assess the effect of olanzapine on the special senses.

8.2.9.2 Special Senses Events Considered to be Drug-related

There were no clinically important adverse events in this body system that were judged to be causally related to olanzapine therapy.

8.2.9.3 Special Senses Events Considered Unlikely to be Drug-related

8.2.9.3.1 Deaths

There were no deaths in olanzapine exposed patients that were due to events involving the special senses.

8.2.9.3.2 Other Serious Adverse Events

Patient **HGAJ 25-148** was a 37 y.o. white male with elevated optic discs noted at baseline. He began olanzapine 20 mg/day and re-examination about 2 months later revealed further disc elevation and hemorrhage in the right eye, suggestive of papilledema. A neurology work-up ensued and resulted in the diagnosis of pseudotumor cerebri. He was treated with Diamox and olanzapine was continued. The sponsor requested that treatment be stopped after 224 days of treatment. This condition was unlikely to be related to olanzapine given baseline abnormalities.

No other treatment-emergent serious adverse events involving the special senses were reported.

8.2.9.3.3 Dropouts due to Adverse Events

Among olanzapine patients within the Primary Safety Database (N=2500), there were two patients who dropped out due to amblyopia: **HGAJ 25-499** and **817-6442**. Both events consisted of blurred vision; in the former patient, diabetes mellitus may have contributed to the event. No placebo or haloperidol patient dropped out for this event. The incidence of events coded as amblyopia in the acute, placebo-controlled study pool was comparable between olanzapine and placebo (4.8% vs. 4.2%, respectively; p=1.000, Fisher's exact test). These data do not suggest a relationship to olanzapine.

Also, one patient (**HGAJ 17-99**) was discontinued by the study medical director due to the diagnosis of primary open-angle glaucoma after more than a year of olanzapine therapy.

8.2.9.3.4 Ophthalmology Examinations

Eye examinations were scheduled at baseline and periodically throughout studies HGAD and HGAJ. In both studies, analyses of mean visual acuity change for near and distance vision and mean intraocular pressure change over the course of the study were not clinically significant.

Assessments of the physical components of the eyes and visual

fieilds were performed, and no consistent abnormal ophthalmologic changes referable to one treatment group were identified. The examiners did not identify any patients receiving olanzapine therapy (including patients with sequential treatment of haloperidol and olanzapine) with drug-induced particle deposits of the lens. Corneal change across both studies and all phases was typically exogenous or degenerative in nature.

Retinal change included macular and peripheral abnormalities associated with increasing age, other medical conditions, isolated findings with no other retinal alterations, and abnormalities that did not progress over time.

8.2.9.4 Summary and Conclusions

No adverse events involving the special senses were identified as being causally related to olanzapine treatment. Additionally, there were no findings evident from ophthalmology examinations of patients from the acute and extension phases of studies HGAD and HGAJ which were attributed to olanzapine.

8.2.10 Genitourinary

8.2.10.1 Adequacy of Assessment of Genitourinary System

In addition to recording genitourinary adverse events, serum electrolytes, serum uric acid, BUN, creatinine, and urinalysis analytes were measured on each visit in patients in the primary integrated database. This is considered an adequate assessment of the effects of olanzapine on the genitourinary system.

8.2.10.2 Events Considered Likely to be Drug-related

There were no genitourinary events that were considered likely to be drug related.

8.2.10.3 Events Considered Unlikely to be Drug-related

8.2.10.3.1 Deaths

There were no deaths related to the genitourinary system in the olanzapine integrated safety database.

8.2.10.3.2 Other Serious Adverse Events

A number of serious adverse events involving the genitourinary system were observed among olanzapine patients in Primary Safety Database (N=2500); most were serious because they resulted in hospitalization, but none were felt to be causally linked to olanzapine treatment: bladder carcinoma (**HGAJ 6-817**), urinary tract stones (**HGAJ 315-3146** and **106-2037**), pyelonephritis (**HGAJ 328-3070**), metrorrhagia (**E003 402-4028** and **906-9117**), prostatitis

(**HGAJ 300-2804**), and urinary tract infection with sepsis (**HGAO 16-1618**). No such events were reported in the Secondary Database.

8.2.10.3.3 Dropouts due to Adverse Events

Two olanzapine patients in the Primary Safety Database dropped out of treatment due to urinary retention (**E003 301-3009** and **HGAJ 24-730**). No placebo or haloperidol patients dropped out for this reason. Both events were noted within the first 2 weeks of olanzapine therapy in middle-aged males. Neither is known to progress to a more serious condition (e.g. pyelonephritis).

The incidence of all events coded as urinary retention in this database was 0.3% (8/2500), 0.0% (0/236), and 0.0% (0/810) in olanzapine, placebo, and haloperidol patients, respectively. The differences between olanzapine and the control groups are not statistically significant (α=0.10). However, this incidence may considerably underestimate the true incidence of urinary retention, since some patients with clinically significant urinary retention may develop other urinary tract conditions (e.g. urinary tract infections) which are coded in lieu of the antecedent urinary retention. Additionally, a causal link to olanzapine is plausible given its antimuscarinic activity.

To further explore this possibility, the reporting of any adverse event which suggested the occurrence of either urinary retention or urinary tract infection was examined in the olanzapine and placebo groups within the Primary Safety Database. The identified events were: urinary retention, urination impaired, urinary tract infection, dysuria, urinary frequency, pyuria, cystitis, and pyelonephritis. The proportion of patients reporting at least one of these events was calculated for each group; numerators were adjusted so that no patient was counted twice within a treatment group. These events were more common in the olanzapine group, although proportions did not differ significantly: olanzapine 4.7% (118/2500) and placebo 3.4% (8/236) (p=0.419, Fisher's exact test).

Overall, these data are not felt to support the possibility that urinary retention is a drug-related event for olanzapine. But it must be noted that the small size of the placebo group, relative to the olanzapine group in the Primary Safety Database (236 vs. 2500), appreciably diminishes the statistical power to detect a difference and so a causal link cannot be entirely ruled out.

In an exploratory analysis of serum electrolytes, BUN, creatinine, uric acid, and urinalysis analytes within the acute, placebo-controlled study pool, the only remarkable findings were significant differences between olanzapine and placebo with respect to mean change from baseline to endpoint for three parameters:

	Olanzapine	Placebo	p-value
Serum Uric Acid (μmol/L)	+30.35	+3.27	<0.001
Urine Specific Gravity	-0.002	0.000	0.037
Urine pH	-0.13	+0.04	0.022

These mean changes were felt to be small relative to typical values and of no clinical significance in light of the absence of other significant laboratory or clinical findings. No olanzapine patients in this database experienced treatment-emergent gout.

8.2.10.4 Summary Statement on the Effects of Olanzapine on the Genitourinary System

There are no genitourinary adverse events that were felt to be drug-related. While urinary retention is possibly related to olanzapine based on its antimuscarinic activity, these data do not clearly support that possibility.

8.2.11 Miscellaneous Events

8.2.11.1 Adequacy of Assessment

Important miscellaneous events were monitored at each visit during the trials in this database by recording patient-reported adverse experiences. This is felt to be adequate to detect any important events not classified in previous body systems.

8.2.11.2 Miscellaneous Events Likely to be Drug-related

There were no miscellaneous events felt to be drug-related.

8.2.11.3 Events Considered Unlikely to be Drug-related

There was one death of uncertain cause: **HGAJ 51-0319** was a 35-year-old black female patient who began olanzapine treatment on January 20, 1994, with the dose eventually increased to 20 mg/day. There was no history of any significant medical problems, but an ECG did suggest an old myocardial infarction.

Concurrent medications included Norinyl for contraception and Ativan for anxiety. Also, she received one 10 mg dose of Procardia on 15 March 1994 for an episode of hypertension. On 10 June 1994, she was begun on Lopid for elevated triglycerides and between 16-18 June 1994, she received Septra for a urinary tract infection. She complained of feeling sick and vomiting on June 20, 1994, went to bed about 10:00 PM, and was found dead the next morning. Autopsy revealed pulmonary edema, pleural adhesions, petechial hemorrhages of the epicardium and endocardium, patent coronary arteries and absence of pathology on cardiac microscopic examination, petechial hemorrhages in the fundus of the stomach, fatty changes in the liver with microscopic examination revealing congested sinusoids and numerous cytoplasmic vacuoles in the

liver, and a parasagital subarachnoid hemorrhage. Microscopic examination of the cerebral cortex and brain stem revealed perineuronal separation. Kidney and adrenal tissues were undergoing autolysis at the time of autopsy, as revealed by microscopic examination. Toxicological examination revealed olanzapine and caffeine present in postmortem blood but did not reveal alcohol, and presumably, did not reveal other substances. Postmortem blood olanzapine concentration was measured as 370 ng/mL; the highest olanzapine concentration observed to date in a patient taking 20 mg/day is 174 ng/mL. The medical examiner's office investigating this case attributed the cause of death to a presumptive overdose of olanzapine which resulted in cardiac failure and pulmonary edema.

Plasma concentrations of olanzapine were measured during the study with the following results:

Dose-duration and Olanzapine Levels for Patient HGAJ 051-0319

Visit #	Date	Dose/Duration of that Dose at Time Measured*	Concentration
3	27-Jan-94	5 mg/day x 7 day	10.7 ng/mL
12	11-Mar-94	15 mg/day x 4 day	32.6 ng/mL
13	18-Mar-94	15 mg/day x 11 day	40.2 ng/mL
15	31-Mar-94	20 mg/day x 13 day	23.1 ng/mL

* Days following a dose increase prior to the concentration measurement.

The next scheduled measurement would have occurred at Visit 19. Pill counts of returned olanzapine for all visits up to and including Visit 18 (10 June 1994, last visit before death), revealed that the patient was returning amounts of olanzapine consistent with correct use of medication as prescribed. Plasma concentrations suggested she was taking medication as prescribed at least through Visit 15 (31 March 1994). At Visit 18, 10 days before death, 144 capsules (5-mg capsules, 720 mg total) were dispensed. At the time that the patient was discovered dead, 108 capsules were found. Therefore, she is presumed to have taken 36 capsules during the interval between her last visit (Visit 18) and her death.

The sponsor makes the argument that post-mortem redistribution of olanzapine might have occurred. No data are available at this time regarding the potential postmortem redistribution of olanzapine. It is very unlikely that the actual cause of this death will become known. No other similar events have been reported.

8.2.11.4 Summary Statement Regarding Olanzapine's Effect on these Miscellaneous Events

There were no adverse events not classifiable in previous body systems which were felt to be drug-related.

There was one death of unknown cause in which olanzapine may have played a role. Available information is difficult to interpret and the other, non-drug-related explanations, exist; thus, this event cannot be attributed to olanzapine with reasonable certainty. Rare cases of unexplained death do occur with antipsychotic treatment and are addressed in labeling. I recommend that this death be similarly addressed.

8.3 Summary of Key Adverse Findings

8.3.1 Cardiovascular

8.3.1.1 Postural Hypotension

In the acute phase, placebo-controlled study pool, a potentially clinically significant postural change in systolic blood pressure (i.e. ≥30 mmHg decrease in systolic BP supine to standing) was a common and drug-related vital sign measurement, occurring in 5.5% of olanzapine and 1.8% of placebo patients. Among olanzapine patients, all such changes were transient, none dropped for this reason, and none experienced significant clinical events attributable to an orthostatic drop in SBP. However, it is possible that orthostatic hypotension may be linked to tachycardia and dizziness associated with olanzapine treatment.

In the human pharmacology studies, where vital sign monitoring was more extensive, postural hypotension occurred early or with the first dose of olanzapine and the effect was more prominent with doses ≥10mg or when olanzapine was combined with ethanol. In those studies, adaptation to this effect was seen as olanzapine reached steady-state concentrations, being most severe as peak plasma concentrations were attained. Adaptation appeared to develop as a result of a compensatory tachycardia, usually in the range 100-140 bpm.

Across the entire Primary Safety Database (2500 olanzapine-treated patients), there were 15 cases syncope in olanzapine exposed patients; 6 occurred in the acute phase of active controlled studies in patients taking olanzapine; one occurred in the 1 mg/day treatment group of study E003. The other nine cases occurred in the extension phases of the protocol. Thus in the acute phases of controlled studies there were 5/1796 (0.28%) cases of syncope (the 1 mg/day group was excluded from safety evaluation statistical calculations) versus 2/810 (0.25%) cases in the active control group (one in each group dropped out). This was not a statistically significant difference by the Fisher's

exact test. In study HGAP one patient dropped out due to syncope in the extension phase of the protocol.

This finding is consistent with the α-1 receptor antagonism of olanzapine. This adverse event should be described under the PRECAUTIONS section of labeling since it could have important consequences in patients with cardiovascular compromise or with concurrent ethanol use.

8.3.1.2 Tachycardia

Tachycardia was reported as a treatment-emergent adverse event in 4.4% of olanzapine vs. 0.8% of placebo patients in this study pool. In the acute, placebo-controled studies, the mean change from baseline to endpoint in standing heartrate for olanzapine was +2.70 bpm and for placebo +0.87 bpm.

Focusing on those patients meeting more severe criteria for a significant increase in pulse measurement (i.e. >120 and an increase ≥15 bpm), 3.9% of these olanzapine and 3.7% of placebo patients met criteria for standing tachycardia.

No patients in the Primary or Secondary Safety Databases dropped out due to tachycardia.

Thus, while it appears that olanzapine is associated with an increase in heartrate, changes were generally not clinically significant and may be related to postural hypotension.

3.3.2 Gastrointestinal

8.3.2.1 Constipation

Constipation was reported as a treatment-emergent adverse event by 9.3% of olanzapine and 3.4% of placebo patients within the acute, placebo controlled study pool. Constipation did not appear to be dose-related. No patient dropped out for this event in the entire safety database and none were considered to progress to more serious conditions, such as megacolon.

This event is likely related to the antimuscarinic activity of olanzapine.

8.3.2.2 Liver Injury

Within the acute, placebo-controlled study pool, examination of the mean changes from baseline to endpoint for liver transaminases did suggest a tendency for olanzapine to be associated with elevations in AST (SGOT), ALT (SGPT), and GGT. Also, the proportion of olanzapine patients in this study pool meeting criteria for a marked elevation of AST, ALT, or GGT was higher than that in the placebo group: olanzapine 2.9% vs.

placebo 0.0%. The highest elevation was about 20X ULN, but most were <8X ULN. None of these patients experienced jaundice or are known to have progressed to liver necrosis or liver failure.

Within the larger Primary Safety Database (2500 olanzapine patients), comparison of exposure adjusted rates (per 100 PEY's)of marked elevations in transaminases did reveal a substantially higher rate for olanzapine: olanzapine= 6.6, placebo= 3.7, and haloperidol= 3.6. Again, none of these patients had jaundice, adverse events attributable to liver dysfunction, or progressed to liver necrosis or failure. A small proportion (0.8%) of olanzapine patients dropped out due to enzyme elevation.

Liver enzyme elevations generally occurred within the first six weeks of therapy with olanzapine and tended to be transient.

It is recommended that this finding be described under ADVERSE EVENTS in labeling.

8.3.3 Hematologic

8.3.3.1 Leukopenia

In the Primary Safety Database (2500 olanzapine patients), 1.0% of olanzapine and no placebo patients experienced a WBC count <3,000/cmm at any time during treatment and 2.1% of olanzapine and 1.3% of placebo patients had a neutrophil count <1,500/cmm at any time on study drug. Most of these olanzapine patients had transiently low counts, while a smaller proportion had counts that showed a plateau over time. Low counts generally emerged in the first six weeks of therapy.

To focus on those patients with more severe abnormalities in this database, 0.04% of olanzapine and no placebo patients had a WBC count < 2,000/cmm; 0.2% of olanzapine and no placebo patients had a neutrophil count < 1,000/cmm in the Primary Safety Database. None of the patients had a progressive decline in WBC or neutrophil count and most rebounded. No patient had a clinical event, such as infection or sepsis, referable to a depressed WBC or neutrophil count. These patients are discussed in section **8.2.3.2.1**.

In the Primary Safety Database, 0.2% (6/2500) olanzapine, 0.2% (2/810) haloperidol, and 0% (0/236) placebo patients dropped out due to leukopenia. Among the 6 olanzapine dropouts, all had a leukocyte count ≥2,600/cmm and none developed relevant symptoms. The available data thus far suggests that, at the recommended doses, olanzapine is free of agranulocytosis. Higher doses of olanzapine may be hematotoxic, however, based on animal studies with much higher doses. It is recommended that this finding be described under ADVERSE EVENTS in labeling. It is judged that

olanzapine treatment at the recommended dosage levels requires no special laboratory surveillance of WBC or other special hematologic precautions.

8.3.4 Metabolic/Endocrine

8.3.4.1 Weight Gain

Weight gain was reported in 5.6% of the olanzapine and 0.8% of the placebo patients in the acute placebo-controlled study pool. This effect did not appear to be dose-related based on fixed dose study data. With respect to mean change from baseline to endpoint in this pool, olanzapine patients gained an average of 2.80 kg (6.2 lbs.) while placebo patients lost 0.41 kg (0.9 lbs.) ($p< 0.001$). Among patients from this pool, 29.3% of olanzapine treated patients and 2.7% of placebo patients gained greater than 7% of their baseline weight ($p< 0.001$).

Across the entire Primary Safety Database, there were 7 olanzapine dropouts due to weight gain.

Analysis of weight gain over time was not provided by the sponsor.

This effect should be described in labeling under PRECAUTIONS.

8.3.4.2 Hyperprolactinemia

In the short-term, placebo controlled study pool, olanzapine patients manifested a mean increase in serum prolactin of 0.15 nmol/L versus an increase of 0.04 nmol/L in the placebo group ($p=0.066$). Applying the Lilly reference range for prolactin (males: 0-0.6 and females: 0-0.8 nmol/L) to this study pool, 34.0% of olanzapine and 13.1% of the placebo patients had elevated prolactin levels during treatment ($p< 0.001$, Fisher's exact test).

Based on an analysis of patients participating in long-term extension treatment with olanzapine, there did seem to be a tendency for prolactin levels to decline substantially after a peak in the first 2-4 weeks of treatment; however, they appear to plateau at about 50% over baseline.

In the Primary Safety Database, no olanzapine patients dropped out because of concern about hyperprolactinemia and few patients had clinical findings, such as galactorrhea, impotence, or amenorrhea, consistent with hyperprolactinemia.

The clinical significance of changes in serum prolactin is not clearly known. Hyperprolactinemia may be of concern in patients with hormonally sensitive neoplasms (e.g. breast cancer) and it has been postulated by some that elevated prolactin levels are a

risk factor for breast cancer. This finding should be described under PRECAUTIONS in labeling.

8.3.5 Nervous

8.3.5.1 Dizziness

Dizziness occurred at a rate of 10.9% of olanzapine versus 4.2% of placebo patients in the acute, placebo-controlled studies. There was no evidence of dose-relatedness. Only rarely did olanzapine patients dropout because of dizziness in the larger Primary Safety Database. The extent to which this adverse event is related to orthostatic hypotension is not known.

8.3.5.2 Extrapyramidal Symptoms

The most common manifestations of extrapyramidal symptoms in the acute, placebo-controlled studies were Parkinsonism (11.7% of olanzapine patients vs. 8.5% of placebo patients), akathisia (7.3% vs. 2.5%), and dystonia (2.0% vs. 0.8%). Across the entire Primary Safety Database, very few (0.3%) patients dropped out due to extrapyramidal symptoms. The standard description of EPS should be included under ADVERSE EVENTS in labeling.

Additionally, although no definitive cases of neuroleptic malignant syndrome were identified in the total safety database, four cases suggestive of NMS were reported and this risk is not ruled out: this patient population was closely monitored and may not be completely representative of the target population. The standard statement regarding neuroleptic malignant syndrome should be included under WARNINGS in labeling.

Experience with the long-term use of olanzapine is limited to date and it is expected that occasional cases of tardive dyskinesia will be observed with chronic use of olanzapine. The standard statement regarding tardive dyskinesia should be included under WARNINGS in labeling.

8.3.5.3 Seizures

In the integrated primary database, 0.88% (22/2500) of patients treated with olanzapine experienced events that were reported as seizures or possible seizures. A dose-relationship was not evident.

Thirty-one schizophrenic patients from two addendum studies, JE-2001 and HGAP, had baseline and treatment EEG data to assess the effect of olanzapine, in doses up to 15 mg/day for durations up to 8 weeks, on brain electrical activity. Two of these patients showed a slowing of the background rhythm on drug compared to

baseline, but none showed evidence of epileptiform activity.

The overall incidence of seizures in medicated patients with schizophrenia and schizoaffective disorder has been shown to be 1% in a prospective study[5]. Thus the incidence of seizures in this database is not higher than that reported in the literature with other antipsychotics. This adverse event should be mentioned in the PRECAUTIONS section of labeling.

8.3.5.4 Somnolence

In the placebo controlled, acute phase study pool, somnolence was experienced as a treatment-emergent adverse event by 26.2% of the olanzapine and 15.3% of the placebo patients. In both of the fixed dose studies HGAD and E003, somnolence did appear to be a dose related event. Few patients (0.4%) in the Primary Safety Database dropped out due to somnolence.

8.3.6 Respiratory

8.3.6.1 Aspiration Pneumonia

Aspiration pneumonia was the cause of death in two elderly patients with Alzheimer's disease in study HGAO. Aspiration pneumonia may be possibly related to the use of olanzapine in susceptible patients; aspiration pneumonia has been linked to the use of other antipsychotic drugs (see references in section **8.2.7.2.1**). However, the relative contributions of olanzapine, age, disease, and other factors such as depressed levels of consciousness in these cases are difficult to estimate. The overall incidence of treatment-emergent adverse events coded as pneumonia did not significantly differ across treatment groups in the Primary safety Database. The possible relationship between the use of olanzapine and rare cases of aspiration pneumonia should be noted as a PRECAUTION in labeling.

9.0 Labeling Review

Based on the preceding review of the clinical data, the draft labeling from the sponsor was reviewed.

From a clinical standpoint, the chemistry, pharmacodynamics, pharmacokinetics, and special populations sections are acceptable as written.

The sponsor states that the effectiveness of olanzapine is demonstrated in 3 well controlled clinical trials. This reviewer

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Bartels, M., Heimann, H., [Cerebral seizures in neuroleptic therapy]. Psychiatr Prax, 12:189-93, 1985

submits that there are two positive studies (HGAD and HGAP), one failed study (E003), and one flawed study (HGAJ). The clinical trials section, wherein subsections 1 and 2 describe studies HGAD and HGAP, respectively, are accurately and fairly described.

Subsection 3, which describes study E003, is accurate but fails to mention that though numerical superiority was achieved on the mentioned rating scales, statistical significance was not. Furthermore, the significant differences in favor of olanzapine were not corrected for multiple comparisons.

Subsection 4 of the clinical trials section, which describes study HGAJ (the large uncontrolled comparison study of haloperidol and olanzapine) is an overpowered study where the statistically significant differences are clinically small and the "numerically superior" differences between olanzapine and haloperidol are neither statistically or clinically significant. Given the poor design of this study and the clinically small significant differences, I recommend that the study not be mentioned at all in labeling to support an efficacy claim. The single dose range of haloperidol combined with the bias of approximately a third of the patients having previously-less-than-positive experience with haloperidol, renders this study an unfair comparison of the two therapeutic modalities.

Subsection 5 of the clinical trials section describes the extension phases of the acute trial protocols. Since these phases did not follow re-randomization and, thus, do not repesent a comparison of randomized samples, data from these phases cannot provide scientific evidence of long-term efficacy. Also, the sponsor again introduces comparative language that hints at superiority of olanzapine over haloperidol. I recommend that this type of comparison be removed from the proposed labeling due to the bias mentioned in the last paragraph.

The INDICATIONS AND USAGE section is accurate as it is written; however, I would recommend that the language be modified to reflect that there were two positive acute phase studies. Again, no claim regarding long-term efficacy can be made based on non-randomized extension treatment groups.

The "Contraindications" section is adequate.

The WARNINGS statement about tardive dyskinesia seems to imply a comparison with haloperidol, which should not be permitted.

The PRECAUTIONS section should include a statement describing the two deaths due to aspiration pneumonia, and a general statement about reports of coincident aspiration pneumonia with neuroleptic treatment (see section 8.2.7.2.1).

The PRECAUTIONS section should also include a general statement regarding the occurrence of rare unexplained deaths with neuroleptic use and a description of the case described in section 8.2.11.2 of this review. This is consistent with labeling practices in other antipsychotic medications.

The PRECAUTIONS section should describe Postural Hypotension as a significant, drug-related event as per section 8.3.1.1.

The PRECAUTIONS section on hyperprolactinemia mentions a comparison with haloperidol, which should be deleted for reasons previously mentioned.

The "Information to Patients" section does not mention risks of tardive dyskinesia or other potential antipsychotic induced movement disorders. Also, it does not mention the risk of potentiated postural hypotension when Zyprexa is used with ethanol.

The "Carcinogenesis, Mutagenesis, Impairment of Fertility" section is adequate from a clinical standpoint.

The last paragraph under the Pregnancy subsection is felt to be inaccurate: there were seven pregnancies during clinical trials, 3 leading to normal births, although one of these infants died about 2 hours after birth due to a cardiovascular defect. There were also 3 therapeutic abortions and one spontaneous abortion (see Volume 1.219, pages 191-193, of the NDA submission).

The "Dose dependent adverse event" subsection, tables 2 and 3 require re-analysis. The sponsor's analysis of dose-dependent adverse events includes the placebo and ersatz-placebo doses. This will produce artificially significant dose-dependent correlations and thus is overly liberal in assigning the cause of adverse events to increasing dose of drug. Tables 2 and 3 in labeling should be replaced with tables 8.1.5.4.1.1 and 8.1.5.4.1.2 from section 8.1.5.4 in this review.

Under ADVERSE REACTIONS, the presented tables and discussions of EPS, laboratory, and vital sign data is cumbersome and obscures important findings in these area, namely postural hypotension, tachycardia, EPS, and weight gain; leukopenia, hyperprolactinemia, and elevated liver transaminases were adequately discussed in previous sections. It is recommended that this area of labeling be abbreviated to reflect primarily the corresponding data in the subsections under section 8.3.

Under DRUG ABUSE AND DEPENDENCE, the final paragraph indicates that there was no evidence of withdrawal signs or symptoms in premarketing trials. This should be deleted since, in the absence of systematic evaluation for such phenomena, they are likely to go undetected. The next sentence indicates that such

an examination was not conducted and it may remain.

Under DOSAGE AND ADMINISTRATION, there is no mention of whether higher doses should be split or whether there is a difference between once-a-day dosing in the morning versus evening. In the clinical efficacy trials, it seems that single doses up to 20mg were satisfactorily tolerated; pharmacokinetic differences between AM and PM dosing have not been explored but, since this drug is associated with somnolence, PM dosing might be preferable from a pharmacodynamic perspective. This should be clarified. As discussed above, claims regarding long-term efficacy should be deleted.

10.0 Conclusions

Olanzapine is effective and appropriately safe in the treatment of schizophrenia when used as labeled. Two studies (HGAP and HGAD) demonstrate efficacy; both of these studies are of adequate design and size. Study E003 does not reach statistical significance and represents a failed study. Study HGAJ is fundamentally flawed and provides little useful efficacy data but did provide a large amount of olanzapine exposure data for safety analysis For the vast majority of patients, the benefits of olanzapine treatment should outweigh the risks by a substantial margin.

11.0 Recommendation

From a clinical standpoint, I recommend that olanzapine be approved as an effective and safe treatment of schizophrenia.

7/29/1996

Paul J. Andreason, M.D.
Medical Review Officer
Psychiatric Drug Products Group

cc: NDA 20-592
HFD-120
HFD-120/TLaughren
PAndreason
GDubitsky
SHardeman

7-29-96
I agree that this NDA is approvable. See memo to file for my more detailed summary comments.
James P. Laughren, MD
TL, PDP

Table 5.1.1.1 Table of All Studies

Dose tolerance studies

F1D-JE-P100	Single-blind, active-controlled and placebo-controlled, parallel, single-center, dose tolerance study; healthy male subjects (N=20); olanzapine dose (0.5-6.0 mg/day, po), haloperidol dose (1.0-3.0 mg/day, po), single escalating doses separated by ≥ 7 days
F1D-JE-P200	Single-blind, placebo-controlled, parallel, single-center, dose tolerance study; healthy male subjects (N=8); olanzapine dose (1.0 mg/day x 3 days, po), multiple doses
F1D-JE-P201	Single-blind, placebo-controlled, parallel, single-center, dose tolerance study; healthy male subjects (N=12); olanzapine dose (1.0-2.5 mg/day x 3 days, po), multiple doses
F1D-LC-HGAA	Single-blind, placebo-controlled, crossover, single-center, dose tolerance study; healthy male subjects (N=4); olanzapine dose (0.5-20.0 mg/day, po), single escalating doses separated by ≥ 5 days of placebo
F1D-LC-HGAC	Single-blind, placebo-controlled, crossover, single-center, dose tolerance study; healthy male subjects (N=5); olanzapine dose (12.0 mg/day x 14 days, po), multiple doses

Pharmacokinetic Studies

--Bioequivalence Studies

F1D-EW-E007*	Open-label, crossover, 2-center, haloperidol tablet vs capsule bioequivalence study; healthy male subjects (N=26); haloperidol dose (5.0 mg, po, each formulation), 2 single doses separated by 14 days
F1D-EW-E008*	Open-label, crossover, 2-center, haloperidol tablet vs capsule bioequivalence study; healthy male subjects (N=25); haloperidol dose (5.0 mg, po, each formulation), 2 single doses separated by 14 days
F1D-EW-HGBW	Open-label, crossover, single-center, tablet vs capsule vs granules bioequivalence study; healthy male subjects (N=20); olanzapine dose (10.0 mg, po, each formulation), 3 single doses separated by 14 days
F1D-JE-205E	Open-label, crossover, single-center, tablet vs capsule, effect of a meal bioequivalence study; healthy male subjects (N=52); olanzapine dose (5.0 mg/day, po, each formulation), 2 single doses separated by 10-16 days
F1D-LC-HGAV	Single-blind, crossover, single-center, tablet vs capsule bioequivalence study; healthy male subjects (N=10); olanzapine dose (5.0 or 15.0 mg, po, each formulation), 4 single doses separated by 7 days
F1D-LC-HGBY	Open-label, crossover, single-center, tablet vs capsule bioequivalence study; healthy male and female subjects (N=49); olanzapine dose (tablets: 1.0, 5.0, 7.5, or 10.0 mg/day, po; capsules: 1.0, 5.0, 10.0, or 15.0 mg/day, po), 3 single doses separated by 14 days

(continued)

Table 5.1.1.1 Table of All Studies (continued)

Pharmacokinetic Studies (continued)

--Pharmacokinetic Studies

F1D-EW-HGCC	Open-label, single-center, pharmacokinetic study; healthy elderly male and female subjects (N=8); olanzapine dose (5.0 mg/day x 14 days, po)
F1D-LC-HGAB	Open-label, single-center, pharmacokinetic study; healthy male subjects (N=4); olanzapine dose (12.5 mg containing 50 _Ci of ^{14}C-radiolabeled olanzapine, po), single dose
F1D-LC-HGAH	Single-blind, crossover, single-center, effect of food pharmacokinetic study; healthy male subjects (N=6); olanzapine dose (5.0-15.0 mg/day, po), 4 single doses separated by 4 days
F1D-LC-HGAI	Open-label, single-center, pharmacokinetic study; healthy male subjects (N=6); olanzapine dose (12.5 mg olanzapine containing approximately 100 _Ci of ^{14}C-radiolabeled olanzapine, po), single dose
F1D-LC-HGAM	Open-label, single-center, pharmacokinetic study; healthy young (N=8) and elderly (N=16) male and female subjects; olanzapine dose (2.5, 5.0, 7.5, and 10.0 mg/day, po), 4 single doses separated by 9-14 days
F1D-LC-HGAU	Open-label, single-center, pharmacokinetic study; healthy and cirrhotic patients (N=9, all male); olanzapine dose (2.5, 5.0, and 7.5 mg, po), 3 single doses over a 21-day period
F1D-LC-HGAW	Open-label, single-center, pharmacokinetic study; healthy and renally impaired male and female subjects (N=16); olanzapine dose (5.0 mg/day, po)
F1D-LC-HGAX	Open-label, single-center, Asians (N=14) vs Caucasians (N=6) pharmacokinetic study; healthy male and female subjects (N=20, all male); olanzapine dose (2.5, 5.0, 10.0, and 15.0 mg/day, po), 4 single doses separated by 9-14 days
F1D-MS-HGCD	Open-label, single-center, pharmacokinetic study; healthy male and female subjects (N=9); olanzapine dose (5.0-10.0 mg/day, po)

(continued)

Table 5.1.1.1 Table of All Studies (continued)

Pharmacokinetic Studies (continued)

--Drug Interaction Studies

F1D-EW-E002	Single-blind, 2-center, placebo-controlled, drug interaction study; healthy male subjects (N=8); placebo or biperiden dose (4.0 mg x 1 day, po), washout period, olanzapine dose (10.0 mg/day x 7 days, po), placebo or biperiden dose (4.0 mg x 1 day, po, on last day of olanzapine dosing)
F1D-EW-HGBC	Open-label, single-center, drug interaction study; healthy male subjects (N=12); olanzapine dose (10.0 mg x 1 day, po), 2-week washout, olanzapine dose (10.0 mg x 1 day, po, on Day 14 of carbamazepine treatment), carbamazepine dose (200 mg twice daily x multiple days, po)
F1D-LC-HGAE	Open-label, single-center, drug interaction study, healthy male subjects (N=6); diazepam dose (10.0 mg x 1 day, po), olanzapine dose (12.5 mg x 1 day, po), olanzapine dose (12.5 mg/day x 9 days, po) + diazepam dose (10.0 mg x 1 day, po, on Day 4 of olanzapine); 1-week washout between dosings
F1D-LC-HGAT	Open-label, single-blind, single-center, crossover, drug interaction study; healthy male and female subjects (N=9); olanzapine dose (7.5 mg, po), cimetidine dose (800 mg, po) + olanzapine dose (7.5 mg, po), Mylanta® dose (30 cc, po) + olanzapine dose (7.5 mg, po), activated charcoal dose (1.0 gm, po) + olanzapine dose (7.5 mg, po); 1-week washout between dosings
F1D-LC-HGBE	Single-blind, single-center, drug interaction study; healthy male subjects (N=19); olanzapine dose (10.0 mg, po), warfarin dose (20.0 mg, po), olanzapine dose (10.0 mg, po) + warfarin dose (20.0 mg, po); 2-week washout between dosings
F1D-MS-E001	Open-label, single-center, drug interaction study; healthy male subjects (N=12); lithium dose (2144 mg x 1 day, po), lithium dose (2144 mg, po) + olanzapine dose (10.0 mg, po) x 1 day, olanzapine dose (10.0 mg/day x 8 days, po) + lithium dose (2144 mg, po) on Day 8
F1D-MS-E002	Open-label, single-center, drug interaction study; schizophrenic patients maintained on levomepromazine (N=1); levomepromazine alone (150 mg twice daily x 7 days, po), then in combination with olanzapine (2.5 mg x 1 day, then 5.0 mg x 1 day, then 10.0 mg/day x 8 days, po)

(continued)

Table 5.1.1.1 Table of All Studies (continued)

Pharmacokinetic Studies (concluded)

--Pharmacodynamic Studies

F1D-LC-HGAN	Open-label, single-center, crossover, pharmacodynamic and drug interaction study; healthy nonalcoholic male subjects (N=15); olanzapine dose (2.5 mg/day x 2 days, 5.0 mg/day x 2 days, 10.0 mg/day x 7 days, po), placebo or EtOH dose (45 mL/70 kg, po)
F1D-LC-HGAQ	Open-label, single-blind, single-center, crossover, pharmacodynamic and drug interaction study; healthy male subjects (N=9); olanzapine dose (5.0-mg single dose, po), imipramine dose (75-mg single dose, po), olanzapine (5.0 mg, po) + imipramine (75 mg, po); 2-week washout between dosings
F1D-EW-HGCE	Double-blind, active-controlled and placebo-controlled, crossover, single-center, cognition and psychomotor performance pharmacodynamic study, healthy elderly male and female subjects (N=16); olanzapine dose (3.0 mg/day, po, maximum of 4 days), haloperidol dose (3.0 mg/day, po, maximum of 4 days), multiple doses
F1D-MC-HGAR	Open-label, single-center, positron emission tomography (PET) study of 5-HT_2:D_2 receptor occupancy; healthy male subjects (N=3); olanzapine dose (10.0 mg/day, po), single dose

Placebo-Controlled (_ Active-Controlled) Studies

F1D-MC-HGAD	Double-blind, active-controlled and placebo-controlled, parallel, 23-center, 6-week acute phase efficacy study with variable length (≥ 1 year) definite + indefinite double-blind extensions; schizophrenic patients (N=335, approx. 65/group); olanzapine dose (Olz-L, 5.0 ± 2.5 mg/day; Olz-M, 10.0 ± 2.5 mg/day; Olz-H, 15.0 ± 2.5 mg/day, po), haloperidol dose (15.0 ± 5.0 mg divided dose, twice daily, po)
F1D-MC-HGAP	Double-blind, placebo-controlled, parallel, 12-center, 6-week acute phase efficacy study; schizophrenic patients (N=152, approx. 50/group); olanzapine dose (1.0 or 10.0 mg/day, po)
F1D-MC-HGAO	Double-blind, placebo-controlled, parallel, 28-center, 8-week acute phase efficacy study; patients with primary degenerative dementia of the Alzheimer's type with psychotic symptoms (N=238); olanzapine dose (1.0-8.0 mg/day, po)

(continued)

Table 5.1.1.1 Table of All Studies (continued)

Active-Controlled Studies

F1D-EW-E003	Double-blind, active-controlled, parallel, 50-center, 6-week acute phase efficacy study with variable length (≥ 1 year) definite + indefinite double-blind extensions; schizophrenic patients (N=431, approx. 86/group); olanzapine dose (1.0 mg; Olz-L, 5.0 ± 2.5 mg/day; Olz-M, 10.0 ± 2.5 mg/day; Olz-H, 15.0 ± 2.5 mg/day, po), haloperidol dose (15.0 ± 5.0 mg/day, po)
F1D-MC-HGAJ	Double-blind, active-controlled, parallel, 186-center, 6-week acute phase efficacy study with indefinite double-blind extension; schizophrenic, schizophreniform disorder, or schizoaffective disorder patients (N=1996); olanzapine dose (5.0, 10.0, 15.0, or 20.0 mg/day, po), haloperidol dose (5.0, 10.0, 15.0, or 20.0 mg/day, po), randomization ratio 2:1 (olanzapine:haloperidol)
F1D-MC-HGBA	Double-blind, active-controlled, parallel, single-center, 8-week efficacy study; therapy-refractive schizophrenic patients (N=14); olanzapine dose (25.0 mg/day, po), chlorpromazine dose (1200 mg/day, po)
F1D-MC-HGBJ	Double-blind, active-controlled, parallel, 5-center efficacy study; schizophrenic patients (none enrolled as of 14 February 1995); olanzapine dose (5.0-20.0 mg/day, po), perphenazine dose (8.0-32.0 mg/day, po)

Uncontrolled Studies

--No Comparator

F1D-EW-E001	Open-label, uncontrolled, dose-ranging, single-center, 4-week efficacy study with 2-week extension; schizophrenic or schizophreniform disorder patients (N=10); olanzapine dose (5.0-30.0 mg/day, po)
F1D-EW-E004	Open-label, uncontrolled, dose-ranging, 4-center, 6-week efficacy study with 20-week extension; schizophrenic or schizophreniform disorder patients (N=9); olanzapine dose (5.0-15.0 mg/day, po, acute phase; 2.5-5.0 mg/day, po, extension phase)
F1D-EW-E005	Open-label, uncontrolled, dose-ranging, 2-center, 6-week efficacy study with 20-week extension; schizophrenic patients (N=9); olanzapine dose (10.0-15.0 mg/day, po, acute phase; 1.0-10.0 mg/day, po, extension phase)
F1D-EW-E010	Open-label, uncontrolled, dose-ranging, 2-center, 6-week efficacy study; schizophrenic or schizophreniform disorder patients (N=4); olanzapine dose (1.0-7.5 mg/day, po)

(continued)

Table 5.1.1.1 Table of All Studies (continued)

Uncontrolled Studies (continued)

--No Comparator (concluded)

F1D-JE-2001	Open-label, uncontrolled, 30-center, 8-week efficacy study with open-label extension; schizophrenic patients (N=81); olanzapine dose (1.0-12.5 mg/day, po)
F1D-JE-202E	Open-label, uncontrolled, 67-center, 5-week dose-finding efficacy study with 3-week maintenance period; schizophrenic patients (N=131); olanzapine dose (2.5-15.0 mg/day, po)
F1D-JE-203E, ext of 202E	Open-label, uncontrolled, 67-center, 2-year efficacy study; schizophrenic patients (N=61); olanzapine dose (2.5-15.0 mg/day, po)
F1D-JE-204E	Open-label, uncontrolled, 6-center, 6-month efficacy study; treatment-resistant schizophrenic patients (N=8); olanzapine dose (5.0-17.5 mg/day, po)
F1D-JE-208E, ext of 204E	Open-label, uncontrolled, 6-center, 12-month efficacy study; treatment-resistant schizophrenic patients (N=1); olanzapine dose (2.5-20.0 mg/day, po)
F1D-MC-HGBB	Open-label, uncontrolled, single-center, 2-year efficacy study; schizophrenic patients (N=3); olanzapine dose (5.0-20.0 mg/day, po)
F1D-MC-HGBI	Open-label, uncontrolled, single-center, 2-year efficacy study; first break and refractory schizophrenic patients (N=2); olanzapine dose (5.0-20.0 mg/day, po)
F1D-MC-HGBT	Open-label, uncontrolled, multicenter, 1-year efficacy study; patients with idiopathic Parkinson's disease, substance-induced psychotic disorder, or substance-induced delirium (N=5); olanzapine dose (1.0-15.0 mg/day, po)
F1D-MC-HGBX	Open-label, uncontrolled, single-center, 2-year safety study; psychotic patients (N=1); olanzapine dose (5.0-20.0 mg/day, po)
F1D-MC-HGCA	Open-label, uncontrolled, single-center, 2-year safety study; psychotic patients (N=1); olanzapine dose (5.0-20.0 mg/day, po)

--With Comparator

F1D-EW-E006	Open-label, active-controlled, 3-center, parallel, efficacy study; schizophrenic or schizophreniform disorder patients (N=9); olanzapine dose (5.0-15.0 mg/day, po), haloperidol dose (10.0-20.0 mg/day, po)

(continued)

Table 5.1.1.1 Table of All Studies (concluded)

Uncontrolled Studies (concluded)

--Open-Label Extension

F1D-EW-E00[illegible] OL	Open-label extension, uncontrolled, 6-center, indefinite extension phase of E003 efficacy study; schizophrenic patients responding to therapy in E003 double-blind phase (N=11); olanzapine dose (5.0, 10.0, 15.0, or 20.0 mg/day, po)
F1D-MC-HGAD-OL	Open-label extension, uncontrolled, 10-center, indefinite extension phase of HGAD efficacy study; schizophrenic patients responding to therapy in HGAD double-blind phase (N=16); olanzapine dose (5.0, 10.0, 15.0, or 20.0 mg/day, po)
F1D-MC-HGAJ-OL	Open-label extension, uncontrolled, 132-center, indefinite extension phase of HGAJ efficacy study; schizophrenic patients nonresponsive to therapy in HGAJ Study Period II or olanzapine responders completing HGAJ Study Period III (N=600); olanzapine dose (5.0, 10.0, 15.0, or 20.0 mg/day, po)
F1D-MC-HGAO-OL	Open-label extension, uncontrolled, 28-center, 14-week extension phase of HGAO efficacy study; patients with primary degenerative dementia of the Alzheimer's type with psychotic symptoms, completion of _4-week acute phase or nonresponders at Visits 7-9 in HGAO (N=189); olanzapine dose (1.0, 2.0, 3.0, 4.0, or 5.0 mg/day, po)
F1D-MC-HGAP-OL	Open-label extension, uncontrolled, 12-center, indefinite extension phase of HGAP efficacy study; schizophrenic patients completing _3 weeks of double-blind therapy (nonresponders) or completing _5 weeks of double-blind therapy (N=124); olanzapine dose (1.0, 5.0, 10.0, 15.0, or 20.0 mg/day, po)[b]

Abbreviation: N = number of subjects/patients enrolled (assigned to receive study medication).

[a] These studies (F1D-EW-E007 and F1D-EW-E008) were excluded from consideration in the Integrated Summary of Safety because they were bioequivalence studies comparing two formulations of haloperidol.

[b] The original protocol specified a dose of 1.0 to 15.0 mg/day; the protocol was amended to specify a dose of 5.0, 10.0, 15.0, or 20.0 mg/day. Some patients received a dose of 1.0 mg/day before the protocol was amended.

Appendix 7.2.1

Table 7.2.1.1 Investigators and sites in study HGAP

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S.G. Dott, M.D. University of Texas Medical Branch	UTMB Department of Psychiatry 1014 Texas Avenue 1.200 Graves Building Galveston, TX 77555-0429
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A.I. Green, M.D. Massachusetts Mental Health Center	74 Fenwood Boston, MA 02115
R.H. Levine, M.D. Private Practice	1236 Park Avenue New York, NY 10128
A.Z. Safferman, M.D. Hillside Hospital	P.O. Box 38 Glen Oaks, NY 11004
G. Pfister, Pharm. D. St. Alexius Medical Center	900 East Broadway Bismark, ND 58502
N.R. Schooler, Ph.D. R.W. Baker, M.D. Western Psychiatric Institute	3811 O'Hara Street Pittsburgh, PA 15213
J.G. Small, M.D. Larue Carter Hospital	1315 W 10th St. Indianapolis, IN 46202-2885
S.M. Stahl, M.D., Ph.D. Clinical Neuroscience Research Center	8899 University Center Lane Suite 130 San Diego, CA 92122
M.R. Thomas, M.D. University of Colorado Health Sciences Center	University North Pavillion 4455 East 12th Avenue Denver CO 80220

Table 7.2.1.2 Inclusion and Exclusion Criteria for HGAP

Inclusion criteria:
a) Male and female patients, between 18 and 65 years of age.
b) Female patients of childbearing potential must have been using medically accepted means of contraception.
c) Patients who met the diagnostic criteria for schizophrenia (295.1 to 295.3, 295.9) according to the DSM-III-R . Residual Type 295.6 was excluded. Patients suffered sufficient symptoms such that the initial score (Visit 1) of severity of illness on the BPRS was at least 24 (score based on a rating scale of 0 to 6) or 42 (score based on a rating scale of 1 to 7). The severity of illness as judged on the CGI Severity scale was at least moderate (score = 4) at Visit 1..
d) Patients who had a level of understanding sufficient to communicate intelligently with the investigator, nurse, and study coordinator.
e) Patients who were reliable and who agreed to cooperate with all tests and examinations required by the protocol.
f) Patients (or a patient's authorized legal representative) who understood the nature of the study and signed an informed consent document.

Exclusion Criteria
a) Patients with schizophreniform disorder/schizoaffective disorder or psychotic disorders other than schizophrenia.
b) Female patients who were either pregnant or lactating.
c) Serious, unstable illnesses including hepatic, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic disease such that hospitalization for the disease was anticipated within 3 months or death was anticipated within 3 years.
d) Parkinson's disease.
e) Uncorrected hypothyroidism or hyperthyroidism.
f) Myasthenia gravis.
g) Narrow-angle glaucoma.
h) Chronic urinary retention and/or clinically significant prostatic hypertrophy.
i) One or more seizures without a clear and resolved etiology. The investigator was to contact the sponsor prior to entering a patient who had experienced any seizure.
j) Leukopenia or history of leukopenia without a clear and resolved etiology.
k) Current jaundice and/or elevation of total bilirubin, alanine transaminase (ALT/SGPT), aspartate transaminase (AST/SGOT), gamma-glutamyl transferase (GGT), or alkaline phosphatase to any level that exceeded the upper limit of the Lilly reference range. Positive hepatitis surface antigen (HBsAg) or positive IgM fraction of the hepatitis core antibody (anti-HBc[IgM]) was exclusionary. Positive total hepatitis core antibody (anti-HBc)

was not exclusionary.
l) History of severe allergies or multiple adverse drug reactions.
m) DSM-III-R substance (alcohol or other drugs) abuse or dependence within the past 3 months.
n) Any DSM-III-R organic mental disorder.
o) Judged clinically to be at serious suicidal risk.
p) Participation in a clinical trial of another investigational drug within 1 month (30 days) prior to study entry (Visit 1).
q) Any concomitant medication with primarily central nervous system activity, other than those specified.
r) Treatment with an injectable depot neuroleptic within 2 weeks prior to study entry (Visit 1), or within less than one of a patient's dosing intervals between depot neuroleptic injections prior to study entry. The 2-week requirement applied if the dosing interval between injections was shorter than 2 weeks.
s) Treatment with an oral neuroleptic less than 2 days (48 hours) prior to study entry (Visit 1).
t) Documented failure to show at least minimal clinical response to treatment with either:
- Three neuroleptics in three chemical classes dosed at 800 chlorpromazine equivalents per day for at least 6 weeks, or
- Clozapine dosed at 400 mg/day for at least 6 weeks.
u) Previous exposure to olanzapine.
v) Any patient who had received remoxipride within 6 months (180 days) prior to study entry (Visit 1).

Table 7.2.1.3 Schedule of Assessments Study HGAP

	Placebo		Acute Treatment						Chronic Treatment											
Visit	1	2	3	4	5	6	7	8												
Therapy Week			1	2	3	4	5	6	7	8	9	10	11	12	16-20	24	28-48	52	60fcm	Final
In/Outpatient Status	IN	IN	IN	IN	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O
Physical Exam	X																			
Psychiatric Exam	X	X	X																	
Adjust Dosage																				
EFFICACY ASSESSMENTS																				
BANSS(BPRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAFETY ASSESSMENTS:																				
Historical Diagnosis	X																			
Secondary Conditions	X																			
Disease-Related Cond	X																			
Habits (Alcohol)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AIMS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Simpson-Angus Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Barnes Akathisia Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vitals & Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X				X	X	X									X		X		X
Chest X-ray	X																			X
Clinical Laboratory Tests																				
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis Screen	X																			
Urine Drug Screen	X																			
Prolactin		X		X		X	X	X												
Pregnancy Test																				

Table 7.2.1.4 Patient Disposition
F1D-MC-HGAP Acute Phase

Reason for Discontinuation	Placebo (N=50) n (%)	Olz1.0 (N=52) n (%)	Olz10.0 (N=50) n (%)	Total (N=152) n (%)	p-Value*
Reporting Interval Complete	10 (20.0)	12 (23.1)	19 (38.0)	41 (27.0)	.094
Adverse Event	0	5 (9.6)	2 (4.0)	7 (4.6)	.066
Lack of Efficacy	37 (74.0)	32 (61.5)	28 (56.0)	97 (63.8)	.158
Lost to Follow-up	2 (4.0)	0	0	2 (1.3)	
Patient Decision	1 (2.0)	3 (5.8)	1 (2.0)	5 (3.3)	

Patients included in the reasons discontinued, Reporting Interval Complete and Lack of Efficacy, may have continued into the next reporting interval or discontinued from the study.
* Frequencies are analyzed using a Chi-Square test.

Table7.2.1.5 Patient Completion Rates
F1D-MC-HGAP Acute Phase

Treatment Group	N	n[a]	Number (%) of Patients Completing[b] Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Acute Phase
Place	50	49	50 (100.0)	47 (94.0)	44 (88.0)	42 (84.0)	14 (28.0)	10 (20.0)	10 (20.0)
Olz1	52	51	52 (100.0)	47 (90.4)	43 (82.7)	42 (80.8)	17 (32.7)	13 (25.0)	12 (23.1)
Olz10	50	49	50 (100.0)	47 (94.0)	46 (92.0)	43 (86.0)	22 (44.0)	19 (38.0)	19 (38.0)

Abbreviations: N = number of patients randomized; Olz1.0 = olanzapine 1.0 mg/day; Olz10.0 = olanzapine 10.0 mg/day.
[a] Number of patients with baseline and postbaseline Brief Psychiatric Rating Scale total score.
[b] Number of patients with a visit in the corresponding week or the number of patients designated as completing the acute phase
[c] First opportunity to discontinue the acute phase and enter the open-label phase.

Table 7.2.1.6 Patient Characteristics Study HGAP Acute Phase

Treatment Group	N	Age (yrs)		Sex [n (%)]		Race [n (%)]	
		Mean	Range	Male	Female	Caucasian	Non-Caucasian
Placebo	50	36.3	19.2-52.6	33 (66.0)	17 (34.0)	31 (62.0)	19 (38.0)
Olz1.0	52	37.8	20.0-59.8	40 (76.9)	12 (23.1)	39 (75.0)	13 (25.0)
Olz10.0	50	38.8	23.4-62.9	37 (74.0)	13 (26.0)	34 (68.0)	16 (32.0)

Abbreviations: N = number of patients randomized; Olz1.0 = olanzapine 1.0 mg/day; Olz10.0 = olanzapine 10.0 mg/day.

Table 7.2.1.7 Concomitant medications allowed and not allowed in HGAP

Concomitant Medication	PRN	Chronic
Amantadine	N	N
Analgesics (nonnarcotic)	Y	Ya
Anorexics	N	N
Antacids	Y	N
Anti-inflammatory drugs (nonsteroidal)	Y	Ya
Antianginal agents	Y	Ya
Antiarrhythmics	N	N
Antiasthma agents (except steroids b)	Y	Ya
Antibiotics (except erythromycin and other macrolides b and chloramphenicol b)	Y	Ya
Anticoagulants	N	N
Anticonvulsants	N	N
Antidepressants	N	N
Antidiarrheal preparations	Y	N
Antiemetics	N	N
Antihistamines (except diphenhydramine b)	Yc	Yac
Antihypertensives d,e	N	Ya
Benzodiazepines (lorazepam only)	Yf	Yf
Calcium channel blockers	N	Ya
Colchichine	Y	Y
Cough/Cold preparations (except those containing diphenhydramine b)	Y	N
Diuretics	N	Ya
H2 blockers (except cimetidine b)	N	Ya
Hormones	N	Ya
Insulin	Y	Y
Laxatives	Y	Ya
Lithium	N	N
Oral hypoglycemic agents	Y	Y
Other psychotropic drugs	N	N
Psychostimulants	N	N
Steroids	N	N
Tryptophan	N	N

a If being taken before admission to the study
b These specific drugs are exclusionary and may not be used during the study
c Antihistamines are not to be used for sedation
d Clonidine, guanabenz, guanfacine, methyldopa, reserpine, guanethidine, guanadrel, rauwolscine, and betanidine should not be used.
e Beta blockers are not to be used to treat angina
f Lorazepam may be used as indicated in the concomitant medications section in 7.2.1. Other benzodiazepines are not to be used.

Table 7.2.1.8 BPRS Total Score Visitwise Change from Baseline (LOCF) F1D-MC-HGAP Acute Phase

	Week													
Treatment	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Placebo	49	36 78	49	-2.39	49	-2 86	49	-2.47	49	-2.37	49	-0.94	49	-0.22
Olz1 0	51	39 57	51	-2.86	51	-3 06	51	-2.75	51	-2.66	51	-1.49	51	-2.02
Olz10 0	49	37 43	49	-3.49	49	-7 45	49	-7.16	49	-7.31	49	-6.90	49	-7.73
	2-Sided p-Value for Pairwise Comparison													
Olz1 0 vs Placebo				.960		.991		.960		.804		.805		.444
Olz10 0 vs Placebo				.694		108		.163		.151		.054		.014
Olz10 0 vs Olz1 0				652		.104		.142		.089		.085		.078

Table 7.2.1.9 BPRS Total Score Visitwise Change from Baseline (OC)
F1D-MC-HGAP Acute Phase

Treatment	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Placebo	49	36.78	49	-2.39	45	-2.82	44	-2.34	42	-2.12	14	-8.36	9	-10.78
Olz1.0	51	39.57	51	-2.86	46	-3.74	43	-3.63	42	-2.83	17	-7.76	13	-13.08
Olz10.0	49	37.43	49	-3.49	47	-8.11	43	-7.07	42	-7.48	22	-12.59	19	-15.58
						2-Sided p-Value for Pairwise Comparison								
Olz1.0 vs. Placebo				.781		.555		.422		.505		.858		.670
Olz10.0 vs. Placebo				.585		.015		.051		.019		.159		.250
Olz10.0 vs. Olz1.0				.785		.063		.252		.093		.206		.468

Table 7.2.1.10. PANSS Total Score Visitwise Change from Baseline (LOCF)
F1D-MC-HGAP Acute Phase

Treatment	Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Placebo	49	95.63	49	-2.22	49	-1.86	49	-0.84	49	-0.12	49	2.18	49	2.80
Olz1.0	51	100.69	51	-3.82	51	-2.71	51	-3.14	51	-2.04	51	-1.02	51	-1.88
Olz10.0	49	98.31	49	-6.22	49	-12.10	49	-11.24	49	-11.88	49	-11.90	49	-12.31
	2-Sided p-Value for Pairwise Comparison													
Olz1.0 vs. Placebo				.604		.754		.644		.607		.343		.192
Olz10.0 vs. Placebo				.233		.016		.038		.018		.003		.002
Olz10.0 vs. Olz1.0				.333		.032		.096		.057		.037		.051

Table 7.2.1.11 PANSS Total Score Visitwise Change from Baseline (OC)
F1D-MC-HGAP Acute Phase

Treatment	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Placebo	49	95.63	49	-2.22	45	-1.69	44	-0.45	42	0.48	14	-10.43	9	-18.44
Olz1.0	51	100.69	51	-3.82	46	-3.85	43	-4.67	42	-3.38	17	-11.06	13	-20.00
Olz10.0	49	98.31	49	-6.22	47	-13.43	43	-11.63	42	-12.95	22	-22.55	19	-26.00
						2-Sided p-Value for Pairwise Comparison								
Olz1.0 vs. Placebo				.578		.434		.200		.216		.716		.955
Olz10.0 vs. Placebo				.200		.002		.007		<.001		.065		.384
Olz10.0 vs. Olz1.0				.458		.016		.150		.030		.128		.398

Table 7.2.1.12 BPRS Positive Score Visitwise Change from Baseline (LOCF)
F1D-MC-HGAP Acute Phase

Treatment	Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Placebo	49	12.31	49	-0.82	49	-0.88	49	-0.73	49	-0.63	49	-0.24	49	-0.02
Olz1.0	51	13.47	51	-1.06	51	-1.31	51	-1.16	51	-1.04	51	-0.71	51	-0.90
Olz10.0	49	12.88	49	-1.51	49	-2.20	49	-2.55	49	-2.92	49	-2.59	49	-2.92
	2-Sided p-Value for Pairwise Comparison													
Olz1.0 vs. Placebo				.706		.480		.441		.425		.371		.131
Olz10.0 vs. Placebo				.472		.274		.079		.017		.018		.003
Olz10.0 vs. Olz1.0				.721		.682		.304		.098		.125		.109

Table 7.2.1.13 BPRS Positive Score Visitwise Change from Baseline (OC)
F1D-MC-HGAP Acute Phase

Treatment	Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Placebo	49	12.31	49	-0.82	45	-0.82	44	-0.66	42	-0.52	14	-1.64	9	-2.89
Olz1.0	51	13.47	51	-1.06	46	-1.43	43	-1.37	42	-1.31	17	-1.94	13	-4.31
Olz10.0	49	12.88	49	-1.51	47	-2.36	43	-2.56	42	-3.05	22	-4.55	19	-5.47
	2-Sided p-Value for Pairwise Comparison													
Olz1.0 vs. Placebo				.658		.311		.209		.156		.798		.599
Olz10.0 vs. Placebo				.316		.051		.013		<.001		.045		.173
Olz10.0 vs. Olz1.0				.569		.349		.218		.051		.071		.401

Table 7.2.1.14. PANSS Negative Score Visitwise Change from Baseline (LOCF) F1D-MC-HGAP Acute Phase

Treatment	Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Placebo	49	23 92	49	0.22	49	0.24	49	0.31	49	0.82	49	1.06	49	1.04
Olz1 0	51	25 14	51	-1 08	51	-0 04	51	-0.39	51	0.12	51	-0.02	51	0.04
Olz10 0	49	26 39	49	-2.10	49	-3.33	49	-2.76	49	-2.86	49	-3.14	49	-2.82
	2-Sided p-Value for Pairwise Comparison													
Olz1 0 vs. Placebo				.324		.733		.780		.595		.364		.411
Olz10 0 vs. Placebo				.029		.003		.038		.010		.004		.007
Olz10 0 vs Oiz1 0				.209		.007		.067		.035		.037		.050

Table 7.2.1.15 PANSS Negative Score Visitwise Change from Baseline (OC) F1D-MC-HGAP Acute Phase

Treatment	Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Placebo	49	23.92	49	0.22	45	0.51	44	0.61	42	1.21	14	-3.14	9	-5.89
Olz1.0	51	25.14	51	-1.08	46	-0.33	43	-0.63	42	-0.05	17	-2.88	13	-3.46
Olz10.0	49	26.39	49	-2.10	47	-3.64	43	-3.07	42	-3.50	22	-6.18	19	-6.42
	2-Sided p-Value for Pairwise Comparison													
Olz1.0 vs Placebo				.171		.323		.271		.268		.785		.368
Olz10.0 vs Placebo				.019		<.001		.004		<.001		.120		.632
Olz10.0 vs Olz1.0				.309		.005		.068		.007		.189		.132

Table 7.2.1.17 CGI Severity Score Visitwise Change for Baseline (LOCF)
F1D-MC-HGAP Acute Phase

Treatment	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
							Week							
Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Placebo	49	5.00	49	-0.31	49	-0.27	49	-0.29	49	-0.18	49	-0.12	49	-0.12
Olz1.0	51	5.10	51	-0.08	51	-0.04	51	-0.02	51	0.06	51	0.08	51	0.08
Olz10.0	49	4.94	49	-0.18	49	-0.53	49	-0.57	49	-0.59	49	-0.53	49	-0.63
							2-Sided p-Value for Pairwise Comparison							
Olz1.0 vs. Placebo				.112		.279		.183		.228		.399		.439
Olz10.0 vs. Placebo				.365		.181		.183		.095		.106		.036
Olz10.0 vs. Olz1.0				.502		.016		.008		.004		.014		.004

Table 7.2.1.18. CGI Severity Score Visitwise Change from Baseline (OC) F1D-MC-HGAP Acute Phase

Treatment	Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Placebo	49	5.00	49	-0.31	46	-0.30	44	-0.34	42	-0.19	14	-0.64	10	-1.30
Olz1.0	51	5.10	51	-0.08	46	-0.09	43	-0.12	42	-0.02	16	-0.63	13	-0.85
Olz10.0	49	4.94	49	-0.18	47	-0.57	44	-0.57	42	-0.60	22	-1.18	19	-1.47
	2-Sided p-Value for Pairwise Comparison													
Olz1.0 vs. Placebo				.090		.236		.320		.586		.796		.522
Olz10.0 vs. Placebo				.263		.224		.247		.047		.278		.775
Olz10.0 vs. Olz1.0				.570		.017		.034		.013		.411		.314

Appendix 7.2.2
Table 7.2.2.1 List of Investigators and Sites in Study HGAD

Investigator and Site	Address
NC Andreasen, M.D., Ph.D. PJ Perry, M.D. University of Iowa	Department of Psychiatry 200 Hawkins Drive University of Iowa Hospitals and Clinics Iowa City, Iowa 52242
RL Borison, M.D. VA Medical Center	Psychiatry Services 116A-D Augusta, GA 30910
JS Carmen, M.D. Carmen Research	4000 Cumberland Parkway Bldg. 100, Suite A Atlanta, GA 30339
LF Fabre, Jr., M.D., Ph.D. Research Testing Inc.	5503 Crawford Street Houston, TX 77004
WE Fann, M.D. VAMC	Department of Psychiatry 116A 2002 Holcombe Blvd Rm 6C-316 Houston, TX 77030
KS Gujavarty, M.D. Nassau County Medical Center	2201 Hempstead Turnpike East Meadow NY 11554
J Iqbal, M.D. Montifiore Medical Center	Division of Psychiatry 111East 210th Street Bronx, NY 10467
SP James, M.D. Biologicare	16960 Bastanchury Road Suite E Yorba Linda, CA 92686
A Labelle, M.D. Royal Ottowa Hospital	1145 Carling Avenue Ottowa, ON K1Z7K4
RP Landbloom, M.D. St. Paul-Ramsey Medical Center	Department os Psychiatry 640 Jackson Street St. Paul, MN 55101
JB Lohr, M.D. VAMC SanDiego	Psychiatry Service 116A 3350 La Jolla Village Dr. San Diego, CA 92161
GW Macewan, M.D. R Ancill, M.D. St Vincent's Hospital	749 West 33rd Avenue Vancouver, Columbia CA V5Z2K4
H Meltzer, M.D. University Hospital of Cleveland	Hanna Pavillion B-68 2040 Abington Rd Cleveland, OH 44106

CB Nemeroff, M.D., Ph.D. Emory University	The Emory Clinic 1701 Uppergate Drive, NE Atlanta, GA 30322
SG Potkin, M.D. University of California-Irvine	Department of Psychiatry and Human Behavior 101 City Drive South Route 88 Irvine, CA 92668
PP Roy-Byrne, M.D. Harborview Medical Cntr ZA-15	325 9th Ave Seattle, WA 98104
ZA Sharif, M.D. Schizophrenia Research Center	Bldg 40 11th Floor 80-45 Winchester Boulevard Queens Village, NY 11427
GM Simpson, M.D. Medical College of Pennsyvlvania/EPPI	3200 Henry Avenue Philadelphia, PA 19129
JG Small, M.D. LaRue Carter Hospital	1315 W 10th Street Indianapolis, IN 46202-2885
PE Stokes, M.D. Cornell University Medical College	New York Hospitalente Psychobiology/Endcrine Dept. 21 Bloomingdale Road White Plains, NY 10605
JE True, M.D. L Erechefsky, Pharm. D. University of Texas Health Sciences Center	7703 Floyd Curl Drive San Antonio, TX 78223-0991
VB Tuason, M.D. VAMC Albequeque, NM	2100 Ridgecrest Drive S.E. Albequeque, NM 87108
R Williams, M.D. Psychiatric Day Hospital	Calgary General Hospital 841 Center Ave East T2E0A1 Calgary, Alberta CA

Table 7.2.2.2 Inclusion/exclusion criteria for the placebo lead-in period for study HGAD.

Inclusion criteria

a) Male and female patients, between 18 and 65 years of age.

b) Female patients of childbearing potential must have been using a medically accepted means of contraception. Note: Females of childbearing potential were allowed to be randomized by an amendment to HGAD dated 5 February 1993. Canada did not allow women of childbearing potential to enter the study.

c) Patients who met the diagnostic criteria for schizophrenia (295.1 to 295.3, 295.9) according to the DSM-III-R. Patients were experiencing an acute exacerbation of their illness (residual type 295.6 excluded). Initial score of severity of illness on the BPRS had to be at least 24 (score based on a rating scale of 0 to 6). The CGI Severity scale had to be at least moderate (score≥4).

d) Patients who had an educational level and degree of understanding such that they were able to communicate intelligently with the investigator and nurse.

e) Patients who were thought by the investigator to be reliable. They agreed to cooperate with all tests and examinations required by the protocol.

f) Patients who signed an informed consent document.

Exclusion Criteria

a) Patients with schizophreniform disorder.

b) Pregnant or lactating women.

c) Patients with serious illnesses, including hepatic, renal, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, or hematologic disease; parkinsonism, hypothyroidism or hyperthyroidism; myasthenia gravis.

d) Patients with a history of leukopenia, without a clear etiology.

e) Patients with a history of glaucoma.

f) Patients with a history of chronic urinary retention and prostatic hypertrophy.

g) Patients with jaundice or elevation of total bilirubin, alanine transaminase (ALT/SGPT), aspartate transaminase (AST/SGOT), GGT, or alkaline phosphatase to any value that exceeded twice the upper limit of the reference range. Positive hepatitis surface antigen (HbsAg) or positive IgM fraction of the hepatitis core antibody (anti-HBc[IgM]) was exclusionary. Positive total hepatitis core antibody (anti-HBc) was not exclusionary.

Thus, using SciCor's reference ranges, a patient was not to be randomized if entry laboratory values were:

AST >90 U/L
ALT >90 U/L
GGT >100 U/L
Alkaline phosphatase >200 U/L
Total bilirubin >40 mmol/L.

h) Patients with organic brain disease or history of seizures.

i) Patients with a history of severe allergies or multiple adverse drug reactions.

j) Patients taking any other concomitant medication with primarily central nervous system activity other than those allowed.

k) Patients who were known to be clear nonresponders to neuroleptic treatment from psychiatric history.

l) Patients receiving treatment with depot neuroleptic preparation within 6 weeks or with an oral neuroleptic within a minimum of 2 days (48 hours) prior to the start of the study (Visit 1).

m) Patients with drug or alcohol dependence or a history of drug abuse, including alcohol, within the past 3 months.

n) Patients who had participated in a clinical trial of another drug within 1 month prior to study entry.

o) Patients with previous exposure to olanzapine.

Table 7.2.2.4 Schedule of Assessments Study HGAD

	Placebo		Acute Treatment							Chronic Treatment								
Visit	1	2	3	4	5	6	7	8	9									
Therapy Week			1	1	2	3	4	5	6	8	10	12	16-22	24	26-34	36	38-50	52
In/Outpatient Status	IN	IN	IN	IN	IN	I/O	I/O	I/O	I/O	I/O	OUT	OUT	OUT	OUT	OUT	OUT	OUT	OUT
Physical Exam	X																	X
Psychiatric Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust Dosage		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EFFICACY ASSESSMENTS																		
HDRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAMS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life		X													X			X
CGI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAFETY ASSESSMENTS																		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AIMS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Simpson-Angus Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Barnes Akathisia Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vitals & Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X								X					X				X
Eye Exam		X							X					X				X
Chest X-ray	X																	X
Clinical Laboratory Tests																		
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy	X						X			X		X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis Screen	X																	
Urine Drug Screen	X																	X
Prolactin		X			X		X		X			X		X		X		X

Table 7.2.2.5 **Patient Disposition**
F1D-MC-HGAD Acute Phase

Reason for Discontinuation	Placebo (N=68) n (%)	Olz-L (N=65) n (%)	Olz-M (N=64) n (%)	Olz-H (N=69) n (%)	Hal (N=69) n (%)	Total (N=335) n (%)	p-Value*
Reporting Interval Complete	22 (32.4)	27 (41.5)	26 (40.6)	34 (49.3)	30 (43.5)	139 (41.5)	.380
Adverse Event	7 (10.3)	5 (7.7)	1 (1.6)	4 (5.8)	6 (8.7)	23 (6.9)	.329
Lack of Efficacy	32 (47.1)	22 (33.8)	24 (37.5)	18 (26.1)	19 (27.5)	115 (34.3)	.070
Lost to Follow-up	1 (1.5)	2 (3.1)	3 (4.7)	1 (1.4)	5 (7.2)	12 (3.6)	.315
Patient Decision	2 (2.9)	7 (10.8)	7 (10.9)	7 (10.1)	7 (10.1)	30 (9.0)	.430
Criteria not met / Compliance	4 (5.9)	2 (3.1)	3 (4.7)	5 (7.2)	2 (2.9)	16 (4.8)	.725

Patients included in the reason discontinued, Reporting Interval Complete, may have continued into the next reporting interval or discontinued from the study.
RMP.F1DP.JCLLIB(SPATDAD)
RMP.F1DP.SASMACRO(SPATDA)
* Frequencies are analyzed using a Chi-Square test.
XRDS0001

Table 7.2.2.6 Patient Completion Rates F1D-MC-HGAD Acute Phase

Treatment Group	N	n[a]	Number (%) of Patients Completing[b]						
			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Acute Phase
Placebo	68	62	60 (88.2)	55 (80.9)	43 (63.2)	35 (51.5)	30 (44.1)	25 (36.8)	22 (32.4)
Olz-L	65	64	62 (95.4)	55 (84.6)	45 (69.2)	37 (56.9)	35 (53.8)	29 (44.6)	27 (41.5)
Olz-M	64	62	63 (98.4)	61 (95.3)	54 (84.4)	44 (68.8)	31 (48.4)	28 (43.8)	26 (40.6)
Olz-H	69	65	60 (87.0)	58 (84.1)	51 (73.9)	48 (69.6)	42 (60.9)	37 (53.6)	34 (49.3)
Hal	69	68	65 (94.2)	62 (89.9)	59 (85.5)	49 (71.0)	37 (53.6)	31 (44.9)	30 (43.5)

Abbreviations: N = number of patients randomized; Plac = placebo; Olz-L = olanzapine 5.0 ± 2.5 mg/day; Olz-M = olanzapine 10.0 ± 2.5 mg/day; Olz-H = olanzapine 15.0 ± 2.5 mg/day; Hal = haloperidol 15.0 ± 5.0 mg/day.

[a] Number of patients with baseline and postbaseline Brief Psychiatric Rating Scale total score.

[b] Number of patients with a visit in the corresponding week or the number of patients designated as completing the acute phase.

Table 7.2.2.7 Patient Characteristics F1D-MC-HGAD Acute Phase

Treatment Group	N	Age (yrs)		Sex [n (%)]		Race [n (%)]	
		Mean	Range	Male	Female	Caucasian	Non-Caucasian
Placebo	68	35.0	18.2-54.0	62 (91.2)	6 (8.8)	48 (70.6)	20 (29.4)
Olz-L	65	35.7	18.1-60.4	60 (92.3)	5 (7.7)	42 (64.6)	23 (35.4)
Olz-M	64	37.3	18.0-62.9	56 (87.5)	8 (12.5)	46 (71.9)	18 (28.1)
Olz-H	69	35.9	18.8-60.0	54 (78.3)	15 (21.7)	54 (78.3)	15 (21.7)
Hal	69	36.1	18.1-64.7	62 (89.9)	7 (10.1)	40 (58.0)	29 (42.0)

Abbreviations: N = number of patients randomized; Olz-L = olanzapine 5.0 ± 2.5 mg/day; Olz-M = olanzapine 10.0 ± 2.5 mg/day; Olz-H = olanzapine 15.0 ± 2.5 mg/day; Hal = haloperidol 15.0 ± 5.0 mg/day.

Table 7.2.2.8 Concomitant medications allowed and not allowed in HGAD

Concomitant Medication	PRN	Chronic
Allopurinol	N	N
Analgesics (nonnarcotic)	Y	N
Anorexics	N	N
Antacids	Y	N
Anti-inflammatory drugs (nonsteroidal)	Y	N
Antianginal agents	Y	Ya
Antiarrhythmics	N	N
Antiasthma agents	Y	Ya
Antibiotics (except erythromycins)	Y	Ya
Anticoagulants	N	N
Antidepressants	N	N
Antidiarrheal preparations	Y	N
Antihistamines (terfenadine only)	Y	N
Antihypertensives b	N	Ya
Antinauseants	N	N
Colchicine	Y	Y
Cough/Cold preparations (decongestants only)	Y	N
Diuretics	N	Ya
H2 blockers (except cimetidine b)	N	Ya
Hormones	N	Ya
Insulin	Y	Y
Laxatives	Y	N
Oral hypoglycemic agents	Y	Y
Other psychotropic drugs	N	N
Steroids	N	N
Tryptophan	N	N

a If being taken before admission to the study.
b Propranolol, Metoprolol, Acebutolol, Nifedipine, Clonidine, and Aldomet would not have been used

Table 7.2.2.9 Mean Dose by Visit HGAD Acute Phase

Treatment Group		Visit 3		Visit 4		Visit 5		Visit 6		Visit 7		Visit 8		Visit 9	
	N	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std
Placebo	68	0.0	--	0.0	--	0.0	--	0.0	--	0.0	--	0.0	--	0.0	--
Olz-L	65	5.0	0.3	6.0	1.4	6.3	1.4	6.7	1.4	6.6	1.5	6.9	1.3	7.1	1.2
Olz-M	64	10.0	0.2	11.1	1.4	11.6	1.4	11.6	1.5	11.7	1.5	11.6	1.5	11.6	1.4
Olz-H	69	15.0	0.0	15.6	1.4	16.0	1.6	16.3	1.7	16.4	1.7	16.3	1.7	16.1	1.7
Hal	69	14.6	1.1	15.9	3.4	16.5	3.8	16.8	3.8	16.5	4.2	16.2	4.3	16.3	4.1

~~Table 7.2.2.10 BPRS Total Score Visitwise Change from Baseline (LOCF) HGAD Acute Phase~~

Week

Treatme Groups	Baseline n	Baseline Mean	Week 0.5 n	Week 0.5 Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
Placebo	62	39 69	60	-4 02	62	-2.37	62	-2 60	62	-2 94	62	-2.69	62	-3.45	62	-3.69
Olz-L	64	40 70	63	-3.11	64	-4 64	64	-6.23	64	-6.72	64	-6.83	64	-6.08	64	-6.41
Olz-M	62	42.84	62	-5.18	62	-7.79	62	-9.26	62	-9.87	62	-10.82	62	-11.23	62	-12.21
Olz-H	65	42.62	65	-3.95	65	-9.52	65	-11.57	65	-12.38	65	-13.49	65	-13.71	65	-15.18
Hal	68	41.79	68	-7.38	68	-10.04	68	-12.91	68	-13.09	68	-12.93	68	-12.69	68	-12.81

	2-Sided p-Value for Pairwise Comparison						
Olz-L vs Placebo	--	.090	.031	.070	.069	.121	.118
Olz-M vs Placebo	.177	.021	.017	.020	.004	.004	.003
Olz-H vs Placebo	.420	.002	.001	<.001	<.001	<.001	<.001
Hal vs Placebo	.179	.003	<.001	<.001	<.001	.002	.004
Olz-L vs Hal	--	.223	.104	.122	.135	.121	.212
Olz-M vs Hal	.989	.565	.177	.319	.696	.845	.824
Olz-H vs Hal	.573	.802	.531	.957	.863	.729	.306

Table 7.2.2.11. BPRS Total Score Visitwise Change from Baseline (OC) HGAD Acute Phase

Treatme Groups	Baseline n	Baseline Mean	Week 0.5 n	Week 0.5 Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
								Week								
Placebo	62	39.69	60	-4.02	57	-3.18	52	-5.50	41	-10.56	34	-11.26	29	-14.14	24	-15.38
Olz-L	64	40.70	63	-3.11	59	-5.76	52	-9.38	44	-11.32	36	-14.39	34	-13.97	28	-15.86
Olz-M	62	42.84	62	-5.18	61	-8.05	58	-10.22	53	-11.77	42	-16.71	30	-21.10	27	-23.63
Olz-H	65	42.62	65	-3.95	60	-10.80	57	-13.56	51	-16.29	48	-18.23	40	-19.10	36	-22.72
Hal	68	41.79	66	-7.38	64	-11.23	62	-14.56	55	-15.15	48	-15.92	35	-19.26	30	-17.97
								2-Sided p-Value for Pairwise Comparison								
Olz-L vs Placebo				.807		.197		.086		.808		.242		.981		.820
Olz-M vs Placebo				.283		.016		.031		.678		.015		.014		.008
Olz-H vs Placebo				.808		<.001		<.001		.019		.003		.023		.002
Hal vs Placebo				.047		<.001		<.001		.036		.077		.051		.209
Olz-L vs Hal				.024		.014		.023		.063		.588		.041		.288
Olz-M vs Hal				.366		.185		.056		.086		.428		.541		.140
Olz-H vs Hal				.076		.074		.643		.757		.187		.782		.049

Table 7.2.2.15. SANS Summary Score Visitwise Change from Baseline (OC) HGAD Acute Phase

Week

Treatment Groups	Baseline n	Baseline Mean	Week 0.5 n	Week 0.5 Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
Placebo	65	13.11	64	-0.23	58	-0.14	54	-1.41	42	-1.55	35	-2.29	30	-3.03	24	-3.79
Olz-L	65	14.40	65	-1.05	60	-1.62	53	-2.62	45	-2.89	37	-3.22	35	-3.29	28	-3.25
Olz-M	63	12.94	63	-0.03	63	-0.21	60	-1.05	54	-2.19	43	-3.05	30	-3.67	27	-4.33
Olz-H	65	13.42	65	-0.86	60	-2.12	57	-2.77	51	-3.04	48	-3.94	41	-4.51	36	-5.81
Hal	68	13.22	68	-1.00	64	-1.92	62	-2.34	56	-2.96	48	-2.77	35	-2.43	30	-2.27
								2-Sided p-Value for Pairwise Comparison								
Olz-L vs Placebo				.129		.029		.128		.192		.429		.812		.515
Olz-M vs Placebo				.824		.882		.581		.551		.365		.582		.673
Olz-H vs Placebo				.241		.003		.078		.131		.109		.267		.248
Hal vs Placebo				.164		.009		.204		.121		.643		.413		.141
Olz-L vs Hal				.885		.680		.757		.857		.703		.549		.402
Olz-M vs Hal				.108		.011		.061		.315		.625		.170		.053
Olz-H vs Hal				.835		.714		.593		.991		.219		.044		.005

Table 7.2.2.16 CGI Severity Score Visitwise Change from Baseline (LOCF) HGAD Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 0.5 n	Week 0.5 Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
								Week								
Placebo	66	4.88	65	-0.17	66	-0.20	66	-0.21	66	-0.26	66	-0.26	66	-0.30	66	-0.33
Olz-L	65	4.85	65	-0.14	65	-0.29	65	-0.52	65	-0.49	65	-0.51	65	-0.40	65	-0.40
Olz-M	63	5.08	63	-0.37	63	-0.57	63	-0.71	63	-0.75	63	-0.84	63	-0.90	63	-0.95
Olz-H	66	5.05	66	-0.18	66	-0.55	66	-0.86	66	-0.85	66	-0.97	66	-0.95	66	-0.98
Hal	68	4.85	68	-0.51	68	-0.72	68	-0.88	68	-0.91	68	-0.93	68	-1.00	68	-0.94
								2-Sided p-Value for Pairwise Comparison								
Olz-L vs Placebo				.581		.243		.022		.124		.168		.354		.423
Olz-M vs Placebo				.091		.042		.007		.024		.012		.006		.005
Olz-H vs Placebo				.998		.170		.009		.023		.012		.010		.014
Hal vs Placebo				.128		.018		.002		.008		.007		.003		.021
Olz-L vs Hal				.348		.248		.437		.296		.213		.043		.147
Olz-M vs Hal				.824		.794		.738		.769		.943		.863		.555
Olz-H vs Hal				.126		.309		.582		.703		.866		.648		.888

Table 7.2.2.17 CGI Severity Score Visitwise Change from Baseline (OC) HCAD Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 0.5 n	Week 0.5 Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
								Week								
Placebo	66	4.88	65	-0.17	59	-0.24	55	-0.35	42	-0.71	35	-0.80	30	-0.93	24	-1.17
Olz-L	65	4.85	65	-0.14	61	-0.33	53	-0.70	45	-0.76	37	-1.00	35	-0.89	28	-1.07
Olz-M	63	5.08	63	-0.37	63	-0.57	60	-0.77	54	-0.87	43	-1.16	30	-1.50	27	-1.70
Olz-H	66	5.05	66	-0.18	60	-0.63	57	-0.98	51	-1.02	48	-1.23	41	-1.24	36	-1.42
Hal	68	4.85	68	-0.51	64	-0.80	62	-0.98	56	-1.05	48	-1.10	35	-1.37	30	-1.27
								2-Sided p-Value for Pairwise Comparison								
Olz-L vs Placebo				.870		.495		.054		.837		.624		.735		.445
Olz-M vs Placebo				072		.016		.006		.269		.032		.002		.066
Olz-H vs Placebo				942		.010		< .001		.098		.039		.058		.261
Hal vs Placebo				.006		< 001		< .001		.060		.195		.033		.714
Olz-L vs Hal				.004		.004		.091		.093		.428		.011		.235
Olz-M vs Hal				.370		.245		.345		.419		.338		.249		.125
Olz-H vs Hal				.008		341		.953		.839		.412		.741		.421

Table 7.2.3.1 List of Investigators and Sites in Study E003

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Table 7.2.3.2 Inclusion/Exclusion Criteria Study E003

Inclusion Criteria

a) Inpatients of both sexes 18 to 65 years of age or age of legal consent.
b) Diagnostic criteria. Patients must have met the criteria for schizophrenia (295.1 to 295.3, 295.9) according to DSM-III-R. Patients had to be in an acute exacerbation of illness. Residual Type 295.6 was excluded. Initial score of severity of illness on the BPRS total score must have been at least 42 (1 to 7 scale) or at least 24 (0 to 6 scale). The severity of illness as judged by the CGI Severity scale was to be at least moderate (score 4) at Visit 1.
c) Each patient had an educational level and degree of understanding such that he/she could communicate with the investigator and nurse intelligently.
d) Patients should have been thought by the investigator to be reliable. They had to agree to cooperate with all tests and examinations required by the protocol.
e) They had to give informed consent, preferably signed. Oral consent had to be witnessed.
f) In Israel, a patient's inclusion into the study must have been approved by a psychiatrist not involved in the study.

Exclusion Criteria

Patients were excluded from the study for the following reasons:
a) Patients with the diagnosis of schizophreniform disorder.
b) Pregnant and lactating women, women of childbearing potential who intended or were likely to become pregnant and who were not using contraception.
c) Serious illness, including hepatic, renal, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, or hematologic disease; Parkinsonism; hypothyroidism and hyperthyroidism; myasthenia gravis.
d) History of leukopenia of undetermined etiology.
e) History of glaucoma.
f) History of chronic urinary retention and prostatic hypertrophy.
g) Elevation of liver enzymes: total bilirubin, alanine transaminase (ALT/SGPT), aspartate transaminase (AST/SGOT), gamma-glutamyl transferase (GGT), or alkaline phosphatase to any level that exceeded twice the study site's laboratory standard reference as the upper limit of normal; positive hepatitis surface antigen (HBsAg) and/or positive IgM fraction of the hepatitis core antibody (anti-HBc[IgM]); positive total hepatitis core antibody (HBcAb) was not exclusionary if a negative result of the IgM fraction of HBcAb was established. Criteria for Israel: Elevation of liver enzymes: total bilirubin, ALT/SGPT, AST/SGOT, GGT or alkaline phosphatase to any level that exceeded the upper limit of normal of the study site's laboratory standard reference; positive hepatitis surface antigen (HBsAg) and/or positive IgM fraction of the hepatitis core antibody (anti-HBc[IgM]); positive total hepatitis core antibody (HBcAb) was not exclusionary if a negative result of the IgM fraction of HBcAb was established.
h) Organic brain disease or history of seizures.
i) History of severe allergies or multiple adverse drug reactions.
j) Any psychotropic medication other than study drugs and concomitant medications specified.
k) Known clear nonresponders to neuroleptic treatment from past psychiatric history.
l) Treatment with a depot neuroleptic within less than one time interval between the injections, or with an oral neuroleptic within 4 to 7 days prior to the start of the active treatment.
m) Drugs or alcohol dependence and a history of drug abuse, including alcohol, within the past 3 months.
n) Participation in a clinical trial of another drug within 1 month prior to study entry.
o) Previous exposure to olanzapine.
p) An addendum in Sweden excluded patients subjected to compulsory institutional care.

Table 7.2.3.3 Schedule of Assessments Study E003

	Placebo		Acute Treatment							Chronic Treatment								
Visit	1	2	3	4	5	6	7	8	9									
Therapy Week			-5	1	2	3	4	5	6	8	10	12	16-22	24	26-34	36	38-50	52
In/Outpatient Status	IP	IP	IP	IP	IP	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O	I/O
Physical Exam	X								X									X
Psychiatric Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust Dosage			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EFFICACY ASSESSMENTS																		
BPRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PANSS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life		X								X		X		X		X		X
CGI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PCI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAFETY ASSESSMENTS																		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AIMS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Simpson-Angus Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Barnes Akathisia Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vitals & Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X								X									X
Chest X-ray	X																	
Clinical Laboratory Tests																		
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis Screen	X																	
Urine Drug Screen	X																	X
Prolactin		X			X		X		X			X		X		X		X
Hematology, Renal, Hepatic		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 7.2.3.4 Patient Disposition
F1D-EW-E003 Acute Phase

Reason for Discontinuation	Olz1.0 (N=88) n (%)	Olz-L (N=87) n (%)	Olz-M (N=86) n (%)	Olz-H (N=89) n (%)	Hal (N=81) n (%)	Total (N=431) n (%)	p-Value*
Reporting Interval Complete	48 (54.5)	48 (55.2)	53 (61.6)	55 (61.8)	43 (53.1)	247 (57.3)	.660
Satisfactory Response	1 (1.1)	2 (2.3)	2 (2.3)	3 (3.4)	0	8 (1.9)	.541
Adverse Event	10 (11.4)	14 (16.1)	6 (7.0)	8 (9.0)	12 (14.8)	50 (11.6)	.296
Lack of Efficacy	16 (18.2)	15 (17.2)	9 (10.5)	13 (14.6)	16 (19.8)	69 (16.0)	.501
Lost to Follow-up	1 (1.1)	1 (1.1)	2 (2.3)	1 (1.1)	2 (2.5)	7 (1.6)	.907
Patient Decision	8 (9.1)	4 (4.6)	7 (8.1)	8 (9.0)	6 (7.4)	33 (7.7)	.797
Criteria not met / Compliance	4 (4.5)	3 (3.4)	7 (8.1)	1 (1.1)	2 (2.5)	17 (3.9)	.167

Patients included in the reason discontinued, Reporting Interval Complete, may have continued into the next reporting interval or discontinued from the study.

* Frequencies are analyzed using a Chi-Square test.

Table 7.2.3.5. Patient Completion Rates F1D-EW-E003 Acute Phase

Treatment Group	N	n[a]	Number (%) of Patients Completing[b] Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Acute Phase
Olz1.	88	83	82 (93.2)	79 (89.8)	69 (78.4)	63 (71.6)	57 (64.8)	48 (54.5)	48 (54.5)
Olz-L	87	85	84 (96.6)	81 (93.1)	73 (83.9)	69 (79.3)	59 (67.8)	50 (57.5)	48 (55.2)
Olz-	86	83	79 (91.9)	78 (90.7)	72 (83.7)	69 (80.2)	62 (72.1)	55 (64.0)	53 (61.6)
Olz-H	89	85	82 (92.1)	77 (86.5)	72 (80.9)	66 (74.2)	60 (67.4)	55 (61.8)	55 (61.8)
Hal	81	79	75 (92.5)	72 (88.9)	63 (77.8)	54 (66.7)	50 (61.7)	46 (56.8)	43 (53.1)

Abbreviations: N = number of patients randomized; Olz1.0 = olanzapine 1.0 mg/day; Olz-L = olanzapine 5.0 ± 2.5 mg/day; Olz-M = olanzapine 10.0 ± 2.5 mg/day; Olz-H = olanzapine 15.0 ± 2.5 mg/day; Hal = haloperidol 15.0 ± 5.0 mg/day.

[a] Number of patients with baseline and postbaseline Brief Psychiatric Rating Scale total score.

[b] Number of patients with a visit in the corresponding week or the number of patients designated as completing the acute phase.

Table 7.2.3.6 Patient Characteristics, F1D-EW-E003 Acute Phase

Treatment Group	N	Age (yrs) Mean	Range	Sex [n (%)] Male	Female	Race [n (%)] Caucasian	Non-Caucasian
Olz1.0	88	34.0	19.3-62.0	58 (65.9)	30 (34.1)	77 (87.5)	11 (12.5)
Olz-L	87	34.4	18.9-62.3	57 (65.5)	30 (34.5)	75 (86.2)	12 (13.8)
Olz-M	86	35.8	18.7-61.3	55 (64.0)	31 (36.0)	74 (86.0)	12 (14.0)
Olz-H	89	37.3	21.3-64.2	57 (64.0)	32 (36.0)	80 (89.9)	9 (10.1)
Hal	81	35.8	20.0-64.6	48 (59.3)	33 (40.7)	66 (81.5)	15 (18.5)

Abbreviations: N = number of patients randomized; Olz1.0 = olanzapine 1.0 mg/day;

Olz-L = olanzapine 5.0 ± 2.5 mg/day; Olz-M = olanzapine 10.0 ± 2.5 mg/day;

Olz-H = olanzapine 15.0 ± 2.5 mg/day; Hal = haloperidol 15.0 ± 5.0 mg/day.

Table 7.2.3.7 Mean Dose by Visit E003 Acute Phase (mg/day)

Treatment Group	N	Visit 3		Visit 4		Visit 5		Visit 6		Visit 7		Visit 8		Visit 9	
		Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std
Olz 1.0	88	1.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0
Olz-L	87	5.0	0.0	5.5	1.2	6.2	1.3	6.7	1.3	6.8	1.2	6.8	1.2	6.9	1.2
Olz-M	86	10.0	0.0	10.5	1.1	11.0	1.4	11.2	1.5	11.4	1.5	11.3	1.6	11.3	1.6
Olz-H	89	15.0	0.1	15.6	1.2	16.2	1.4	16.5	1.4	16.5	1.4	16.3	1.5	16.4	1.5
Hal	81	15.0	0.0	15.5	2.1	16.7	3.1	17.4	3.5	17.3	3.3	17.7	2.9	17.6	3.1

Table 7.2.3.8. BPRS Total Score Visitwise Change from Baseline (LOCF) F1D-EW-E003 Acute Phase

Treatment	Week													
	Baseline		Week 0.5		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Olz1.0	83	39.49	81	-3.21	83	-5.60	83	-7.39	83	-8.90	83	-10.22	83	-9.64	83	-10.51
Olz-L	85	40.06	84	-3.00	85	-6.42	85	-8.15	85	-10.59	85	-13.04	85	-12.41	85	-13.42
Olz-M	83	40.40	81	-3.68	82	-7.27	83	-10.34	83	-11.99	83	-12.48	83	-12.83	83	-13.83
Olz-H	85	42.31	85	-4.26	85	-6.98	85	-10.52	85	-12.41	85	-14.42	85	-15.86	85	-16.35
Hal	79	41.23	79	-3.87	79	-7.05	79	-8.34	79	-10.54	79	-11.51	79	-12.34	79	-12.44
	2-Sided p-Value for Pairwise Comparison													
Olz1.0 vs Olz-L				.629		.994		.843		.955		.784		.389		.259
Olz1.0 vs Olz-M				.603		.885		.759		.893		.631		.787		.667
Olz1.0 vs Olz-H				.885		.741		.518		.560		.411		.068		.109
Olz1.0 vs Hal				.967		.700		.977		.982		.808		.517		.898
Olz-L vs Hal				.599		.703		.867		.938		.605		.840		.322
Olz-M vs Hal				.574		.809		.738		.912		.821		.689		.768
Olz-H vs Hal				.920		.942		.503		.579		.285		.255		.145

Table 7.2.3.9 BPRS Total Score Visitwise Change from Baseline (OC) F1D-EW-E003 Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 0.5 n	Week 0.5 Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
								Week								
Olz1.0	83	39.49	81	-3.21	82	-5.67	76	-8.17	67	-11.82	60	-14.33	56	-14.61	48	-17.83
Olz-L	85	40.06	84	-3.00	84	-6.49	76	-8.75	73	-12.37	68	-16.75	57	-16.25	50	-19.52
Olz-M	83	40.40	81	3.68	78	-7.60	75	-11.21	70	-13.51	68	-14.74	61	-17.66	53	-19.32
Olz-H	85	42.31	85	-4.26	80	-7.45	73	-12.14	69	-14.64	62	-18.47	59	-21.00	55	-21.38
Hal	79	41.23	79	-3.87	73	-8.23	72	-9.76	61	-13.46	53	-15.53	47	-18.43	44	-19.30
								2-Sided p-Value for Pairwise Comparison								
Olz1.0 vs Olz-L				.802		.638		.753		.910		.448		.572		.563
Olz1.0 vs Olz-M				.722		.166		.061		.307		.749		.109		.489
Olz1.0 vs Olz-H				.377		.207		.019		.152		.095		.005		.157
Olz1.0 vs Hal				.526		.041		.248		.303		.345		.028		.350
Olz-L vs Hal				.375		.109		.398		.349		.810		.092		.695
Olz-M vs Hal				.779		.494		.483		.963		.507		.459		.769
Olz-H vs Hal				.812		.415		.234		.713		.505		.662		.675

Table 7.2.3.10 PANSS Total Score Visitwise Change from Baseline (LOCF) F1D-EW-E003 Acute Phase

Treatment Groups	Baseline		Week 0.5		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Olz1.0	83	100.86	81	-4.33	83	-8.83	83	-11.54	83	-14.40	83	-16.28	83	-15.72	83	-16.83
Olz-L	85	102.73	84	-4.82	85	-10.35	85	-12.29	85	-16.27	85	-20.40	85	-19.85	85	-21.44
Olz-M	83	102.22	81	-5.31	82	-11.61	83	-16.80	83	-19.25	83	-20.31	83	-21.08	83	-22.73
Olz-H	85	105.60	85	-6.62	85	-11.02	85	-17.07	85	-20.24	85	-23.04	85	-25.47	85	-26.67
Hal	79	105.25	79	-6.00	79	-10.95	79	-13.32	79	-17.04	79	-18.76	79	-20.09	79	-20.04
							2-Sided p-Value for Pairwise Comparison									
Olz1.0 vs Olz-L				.783		.944		.760		.744		.862		.516		.327
Olz1.0 vs Olz-M				.815		.852		.606		.824		.851		.664		.522
Olz1.0 vs Olz-H				.636		.769		.469		.562		.413		.099		.097
Olz1.0 vs Hal				.773		.805		.972		.988		.902		.561		.863
Olz-L vs Hal				.569		.858		.790		.735		.767		.954		.424
Olz-M vs Hal				.600		.950		.583		.837		.952		.867		.647
Olz-H vs Hal				.865		.973		.450		.575		.348		.302		.143

Table 7.2.3.11 PANSS Total Score Visitwise Change from Baseline (OC) F1D-EW-E003 Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 0.5 n	Week 0.5 Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
								Week								
Olz1.0	83	100.86	81	-4.33	82	-8.94	76	-12.93	67	-19.31	60	-23.65	56	-24.64	48	-29.38
Olz-L	85	102.73	84	-4.82	84	-10.42	76	-12.95	73	-18.89	68	-26.40	57	-26.02	50	-30.66
Olz-M	83	102.22	81	-5.31	78	-11.95	75	-18.19	70	-22.03	68	-24.07	61	-28.95	53	-31.62
Olz-H	85	105.60	85	-6.62	80	-11.71	73	-19.64	69	-23.70	62	-28.92	59	-33.42	55	-34.89
Hal	79	105.25	79	-6.00	73	-12.88	72	-15.65	61	-21.70	53	-25.15	47	-29.53	44	-30.80
								2-Sided p-Value for Pairwise Comparison								
Olz1.0 vs Olz-L				.823		.592		.987		.822		.652		.798		.815
Olz1.0 vs Olz-M				.627		.196		.054		330		.794		.165		.500
Olz1.0 vs Olz-H				.211		.232		.019		.182		.215		.023		.186
Olz1.0 vs Hal				.334		.055		.237		.349		.429		.069		.469
Olz-L vs Hal				451		.158		.244		.242		.706		.112		.610
Olz-M vs Hal				.628		.520		.466		1.000		.574		.583		.926
Olz-H vs Hal				.790		.454		.249		.717		.686		.739		.584

Table 7.2.3.12 BPRS Positive Score Visitwise Change from Baseline (LOCF) F1D-EW-E003 Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 0.5 n	Week 0.5 Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
								Week								
Olz1.0	83	11.98	81	-0.84	83	-1.59	83	-2.24	83	-2.81	83	-2.88	83	-2.80	83	-3.07
Olz-L	85	12.66	84	-1.08	85	-2.01	85	-2.89	85	-3.49	85	-4.20	85	-4.21	85	-4.51
Olz-M	83	12.19	81	-1.10	82	-2.30	83	-3.10	83	-3.63	83	-3.92	83	-4.16	83	-4.25
Olz-H	85	13.19	85	-1.14	85	-2.06	85	-3.44	85	-4.06	85	-4.69	85	-5.22	85	-5.32
Hal	79	12.73	79	-1.53	79	-2.63	79	-3.24	79	-3.87	79	-4.58	79	-4.82	79	-4.82
								2-Sided p-Value for Pairwise Comparison								
Olz1.0 vs Olz-L				.494		.697		.407		.582		.234		.057		.038
Olz1.0 vs Olz-M				.992		.584		.600		.897		.897		.353		.367
Olz1.0 vs Olz-H				.757		.652		.098		.176		.044		.004		.008
Olz1.0 vs Hal				.414		.286		.261		.471		.164		.022		.090
Olz-L vs Hal				.832		.490		.754		.856		.823		.669		.724
Olz-M vs Hal				.416		.602		.523		.540		.192		.150		.394
Olz-H vs Hal				.583		.507		.637		.554		.579		.637		.379

Table 7.2.3.13 BPRS Positive Score Visitwise Change from Baseline (OC) F1D-EW-E003 Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 0 5 n	Week 0 5 Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
								Week								
Olz1.0	83	11.98	81	-0.84	82	-1.61	76	-2.50	67	-3.61	60	-3.82	56	-3.96	48	-4.90
Olz-L	85	12.66	84	-1.08	84	-2.01	76	-2.92	73	-3.84	68	-5.15	57	-5.19	50	-5.92
Olz-M	83	12.19	81	-1.10	78	-2.33	75	-3.24	70	-4.03	68	-4.32	61	-5.31	53	-5.47
Olz-H	85	13.19	85	-1.14	80	-2.18	73	-3.86	69	-4.68	62	-5.69	59	-6.59	55	-6.58
Hal	79	12.73	79	-1.53	73	-2.95	72	-3.65	61	-4.43	53	-5.68	47	-6.21	44	-6.39
								2-Sided p-Value for Pairwise Comparison								
Olz1.0 vs Olz-L				.548		.442		.492		.823		.109		.110		.245
Olz1.0 vs Olz-M				.518		.114		.156		.391		.403		.032		.404
Olz1.0 vs Olz-H				.424		.214		.013		.083		.022		_.001		.060
Olz1.0 vs Hal				.053		.002		.022		.109		.005		_.001		.042
Olz-L vs Hal				.175		.017		.106		.159		.169		.052		.339
Olz-M vs Hal				.196		.122		.374		.433		.034		.140		.196
Olz-H vs Hal				.244		.058		.854		.931		.521		.884		.785

Table 7.2.3.14 PANSS Negative Score Visitwise Change from Baseline (LOCF) F1D-EW-E003 Acute Phase

Treatment Groups	Week													
	Baseline		Week 0 5		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Olz1 0	83	25 59	81	-0 67	83	-1 96	83	-2 82	83	-3 73	83	-4.18	83	-4.23	83	-4 35
Olz-L	85	27 08	84	-0 98	85	-2 64	85	-2.69	85	-3.73	85	-4.67	85	-4.72	85	-5.05
Olz-M	83	26 14	81	-1 42	82	-2 88	83	-4 02	83	-4.47	83	-4.48	83	-4.84	83	-5.42
Olz-H	85	27 87	85	-1 53	85	-2.72	85	-4.11	85	-5.07	85	-5.65	85	-6.19	85	-6.64
Hal	79	27 89	79	-1 20	79	-2 35	79	-3 01	79	-3.90	79	-4.48	79	-4.67	79	-4.81

	2-Sided p-Value for Pairwise Comparison						
Olz1 0 vs Olz-L	.935	569	.634	.574	.987	.764	.561
Olz1 0 vs Olz-M	.439	721	.616	.965	.786	.962	.746
Olz1 0 vs Olz-H	.187	.468	.607	.586	.510	.265	.187
Olz1.0 vs Hal	.461	.783	.920	.816	.907	.854	.962
Olz-L vs Hal	.406	.775	.710	.746	.894	.911	.597
Olz-M vs Hal	974	.938	.548	.777	.881	.887	.786
Olz-H vs Hal	.582	.665	.539	.434	.439	.360	.208

Table 7.2.3.15 PANSS Negative Score Visitwise Change from Baseline (OC) F1D-EW-E003 Acute Phase

Treatment	Week													
	Baseline		Week 0 5		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Olz1.0	83	25 59	81	-0 67	82	-1 99	76	-3 08	67	-4.78	60	-5.97	56	-6 29	48	-6 90
Olz-L	85	27 08	84	-0 98	84	-2.67	76	-2 82	73	-4.26	68	-5.90	57	-5.72	50	-6 26
Olz-M	83	26 14	81	-1 42	78	-2 99	75	-4 41	70	-5.27	68	-5.44	61	-6.48	53	-7 60
Olz-H	85	27 87	85	-1 53	80	-2 80	73	-4.38	69	-5.48	62	-6.27	59	-7.24	55	-8 00
Hal	79	27 89	79	-1 20	73	-2 84	72	-3 60	61	-5.00	53	-5.87	47	-6.36	44	-6 73
	2-Sided p-Value for Pairwise Comparison															
Olz1.0 vs Olz-L				542		349		780		536		808		600		634
Olz1 0 vs Olz-M				160		156		126		546		731		739		516
Olz1 0 vs Olz-H				090		251		149		467		840		453		320
Olz1.0 vs Hal				275		183		447		593		705		517		688
Olz-L vs Hal				620		667		301		253		533		251		384
Olz-M vs Hal				761		951		451		962		472		729		831
Olz-H vs Hal				562		835		500		862		853		954		574

Table 7.2.3.16 CGI Severity Score Visitwise Change from Baseline (LOCF) F1D-EW-E003 Acute Phase

Treatment Groups	Week													
	Baseline		Week 0 5		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Olz1 0	83	5 19	81	-0 19	83	-0 33	83	-0.51	83	-0.71	83	-0.78	83	-0.75	83	-0.84
Olz-L	85	5 28	84	-0 24	85	-0 38	85	-0.62	85	-0.79	85	-0.95	85	-0.89	85	-0.99
Olz-M	83	5 14	82	-0.16	83	-0 51	83	-0 75	83	-0.87	83	-1.02	83	-1.14	83	-1.22
Olz-H	85	5 49	85	-0.22	85	-0.53	85	-0.84	85	-1.04	85	-1.22	85	-1.40	85	-1.52
Hal	79	5 33	79	-0.18	79	-0.48	79	-0.63	79	-0.90	79	-0.94	79	-1.03	79	-1.10
	2-Sided p-Value for Pairwise Comparison													
Olz1.0 vs Olz-L				.076		.104		.164		.349		.252		19		.130
Olz1 0 vs Olz-M				.780		.345		.468		.489		.363		056		.055
Olz1.0 vs Olz-H				578		.191		.118		.138		.041		.003		.003
Olz1.0 vs Hal				.692		.299		.525		.275		.379		.130		.238
Olz-L vs Hal				.170		.569		.459		.862		.864		.985		.755
Olz-M vs Hal				.490		.894		.947		.661		.997		.735		.487
Olz-H vs Hal				.888		.829		.373		.738		.264		.177		.077

Table 7.2.3.17. CGI Severity Score Visitwise Change from Baseline (OC) F1D-EW-E003 Acute Phase

Treatment Groups	Week													
	Baseline		Week 0.5		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Olz1.0	83	5.19	81	-0.19	82	-0.33	78	-0.58	68	-0.99	60	-1.22	56	-1.29	48	-1.54
Olz-L	85	5.28	84	-0.24	84	-0.37	77	-0.62	73	-0.88	69	-1.16	58	-1.09	50	-1.40
Olz-M	83	5.14	82	-0.16	79	-0.49	75	-0.76	70	-0.91	68	-1.15	61	-1.44	53	-1.58
Olz-H	85	5.49	85	-0.22	80	-0.56	73	-1.01	69	-1.28	63	-1.60	59	-1.93	55	-2.15
Hal	79	5.33	79	-0.18	73	-0.55	72	-0.72	61	-1.15	53	-1.30	47	-1.57	44	-1.73
	2-Sided p-Value for Pairwise Comparison													
Olz1.0 vs Olz-L			.605		.764		.826		.585		.710		.331		.536	
Olz1.0 vs Olz-M			.702		.191		.259		.712		.748		.328		.701	
Olz1.0 vs Olz-H			.749		.067		.009		.082		.038		.002		.006	
Olz1.0 vs Hal			.938		.059		.279		.327		.600		.118		.319	
Olz-L vs Hal			.553		.109		.389		.129		.379		.013		.107	
Olz-M vs Hal			.763		.548		.972		.180		.398		.501		.513	
Olz-H vs Hal			.691		.922		.127		.475		.139		.151		.089	

Table 7.2.4.1 Inclusion criteria for Study HGAJ

a) Male or female patients, 18 years old and older.
b) Female patients of childbearing potential. Patients must be using a medically accepted means of contraception.
c) Allowable diagnoses (DSM-III-R):
Schizophrenia (295.1 through 295.3, 295.6, 295.9) Schizophreniform disorder (295.40) Schizoaffective disorder, bipolar type or depressive type (295.70).
d) Clinical grounds for initiation of or change in neuroleptic therapy:
Patients experiencing clinically significant psychosis (positive and/or negative) who are either receiving no neuroleptic treatment or are demonstrating less than a clinically optimal response to their current neuroleptic treatment. These patients must have a total initial score on the BPRS, extracted from the PANSS (normalized, items rated 0 to 6), of at least 18.
or
Patients who have recently experienced (within 4 weeks of Visit 1 with depot neuroleptic therapy or within 6 days of Visit 1 with oral neuroleptic therapy) an adverse event that reasonably can be attributed to their current neuroleptic treatment (unless the neuroleptic is haloperidol) and who are no longer tolerating treatment can enter the study without the required minimum extracted BPRS score.
e) Patients should have a level of understanding sufficient to communicate intelligently with the investigator, nurse, and study coordinator.
f) Patients must be reliable. They must agree to cooperate during the administration of all tests and examinations required by the protocol.
g) Patients must understand the nature of the study and must either sign an informed consent document or give oral consent which must be witnessed.

Exclusion Criteria

Patients fulfilling the following criteria will be excluded from the study:
a) Patients under 18 years old.
b) Female patients who are either pregnant or lactating.
c) Serious, unstable illnesses including hepatic, gastroenterologic, renal, respiratory, cardiovascular
(including ischemic heart disease), endocrinologic, neurologic, hematologic, or immunologic disease such that hospitalization for the disease is anticipated within 3 months or death is expected within 3 years.
d) Parkinson's disease.
e) Uncorrected hypothyroidism or hyperthyroidism.
f) Myasthenia gravis.
g) Narrow-angle glaucoma.
h) Chronic urinary retention and/or clinically significant prostatic hypertrophy.
i) One or more seizures without a clear and resolved etiology. The investigator must contact the contract research organization prior to entering a patient who has experienced any seizure.
j) Leukopenia or history of leukopenia without a clear and resolved

etiology.
k) Current jaundice and/or elevation of total bilirubin, SGOT (AST), SGPT (ALT), GGT, or alkaline phosphatase to any level that exceeds the upper limit of the Lilly reference range. Positive hepatitis surface antigen (HbsAg) or positive IgM fraction of the hepatitis core antibody (anti-HBc(IgM)) are exclusionary. Positive total hepatitis core antibody (anti-HBc) is not exclusionary.
l) Any adverse drug reaction to haloperidol of sufficient severity to discontinue haloperidol during the last 3 months.
m) History of severe allergic adverse drug reactions, particularly to haloperidol.
n) DSM-III-R substance (alcohol or other drugs) abuse or dependence within past 3 months.
o) Any DSM-III-R organic mental disorder.
p) Judged clinically to be at serious suicidal risk.
q) Participation in a clinical trial of another investigational drug within 1 month (30 days) prior to initiation of active treatment.
r) Previous exposure to olanzapine.
s) Any other concomitant medication with primarily central nervous system activity, other than specified in Section 3.8 of this protocol.
t) Treatment with an injectable depot neuroleptic within 2 weeks prior to the start of active treatment, or within less than one of the patient's dosing intervals between depot neuroleptic injections prior to the start of active treatment. The 2-week requirement will apply if the dosing interval between injections is shorter than 2 weeks.
u) Treatment with an oral neuroleptic less than 2 days (48 hours) prior to the start of the active treatment and less than 1 day prior to Visit 1.
v) Treatment with lithium, anticonvulsants, benzodiazepines (except as allowed by the protocol), antidepressants (except fluoxetine, see below), psychostimulants, reversible monoamine oxidase inhibitor (MAOI), reserpine, guanethidine, or guanadrel within 1 week prior to the start of the active treatment.
w) Treatment with nonreversible MAOI within 2 weeks prior to the start of active treatment.
x) Treatment with fluoxetine within 4 weeks prior to the start of active treatment.
y) A documented history in the past 2 years of failure to show any significant clinical response to three neuroleptics in three different chemical classes with a minimum dose of 800 chlorpromazine equivalents/day for at least 6 weeks each or failure on clozapine 450 mg/day or greater for at least 6 weeks.
z) Any patient who has received remoxipride within 6 months (180 days) prior to initiation of active
treatment.

Table7.2.4.2. Patient Characteristics HGAJ Acute Phase

Treatment Group	N	Age (yrs) Mean	Age (yrs) Range	Sex [n (%)] Male	Sex [n (%)] Female	Race [n (%)] Caucasian	Race [n (%)] Non-Caucasian
Olz	1336	38.7	18.2-86.0	869 (65.0)	467 (35.0)	1078 (80.7)	258 (19.3)
Hal	660	38.3	18.0-79.6	427 (64.7)	233 (35.3)	523 (79.2)	137 (20.8)

Abbreviations: N = number of patients randomized; Olz = olanzapine 5.0, 10.0, 15.0, 20.0 mg/day; Hal = haloperidol 5.0, 10.0, 15.0, 20.0 mg/day.

Table 7.2.4.3. Patient Disposition HGAJ Acute Phase

Reason for Discontinuation	Olz (N=1336) n	Olz (N=1336) (%)	Hal (N=660) n	Hal (N=660) (%)	Total (N=1996) n	Total (N=1996) (%)	p-Value*
Reporting Interval Complete	888	(66.4)	309	(46.8)	1197	(59.9)	<.001
Adverse Event	60	(4.5)	48	(7.3)	108	(5.4)	.010
Lack of Efficacy	277	(20.7)	212	(32.1)	489	(24.5)	<.001
Lost to Follow-up	15	(1.1)	11	(1.7)	26	(1.3)	.313
Patient Decision	48	(3.6)	49	(7.4)	97	(4.9)	<.001
Criteria not met / Compliance	44	(3.3)	29	(4.4)	73	(3.7)	.218
Sponsor Decision	4	(0.3)	2	(0.3)	6	(0.3)	.989

Patients included in the reasons discontinued, Reporting Interval Complete and Lack of Efficacy, may have continued into the next reporting interval or discontinued from the study.
* Frequencies are analyzed using a Chi-Square test.

Table 7.2.4.4 Patient Completion Rates HGAJ Acute Phase

Treatment Group	N	n*	Number (%) of Patients Completing† Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Acute Phase
Olz	1336	1312	1336 (100.0)	1268 (94.9)	1211 (90.6)	1171 (87.6)	1006(75.3)	904 (67.7)	888(66.4)
Hal	660	636	660 (100.0)	601 (91.1)	568 (86.1)	540 (81.8)	396 (60.0)	317 (48.0)	309 (46.8)

Abbreviations: N = number of patients randomized; Olz = olanzapine 5.0, 10.0, 15.0, 20.0 mg/day; Hal = haloperidol 5.0, 10.0, 15.0, 20.0 mg/day.

* Number of patients with baseline and postbaseline Brief Psychiatric Rating Scale total score.

† Number of patients with a visit in the corresponding week or the number of patients designated as completing the acute phase.

Table 7.2.4.5 Concomitant medications allowed and not allowed in EGAJ

Concomitant Medication	PRN	Chronic
Allopurinol	N	Ya
Amantadine	N	N
Analgesics (nonnarcotic)	Y	Ya
Anorexiants	N	N
Antacids	Y	N
Anti-inflammatory drugs (nonsteroidal)	Y	Ya
Antifungal agents	Y	Ya
Antiarrhythmics	N	N
Antiasthma agents (except steroids b)	Y	Ya
Antibiotics (except erythromycin and other macrolides b and chloramphenicol b)	Y	Yc
Anticoagulants	N	N
Anticonvulsants	N	N
Antidepressants	N	N
Antidiarrheal preparations	Y	N
Antiemetics	N	N
Antihistamines (except diphenhydramine b)	Yc	Yac
Antihypertensives d,e	N	Ya
Benzodiazepines	Y	Y
Calcium channel blockers	N	Ya
Colchicine	Y	Y
Cough/Cold preparations (except those containing diphenhydramine b)	Y	N
Diuretics	N	Ya
H2 blockers (except cimetidine b)	N	Ya
Hormones	N	Ya
Insulin	Y	Y
Laxatives	Y	Ya
Lithium	N	N
Oral hypoglycemic agents	Y	Y
Other psychotropic drugs	N	N
Psychostimulants	N	N
Steroids	N	N
Tranquilizers	N	N

a If being taken before admission to the study.
b These specific drugs are exclusionary and must not be used during the study.
c Antihistamines inclined to be used for sedation.
d Clonidine, guanabenz, guanadrel, guanfacine, reserpine, guanethidine, guanadrel, methyldopa, and hemedrine should not be used.
e Beta blockers are not to be used to treat hypertension.

7.2.3.6 Mean Dose by Visit HGAJ Acute Phase (mg/day)

Treatment Group		Visit 3		Visit 4		Visit 5		Visit 6		Visit 7		Visit 8	
	N	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std
Olz	1336	5.0	0.6	8.4	2.3	11.5	3.8	13.8	5.4	14.5	5.5	14.6	5.5
Hal	660	5.0	0.4	8.3	2.3	10.9	3.9	12.7	5.4	13.4	5.4	13.8	5.5

Table 7.2.4.7 BPRS Total Score Visitwise Change from Baseline (LOCF) HGAJ Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
Olz	1312	33.05	1310	-3.42	1311	-6.11	1312	-8.21	1312	-9.38	1312	-10.50	1312	-11.00
Hal	636	34.09	635	-3.43	636	-5.89	636	-7.08	636	-7.66	636	-8.05	636	-8.00
								2-Sided p-Value for Pairwise Comparison						
Olz vs Hal				.145		.051		.056		.026		.012		.015

Table 7.2.4.8 BPRS Total Score Visitwise Change from Baseline (OC) HGAJ Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
Olz	1312	33.05	1310	-3.42	1248	-6.54	1188	-9.19	1150	-10.75	997	-13.48	899	-15.06
Hal	636	34.09	635	-3.43	592	-6.46	556	-8.25	532	-9.00	391	-11.54	314	-12.76
								2-Sided p-Value for Pairwise Comparison						
Olz vs Hal				.990		.828		.061		.001		.002		< .001

Table7.2.4.9 PANSS Total Score Visitwise Change from Baseline (LOCF) HGAJ Acute Phase

Treatment Groups	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Olz	1312	90.11	1310	-5.03	1311	-9.46	1312	-13.08	1312	-15.03	1312	-16.88	1312	-17.70
Hal	636	92.10	635	-5.51	636	-9.68	636	-11.76	636	-12.81	636	-13.45	636	-13.37
							2-Sided p-Value for Pairwise Comparison							
Olz vs Hal				.313		.181		.178		.106		.044		.051

Table 7.2.4.10 PANSS Total Score Visitwise Change from Baseline (OC) HGAJ Acute Phase

Treatment Groups	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Olz	1312	90.11	1310	-5.03	1248	-10.13	1187	-14.65	1149	-17.33	996	-22.06	899	-24.75
Hal	636	92.10	635	-5.51	592	-10.55	556	-13.62	532	-14.93	391	-19.49	314	-21.55
							2-Sided p-Value for Pairwise Comparison							
Olz vs Hal				.417		.604		.210		.010		.014		.005

Table 7.2.4.11 BPRS Positive Total Score Visitwise Change from Baseline (LOCF) HGAJ Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
							Week							
Olz	1312	10.24	1311	-1.07	1311	-1.85	1312	-2.50	1312	-2.91	1312	-3.27	1312	-3.44
Hal	636	10.43	635	-1.11	636	-2.00	636	-2.53	636	-2.68	636	-2.81	636	-2.84
							2-Sided p-Value for Pairwise Comparison							
Olz vs Hal				.316		.353		.777		.361		.120		.126

Table 7.2.4.12 BPRS Positive Total Score Visitwise Change from Baseline (OC) HGAJ Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
							Week							
Olz	1312	10.24	1311	-1.07	1250	-1.99	1189	-2.80	1152	-3.31	997	-4.19	899	-4.66
Hal	636	10.43	635	-1.11	592	-2.16	556	-2.85	532	-3.02	392	-3.73	314	-4.21
							2-Sided p-Value for Pairwise Comparison							
Olz vs Hal				.725		.261		.753		.148		.035		056

Table 7.2.4.13 PANSS Negative Total Score Visitwise Change from Baseline (LOCF) HGAJ Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
Olz	1312	24.02	1311	-1.17	1311	-2.28	1312	-3.28	1312	-3.79	1312	-4.23	1312	-4.46
Hal	636	24.47	635	-1.37	636	-2.33	636	-2.75	636	-3.08	636	-3.23	636	-3.18
								2-Sided p-Value for Pairwise Comparison						
Olz vs Hal				.713		.341		.151		.090		.046		.032

Table 7.2.4.14 PANSS Negative Total Score Visitwise Change from Baseline (OC) HGAJ Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
Olz	1312	24.02	1311	-1.17	1249	-2.36	1190	-3.51	1152	-4.22	996	-5.35	899	-6.06
Hal	636	24.47	635	-1.37	592	-2.43	556	-3.05	532	-3.44	392	-4.62	314	-4.97
								2-Sided p-Value for Pairwise Comparison						
Olz vs Hal				.240		.755		.076		.007		.022		.003

Table 7.2.4.15 CGI Severity Score Visitwise Change from Baseline (LOCF) HGAJ Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
						Week								
Olz	1318	4.68	1318	-0.19	1318	-0.39	1318	-0.56	1318	-0.70	1318	-0.83	1318	-0.97
Hal	640	4.73	639	-0.18	639	-0.39	640	-0.51	640	-0.56	640	-0.62	640	-0.68
						2-Sided p-Value for Pairwise Comparison								
Olz vs Hal				.089		.445		.306		.238		.044		.029

Table 7.2.4.16 CGI Severity Score Visitwise Change from Baseline (OC) HGAJ Acute Phase

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
						Week								
Olz	1318	4.68	1318	-0.19	1261	-0.41	1198	-0.62	1161	-0.80	1004	-1.09	898	-1.39
Hal	640	4.73	639	-0.18	592	-0.43	559	-0.60	534	-0.67	392	-0.93	315	-1.17
						2-Sided p-Value for Pairwise Comparison								
Olz vs Hal				.724		.724		.586		.010		.004		< .001

APPENDIX 8.0

Table 8.1.1.1 Deaths During Study or Within 30 Days of Study Discontinuation, Overall Integrated Database.

Study Drug	Study	Inv-Pt No.	Age	Gender	Dose	Duration	Associated Adverse Events a (Cause of Death)
Olanzapine	E003	103-1105	26	M	15 mg/day	49 days	Suicide by hanging
Olanzapine	E003	105-1056	32	M	7.5 mg/day	19 days	Suicide by jumping from window. Death occurred after study participation but within 30 days of study discontinuation.
Olanzapine	E003	105-1061	18	M	12.5 mg/day	37 days	Suicide by shooting
Olanzapine	HGAJ	035-0206	37	M	15 mg/day	15 days	Heart arrest, Arterial thrombosis. Patient diagnosed with severe atherosclerotic occlusion of the cardiac arteries, including total blockage of the right descending artery with a thrombus overlying plaque, that led to coronary thrombosis and death. The patient's father died at age 39 of a similar medical condition.
Olanzapine	HGAJ	040-0850	38	F	15 mg	59 days	Suicide by jumping off bridge.
Olanzapine	HGAJ	042-0507	41	M	5 mg	270 days	Suicide by slashing wrists/death due to blood loss.
Olanzapine	HGAJ	049-1257	28	M	20 mg	217 days	Suicide by jumping in front of subway train. Death occurred after study participation but within 30 days of study discontinuation.
Olanzapine	HGAJ	051-0319	35	F	20 mg	141 days	Lung edema, Sudden death, Subarachnoid hemorrhage, Petechia .
Olanzapine	HGAJ	069-1309	52	F	20 mg	22 days	Suicide. Death occurred after study participation but within 30 days of study discontinuation.
Olanzapine	HGAJ	203-2490	40	M	10 mg	168 days	Suicide by cutting ulnar arteries/bleeding to death.
Olanzapine	HGAJ	306-2837	47	M	10 mg	121 days	Suicide by jumping out of window
Olanzapine	HGAJ	329-3158	19	M	20 mg	99 days	Suicide, method unspecified.
Olanzapine	HGAJ	338-3266	28	M	5 mg	64 days	Suicide by overdose of multiple medications and alcohol.
Olanzapine	HGAJ	752-6057	63	M	5 mg	20 days	Coronary artery disorder, Myocardial infarct, Lung edema, Brain edema. Death occurred after study participation but within 30 days of study discontinuation.
Olanzapine	HGAJ	990-7728	44	F	15 mg	60 days	Accidental injury
Olanzapine	HGAO	006-0615	71	M	5 mg	122 days	Apnea, Aspiration pneumonia

Olanzapine	HGAO	012-1208	80	M	5 mg	46 days	Patient had aspiration pneumonia and family declined feeding tube. Patient developed dysphagia and aspiration pneumonia on 12 Dec 94 while taking olanzapine which was then discontinued 15 Dec 94. Death occurred [ ] [ ]
Olanzapine	HGAO	019-1903	78	M	1 mg	13 days	Cerebrovascular accident
Olanzapine	HGAO	020-2003	88	M	1 mg	11 days	Patient reported to have died from congestive heart failure. Death occurred after study participation but within 30 days of study discontinuation.
Olanzapine	HGAO	022-2210	88	F	3 mg	37 days	Respiratory disorder. Death occurred after study participation but within 30 days of study discontinuation.
Olanzapine	HGAP	005-1215	63	M	15 mg	65 days	Myocardial infarct
Olanzapine	F1D-MC-HGBT	241-2409	71	M			The patient died 7 days post-operatively from heart failure after undergoing hip replacement. Olanzapine had been discontinued the day prior to surgery.
Haloperidol	E003	302-3028	35	M	20 mg	56 days	Suicide by jumping from 4th floor window. Hemorrhage. Death occurred after study participation but within 30 days of study discontinuation.
Haloperidol	HGAJ	041-0394	45	M	20 mg	417 days	Death. Patient found dead in his apartment. Investigator attributed death to natural causes. COSTART classification term to be updated to sudden death on Form FDA 1639 Drug Experience Report.. Death occurred 25 days after study participation.
Haloperidol	HGAJ	321-3136	43	M	20 mg	206 days	Heart arrest, Coma
Placebo	HGAD	020-1957	34	M	NA	NA	Suicide
Placebo	HGAO	007-0712	87	M	NA	NA	Myocardial infarct, confusion

Abbreviations: Inv-Pt No. = investigator-patient number; M = male; F = female.
a COSTART classification terms contained in integrated primary safety database and FDA Form 1639 Drug Experience Reports.

Table8.1.2.2.2 Adverse Events Reported as Reason for Discontinuation in Olanzapine-Treated Patients Primary Integrated Database	Olanzapine (N=2500) n (%)
Event Classification	
Patients Discontinued	372 (14.9)
Schizophrenic reaction	62 (2.5)
Depression	44 (1.8)
Hostility	17 (0.7)
Suicide attempt	17 (0.7)
SGPT increased	15 (0.6)
Unintended pregnancy[a]	5 (0.6)
Creatine phosphokinase increased	14 (0.6)
Agitation	12 (0.5)
Convulsion	12 (0.5)
Somnolence	9 (0.4)
Weight gain	7 (0.3)
Intentional overdose	6 (0.2)
Anxiety	5 (0.2)
Diarrhea	5 (0.2)
Lab test abnormal	5 (0.2)
Personality disorder	5 (0.2)
Accidental injury	4 (0.2)
GGT increased	4 (0.2)
Hypertension	4 (0.2)
Leukopenia	4 (0.2)
Liver function tests abnormal	4 (0.2)
Paranoid reaction	4 (0.2)
Accidental overdose	3 (0.1)
Grand mal convulsion	3 (0.1)
Hypertonia	3 (0.1)
Insomnia	3 (0.1)
Nervousness	3 (0.1)
Overdose	3 (0.1)
Peripheral edema	3 (0.1)
Rash	3 (0.1)
Metrorrhagia[a]	1 (0.1)
Akathisia	2 (0.1)
Allergic reaction	2 (0.1)
Amblyopia	2 (0.1)
Asthenia	2 (0.1)
Bilirubinemia	2 (0.1)
Cerebrovascular accident	2 (0.1)
Delusions	2 (0.1)

Drug dependence	2 (0.1)
Headache	2 (0.1)
Hepatitis	2 (0.1)
Intentional injury	2 (0.1)
Syncope	2 (0.1)
Thinking abnormal	2 (0.1)
Urinary retention	2 (0.1)
Abdominal pain	1 (0.0)
Abnormal stools	1 (0.0)
Acne	1 (0.0)
Anemia	1 (0.0)
Apnea	1 (0.0)
Asthma	1 (0.0)
Bladder neoplasm	1 (0.0)
Bradycardia	1 (0.0)
Breast carcinoma	1 (0.0)
Cellulitis	1 (0.0)
Confusion	1 (0.0)
Creatinine increased	1 (0.0)
Dehydration	1 (0.0)
Depersonalization	1 (0.0)
Diabetes mellitus	1 (0.0)
Dizziness	1 (0.0)
Dyspnea	1 (0.0)
Dystonia	1 (0.0)
Eczema	1 (0.0)
Emotional lability	1 (0.0)
Endocrine disorder	1 (0.0)
Euphoria	1 (0.0)
Eye disorder	1 (0.0)
Fever	1 (0.0)
Flatulence	1 (0.0)
Hallucinations	1 (0.0)
Heart arrest	1 (0.0)
Hemoptysis	1 (0.0)
Herpes simplex	1 (0.0)
Hypoglycemia	1 (0.0)
Hyponatremia	1 (0.0)
Hypothyroidism	1 (0.0)
Incoordination	1 (0.0)
Libido increased	1 (0.0)
Lymphoma-like reaction	1 (0.0)
Myocardial infarct	1 (0.0)
Myoclonus	1 (0.0)
Myopathy	1 (0.0)

Neoplasm	1 (0.0)
Neurosis	1 (0.0)
Pain	1 (0.0)
Pancreatitis	1 (0.0)
Pathological fracture	1 (0.0)
Peptic ulcer	1 (0.0)
Psychotic depression	1 (0.0)
Respiratory disorder	1 (0.0)
Sudden death	1 (0.0)
Thrombocytopenia	1 (0.0)
Tooth disorder	1 (0.0)
Tremor	1 (0.0)
Urinary tract infection	1 (0.0)
Urticaria	1 (0.0)
Vascular anomaly	1 (0.0)
Ventricular arrhythmia	1 (0.0)
Vomiting	1 (0.0)

[a] Denominator used was for females only (N=892).

Table 8.1.5.2.1. Treatment-Emergent Adverse Events Placebo-Controlled Integrated Database Acute Phase (Events Ordered by Body System and by Decreasing Frequency Within the Olanzapine Treatment Group).

	Percentage of Patients Reporting Event	
Body System/Adverse Eventa	Olanzapine (N=248)	Placebo (N=118)
Body As a Whole		
Headache	17	15
Pain	10	9
Fever	5	3
Abdominal pain	4	2
Back pain	4	3
Chest pain	4	2
Surgical procedure	3	2
Neck rigidity	2	1
Intentional injury	1	0
Cardiovascular System		
Postural hypotension	5	2
Tachycardia	4	1
Hypotension	2	1
Digestive System		
Constipation	9	3
Dry mouth	7	4
GGT increased	2	1
Increased appetite	2	1
Hemic and Lymphatic System		
Leukopenia	1	0
Metabolic and Nutritional Disorders		
SGPT increased	8	3
Weight gain	6	1
Edema	2	0
Peripheral edema	2	0
SGOT increased	2	0
Creatine phosphokinase increased	1	0
Musculoskeletal System		
Arthralgia	3	2
Joint disorder	2	1
Twitching	2	1
Nervous System		
Somnolence	26	15
Agitation	23	17
Insomnia	20	19
Nervousness	16	14
Hostility	15	14

Table 8.1.5.2.1 Treatment-Emergent Adverse Events Placebo-Controlled Integrated Database Acute Phase (Events Ordered by Body System and by Decreasing Frequency Within the Olanzapine Treatment Group)
(continued)

Body System/Adverse Eventa	Percentage of Patients Reporting Event	
	Olanzapine (N=248)	Placebo (N=118)
Nervous System (cont.)		
Dizziness	11	4
Anxiety	9	8
Personality disorder	8	4
Akathisia	5	1
Hypertonia	4	3
Speech disorder	4	1
Tremor	4	3
Amnesia	2	0
Drug dependence	2	0
Euphoria	2	0
Neurosis	1	0
Respiratory System		
Rhinitis	10	6
Cough increased	5	3
Pharyngitis	5	3
Skin and Appendages		
Fungal dermatitis	2	0
Vesiculobullous rash	2	1
Special Senses		
Amblyopia	5	4
Blepharitis	2	1
Corneal lesion	1	0
Urogenital System		
Menstrual disorderb	2	0

a Events reported by at least 1% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abnormal dreams, accidental injury, anorexia, apathy, asthenia, cogwheel rigidity, confusion, conjunctivitis, diarrhea, depression, dysmenorrheab, dyspepsia, ecchymosis, emotional lability, hallucinations, hyperkinesia, hypertension, hypokinesia, libido increased, myalgia, nausea, paranoid reaction, paresthesia, pruritus, rash, schizophrenic reaction, sweating, thinking abnormal, tooth caries, vaginitisb, vomiting.

b Denominator used was for females only (olanzapine, N=41; placebo, N=23).

Table 8.1.5.2.2 Other Events Observed During the Premarketing Evaluation of olanzapine-Primary safety database (N=2500). Events listed in the above table (8.1.5.2.1) are not included in this table.

Body As A Whole--*Frequent:* flu syndrome and suicide attempt; *Infrequent:* allergic reaction, chills, chills and fever, cyst, face edema, hangover effect, intentional overdose, malaise, moniliasis, neck pain, overdose, pelvic pain, and photosensitivity reaction; *Rare:* abdomen enlarged, hypothermia, and sudden death.

Cardiovascular System--*Infrequent:* cerebrovascular accident, hemorrhage, migraine, palpitation, syncope, vasodilatation, and ventricular extrasystoles; *Rare:* AV block, atrial arrhythmia, bundle branch block, congestive heart failure, heart arrest, QT interval prolonged, thrombophlebitis, and ventricular arrhythmia.

Digestive System--*Frequent:* increased salivation, nausea and vomiting, and thirst; *Infrequent:* aphthous stomatitis, dysphagia, eructation, esophagitis, fecal incontinence, flatulence, gastritis, gastroenteritis, gingivitis, glossitis, hepatitis, melena, mouth ulceration, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, and tongue edema; *Rare:* colitis, enteritis, esophageal ulcer, hematemesis, nausea vomiting and diarrhea, pancreatitis, and tongue discoloration.

Endocrine System--*Infrequent:* diabetes mellitus and goiter; *Rare:* diabetic acidosis, hyperthyroidism, and hypothyroidism.

Hemic and Lymphatic System--*Infrequent:* cyanosis, leukocytosis, lymphadenopathy, and thrombocythemia; *Rare:* lymphoma like reaction.

Metabolic and Nutritional Disorders--*Frequent:* weight loss; *Infrequent*: alkaline phosphatase increased, bilirubinemia, dehydration, hyperglycemia, hyperkalemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, and water intoxication; *Rare:* hypercholesteremia, and hyperlipemia.

Musculoskeletal System--*Infrequent:* arthritis, bursitis, leg cramps, myasthenia, and rheumatoid arthritis; *Rare:* bone pain, myopathy, and tetany.

Nervous System--*Frequent:* extrapyramidal syndrome and tardive dyskinesia; *Infrequent:* abnormal gait, antisocial reaction, ataxia, buccoglossal syndrome, CNS stimulation, coma, convulsion, delirium, depersonalization, dyskinesia, dystonia, grand mal convulsion, hypesthesia, hypotonia, incoordination, libido decreased, oculogyric crisis, stupor, vertigo, and withdrawal syndrome; *Rare:* acute brain syndrome, choreoathetosis, facial paralysis, intracranial hypertension, myoclonus, neuralgia, neuropathy, nystagmus, psychotic depression, and subarachnoid hemorrhage.

Respiratory System--*Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, and voice alteration; *Rare:* aspiration pneumonia, hypoventilation, hypoxia, laryngitis, lung edema, and pleural effusion.

Skin and Appendages--*Infrequent:* alopecia, contact dermatitis, dry skin, eczema, herpes simplex, herpes zoster, hirsutism, seborrhea, skin ulcer, and urticaria; *Rare:* exfoliative dermatitis, maculopapular rash, and skin discoloration.

Special Senses--*Infrequent:* cataract specified, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye pain, taste perversion, and tinnitus; *Rare:* abnormality of accommodation, cataract not otherwise specified, corneal opacity, glaucoma, iritis, keratoconjunctivitis, mydriasis, optic atrophy, optic neuritis, papilledema, pigment deposits lens, retinal degeneration, retinal detachment, and retinal pigmentation.

Urogenital System--*Frequent:* hematuria, metrorrhagia*, urinary incontinence, and urinary tract infection; *Infrequent:* abnormal ejaculation*, abortion*, amenorrhea*, breast pain, cystitis, dysuria, female lactation, impotence*, menorrhagia*, polyuria, pyuria, urinary retention, urinary frequency, urination impaired, uterine fibroids enlarged*, uterine hemorrhage*, and vaginal hemorrhage*; *Rare:* albuminuria, breast neoplasm, oliguria, and priapism*.

*Adjusted for gender.

Table 8.1.6.1.1 Laboratory tests performed in the olanzapine clinical development program.

Liver	**Electrolytes**
ALT/SGPT	Sodium
AST/SGOT	Potassium
GGT	Chloride
Alk. Phosphatase	Bicarbonate
Bilirubin	**Nutritional**
Muscle	Glucose, fasting
Creatine Kinase	Glucose, non-fasting
Kidney	Protein
Creatinine	Cholesterol
Urea	HDL Cholesterol
Uric Acid	LDL Cholesterol
Phosphate	Triglycerides
Calcium	Albumin
Erythrocytes	**Leukocytes**
Hemoglobin	Bands
Hematocrit	Neutrophils
MCV	Lymphocytes
MCH	Monocytes
Urine	Eosinophils
Specific Gravity	Basophils
pH	Platelets
Other	
Prolactin by RIA	

Table 8.1.6.3.1.1 Clinical Chemistry Analytes
Mean Change from Baseline to Endpoint
Placebo-Controlled Integrated Database Acute Phase

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy (Int*1)
AST	U/L	Olz	243	20.90	9.95	4.65	18.61	.087
		Placebo	115	21.41	9.52	-0.09	9.89	(.152)
ALT	U/L	Olz	243	26.89	18.15	13.13	55.19	.062
		Placebo	115	28.82	21.48	-0.53	18.95	(.219)
CPK	U/L	Olz	243	176.78	350.04	11.96	377.60	.246
		Placebo	115	140.21	161.56	25.88	255.80	(.436)
ALKPH	U/L	Olz	243	75.58	21.56	1.63	12.52	.002
		Placebo	115	78.86	30.95	-3.33	16.24	(.455)
GGT	U/L	Olz	243	29.93	19.88	4.08	16.30	<.001
		Placebo	115	34.24	24.16	-4.12	16.99	(.575)
BUN	mmol/L	Olz	243	4.36	1.26	-0.00	1.33	.166
		Placebo	115	4.38	1.35	-0.14	1.31	(.416)
CREAT	umol/L	Olz	243	97.12	14.17	0.16	10.46	.861
		Placebo	115	99.33	15.30	-0.72	10.90	(.150)
CALC	mmol/L	Olz	243	2.33	0.12	-0.03	0.13	.081
		Placebo	115	2.31	0.11	-0.01	0.12	(.883)
PHOS	mmol/L	Olz	243	1.21	0.18	0.02	0.22	.003
		Placebo	115	1.25	0.21	-0.04	0.21	(.780)
TPROT	g/L	Olz	243	71.05	5.46	-1.09	5.02	.191
		Placebo	115	71.52	5.16	-0.57	5.40	(.398)
ALBUM	g/L	Olz	243	41.81	3.67	-1.46	3.35	.001
		Placebo	115	41.62	3.80	-0.08	3.53	(.935)
NFGLU	mmol/L	Olz	243	5.26	1.19	0.16	1.59	.115
		Placebo	115	5.38	1.29	-0.16	1.31	(.381)
UR AC	umol/L	Olz	243	306.60	67.96	30.35	49.48	<.001
		Placebo	115	310.28	78.28	3.27	43.32	(.622)

Table 8.1.6.3.1.1 Clinical Chemistry Analytes
Mean Change from Baseline to Endpoint
Placebo-Controlled Integrated Database Acute Phase (concluded)

				Baseline		Change to Endpoint		
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1) p-Values
CHOL	mmol/L	Olz	243	5.04	1.14	0.23	0.93	<.001
		Placebo	115	5.17	1.12	-0.30	0.75	(.532)
T.BILI	umol/L	Olz	243	8.83	4.52	-0.33	3.51	<.001
		Placebo	115	8.44	3.65	1.48	4.35	(.188)
SODIUM	mmol/L	Olz	243	139.30	3.11	0.32	3.25	.314
		Placebo	115	139.30	2.23	0.07	2.72	(.436)
POTAS	mmol/L	Olz	243	4.33	0.37	-0.11	0.41	.344
		Placebo	115	4.31	0.34	-0.07	0.40	(.396)
CHLOR	mmol/L	Olz	243	105.05	3.99	0.90	4.00	.062
		Placebo	115	104.98	2.93	0.25	3.28	(.053)
BICARB	mmol/L	Olz	243	23.92	2.63	-0.19	2.84	.367
		Placebo	115	23.87	2.77	0.20	2.99	(.921)
PROLAC	nmol/L	Olz	225	0.35	0.47	0.15	0.38	.066
		Placebo	111	0.32	0.30	0.04	0.33	(.657)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Table 8.1.6.3.1.2 Hematology Analytes
Mean Change from Baseline to Endpoint
Placebo-Controlled Integrated Database Acute Phase

				-----Baseline------		Change to -----Endpoint-----		p-Values
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)
HCT	1	Olz	243	0.45	0.04	-0.01	0.03	.004
		Placebo	114	0.44	0.05	0.00	0.03	(.242)
HGB	mml/L-Fe	Olz	243	9.34	0.80	-0.20	0.56	<.001
		Placebo	114	9.29	1.02	0.01	0.55	(.130)
RBC	TI/L	Olz	243	4.98	0.47	-0.08	0.30	<.001
		Placebo	114	4.94	0.50	0.02	0.30	(.100)
MCHC	mml/L-Fe	Olz	243	20.92	1.01	-0.04	1.04	.621
		Placebo	114	21.05	0.99	0.03	0.97	(.842)
MCH	fmol(Fe)	Olz	243	1.88	0.11	-0.01	0.06	.667
		Placebo	114	1.89	0.14	-0.00	0.06	(.205)
WBC	GI/L	Olz	243	8.16	2.73	-0.36	2.23	.281
		Placebo	114	8.00	2.73	-0.22	2.25	(.157)
POLYS	GI/L	Olz	243	5.14	2.37	-0.28	2.07	.249
		Placebo	114	4.99	2.37	-0.10	2.10	(.265)
LYMPHS	GI/L	Olz	243	2.25	0.70	-0.08	0.60	.374
		Placebo	114	2.23	0.69	-0.05	0.56	(.198)
MONOS	GI/L	Olz	243	0.53	0.20	-0.01	0.18	.258
		Placebo	114	0.54	0.19	-0.04	0.17	(.749)
EOSN	GI/L	Olz	243	0.18	0.16	0.01	0.12	.008
		Placebo	114	0.18	0.16	-0.03	0.12	(.986)
BASO	GI/L	Olz	243	0.07	0.03	-0.00	0.03	.397
		Placebo	114	0.06	0.04	-0.00	0.03	(.160)
MCV	fL	Olz	243	89.84	5.71	-0.37	3.60	.509
		Placebo	114	89.55	5.90	-0.03	3.37	(.802)
PLTCT	GI/L	Olz	243	274.77	63.41	-8.71	47.50	.726
		Placebo	114	283.29	70.43	-6.14	43.24	(.911)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Table 8.1.6.3.1.3. Urinary Analytes Mean Change from Baseline to Endpoint Placebo-Controlled Integrated Database Acute Phase

				-----Baseline------		Change to -----Endpoint-----		p-Values
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)
U-SPGR	NO UNITS	Olz	240	1.02	0.01	-0.00	0.01	.037
		Placebo	113	1.02	0.01	0.00	0.01	(.453)
U-PH	U	Olz	240	6.06	0.77	-0.13	0.96	.022
		Placebo	113	6.03	0.75	0.04	0.86	(.211)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Table 8.1.6.3.2.1 Criteria for Identifying Patients with Potentially Clinically Significant Change in Clinical Chemistry Analytes

Analyte	Unit	Low	High
AST/SGOT	U/L		150
ALT/SGPT	U/L		165
CPK: Female	U/L		507
Male	U/L		594
Alkaline phosphatase	U/L		420
GGT: Female	U/L		135
Male	U/L		195
Urea nitrogen	mmol/L		10.71
Creatinine	μmol/L		176.8
Calcium	mmol/L	1.7465	2.994
Phosphorus	mmol/L	0.48435	1.77595
Sodium	mmol/L	129	160
Total protein	g/L	50	
Albumin	g/L	25	
Glucose (nonfasting)	mmol/L	2.4975	13.875
Uric acid: Female	μmol/L		505.58
Male	μmol/L		624.54
Total cholesterol	mmol/L		15.516
Total bilirubin	μmol/L		34.2

Table 8.1.6.3.2.2 Criteria for Identifying Patients with Potentially Clinically Significant Change in Hematology Analytes

Analyte	Unit	Low	High
Hematocrit: Female	1	0.32	0.50
Male	1	0.37	0.55
Hemoglobin: Female	mml/L (Fe)	5.8957	10.2399
Male	mml/L (Fe)	7.1369	11.4811
RBC	TI/L	3	6
WBC	GI/L	2.8	16.0
Platelet count	GI/L	75	700
Neutrophils	% WBC	15	
Eosinophils	% WBC		10

Table 8.1.6.3.2.3 Criteria for Identifying Patients with Potentially Clinically Significant Change in Urinary (UA) Analytes

Analyte	Low	High
UA-Specific Gravity	1.001	1.035
UA-pH	4.6	8.0
UA-RBC		increase ≥2 and score ≥3
UA-WBC		increase ≥2 and score ≥3
UA-Casts		increase ≥2 and score ≥3
UA-Protein		increase ≥2 and score ≥3
UA-Ketones		increase ≥2 and score ≥3
UA-Glucose		increase ≥2 and score ≥3

TABLE 8.1.6.3.2.4

Proportions of Patients Having Potentially Clinically Significant Changes in Chemistry Variables in the Acute Phase of Placebo-Controlled Studies

Variables	OLANZAPINE			PLACEBO			HALOPERIDOL			p-value (Olanz vs Plac)
	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%	
CPK-High	229	12	5%	108	2	2%	62	1	2%	0.240
GGT-High	243	1	<1%	115	0	0%	66	0	0%	0.559
Glucose-High	243	1	<1%	115	1	<1%	66	1	2%	0.540
Phosphorus-High	238	1	<1%	113	0	0%	66	1	2%	1.00
SGOT-High	243	2	<1%	114	0	0%	66	0	0%	1.00
SGPT-High	243	6	3%	115	0	0%	65	0	0%	0.183

TABLE 8.1.6.3.2.5

Proportions of Patients Having Potentially Clinically Significant Changes in Hematology Variables in the Acute Phase of Placebo-Controlled Studies

Variables	OLANZAPINE			PLACEBO			HALOPERIDOL			p-value (Olanz vs Plac)
	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%	
Hematocrit-High	238	2	<1%	113	0	0%	65	1	2%	1.00
Hematocrit-Low	241	3	1%	109	0	0%	66	0	0%	0.555
RBC-High	238	1	<1%	114	2	2%	63	0	0%	0.246
WBC-High	239	3	1%	110	0	0%	64	1	2%	0.555
Eosinophils-High	242	2	<1%	110	0	0%	66	0	0%	1.00

TABLE 8.1.6.3.2.6

Proportions of Patients Having Potentially Clinically Significant Changes in Urinalysis Variables in the Acute Phase of Placebo-Controlled Studies

Variables	OLANZAPINE			PLACEBO			HALOPERIDOL			p-value (Olanz vs Plac)
	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%	
Glucose-High	240	1	<1%	113	2	2%	65	0	0%	0.241
RBC-High	237	1	<1%	112	0	0%	65	0	0%	1.00

Table 8.1.7.3.1 Vital Signs and Weight
Mean Change from Baseline to Endpoint
Placebo-Controlled Integrated Database Acute Phase

		Baseline		Endpoint		Change			Overall
		Mean	Std	Mean	Std	n	Mean	Std	p-Value
Vital	Pooled Therapy								
Orthostatic Sys BP	Olz	-0.52	10.89	-1.35	11.43	237	-0.83	12.99	.246
	Placebo	-1.86	11.12	-1.36	10.08	112	0.50	11.67	
Standing Diastolic BP	Olz	78.96	10.19	79.95	10.32	240	0.99	12.07	.406
	Placebo	79.73	10.12	79.50	11.22	113	-0.22	14.39	
Standing Pulse	Olz	87.61	14.61	90.31	13.23	237	2.70	15.70	.125
	Placebo	87.88	12.90	88.76	12.92	111	0.87	13.81	
Standing Systolic BP	Olz	117.77	15.25	119.93	15.14	240	2.16	14.61	.089
	Placebo	117.72	15.63	117.71	14.99	113	-0.01	14.41	
Supine Diastolic BP	Olz	75.53	9.99	75.47	9.73	240	-0.06	11.40	.559
	Placebo	75.60	9.10	75.50	9.33	114	-0.10	10.53	
Supine Pulse	Olz	79.36	13.51	81.00	12.65	240	1.65	14.18	.560
	Placebo	79.72	12.24	80.52	12.49	114	0.80	14.27	
Supine Systolic BP	Olz	117.01	13.40	118.52	14.01	240	1.51	14.83	.824
	Placebo	115.50	13.66	116.73	12.51	114	1.23	13.66	

Table 8.1.7.3.1 **Vital Signs and Weight**
Mean Change from Baseline to Endpoint
Placebo-Controlled Integrated Database Acute Phase
(concluded)

		Baseline		Endpoint		Change			Overall
		Mean	Std	Mean	Std	n	Mean	Std	p-Value
Vital	Pooled Therapy								
Temperature (C)	Olz	36.54	0.49	36.61	0.48	241	0.07	0.57	.475
	Placebo	36.59	0.43	36.72	0.48	114	0.13	0.51	
Weight(kg)	Olz	79.63	18.33	82.42	17.50	239	2.80	6.78	<.001
	Placebo	79.90	17.00	79.49	17.15	113	-0.41	2.90	

Table 8.1.7.3.2.1 Criteria for Identifying Patients with Potentially Clinically Significant Change in Vital Signs and Weight.

Parameter	Low	High
Supine systolic BP (mm Hg)	90 and decrease 20	180 and increase 20
Standing systolic BP (mm Hg)	90 and decrease 20	180 and increase 20
Supine diastolic BP (mm Hg)	50 and decrease 15	105 and increase 15
Standing diastolic BP (mm Hg)	50 and decrease 15	105 and increase 15
Supine pulse (bpm)	<50 and decrease 15	>120 and increase 15
Standing pulse (bpm)	<50 and decrease 15	>120 and increase 15
Temperature (F)a	--	101 F and increase 2
Weight (kg)	decrease 7%	increase 7%
Orthostatic hypotension (mm Hg)b	30 mm Hg decrease in systolic BP (supine to standing)	--

a Converted to Celsius for analysis.

b In the individual clinical study reports, the criterion for orthostatic hypotension was a 20 mm Hg decrease in systolic blood pressure (BP) (supine to standing).

Table 8.1.7.3.2.2. Incidence of Potentially Clinically Significant Changes in Vital Signs and Weight Placebo-Controlled Integrated Database Acute Phase

Abnormal Vitals		Olz			Placebo			Fisher's Exact	Cochran-Mantel-Haenszel
		N	n	%	N	n	%	P-value	P-value
Vital	Direction								
Orthostatic Sys BP	Decrease	237	13	5.5%	111	2	1.8%	.158	.172
Standing Diastolic BP	High	239	10	4.2%	112	3	2.7%	.762	.365
	Low	239	0	0.0%	113	3	2.7%	.032	.003
Standing Pulse	High	232	9	3.9%	109	4	3.7%	1.00	.744
	Low	237	0	0.0%	111	0	0.0%	n/a	n/a
Standing Systolic BP	High	240	1	0.4%	113	0	0.0%	1.00	.557
	Low	231	17	7.4%	107	6	5.6%	.647	.775
Supine Diastolic BP	High	238	0	0.0%	114	2	1.8%	.104	.061
	Low	240	6	2.5%	114	1	0.9%	.436	.485
Supine Pulse	High	239	1	0.4%	114	0	0.0%	1.00	.556
	Low	239	4	1.7%	114	1	0.9%	1.00	.766
Supine Systolic BP	High	240	0	0.0%	114	0	0.0%	n/a	n/a
	Low	235	13	5.5%	109	3	2.8%	.409	.535
Temperature (C)	High	241	1	0.4%	114	0	0.0%	1.00	.557
Weight (kg)	Gain	239	70	29.3%	113	3	2.7%	<.001	<.001
	Loss	239	6	2.5%	113	7	6.2%	.126	.126

Table 8.1.8.3.1 ECG Intervals and Heart Rate Mean Change from Baseline to Endpoint
Placebo-Controlled Integrated Database Acute Phase

		Baseline		Endpoint		Change			Overall
		Mean	Std	Mean	Std	n	Mean	Std	p-Value
ECG Interval	Pooled Therapy								
ECG Heart Rate (bpm)	Olz	76.25	14.25	78.69	13.90	210	2.44	15.52	.121
	Placebo	77.34	13.75	77.40	12.65	98	0.06	12.94	
ECG PR Interval (sec)	Olz	0.16	0.02	0.16	0.02	209	0.00	0.01	.585
	Placebo	0.16	0.01	0.16	0.02	98	-0.00	0.01	
ECG QRS Interval (sec)	Olz	0.08	0.01	0.08	0.01	210	-0.00	0.01	.802
	Placebo	0.08	0.01	0.08	0.01	98	0.00	0.01	
ECG QT corrected (msec)	Olz	390.06	21.63	391.39	22.22	210	1.32	25.84	.297
	Placebo	392.80	20.88	391.71	19.38	98	-1.09	20.24	
ECG QT Interval (msec)	Olz	349.81	32.85	345.00	29.72	210	-4.81	31.01	.310
	Placebo	349.39	30.96	347.55	27.02	98	-1.84	27.86	

Table 8.1.8.3.2.2. Incidence of Potentially Clinically Significant Change in ECG Intervals and Heart Rate Placebo-Controlled Integrated Database Acute Phase

Abnormal ECG Intervals		Olz			Placebo			Fisher's Exact	Cochran-Mantel-Haenszel
		N	n	%	N	n	%	P-value	P-value
ECG Interval	Direction								
ECG Heart Rate	High	209	2	1.0%	98	1	1.0%	1.00	.742
	Low	209	0	0.0%	98	0	0.0%	n/a	n/a
ECG PR Interval	High	191	7	3.7%	95	2	2.1%	.722	.527
ECG QRS Interval	High	179	10	5.6%	83	6	7.2%	.589	.785
ECG QT corrected	High	202	11	5.4%	92	4	4.3%	.783	.639
ECG QT Interval	High	209	0	0.0%	98	0	0.0%	n/a	n/a

ADDENDUM TO:

Review and Evaluation of Clinical Data
NDA # 20-592

Sponsor:	Eli Lilly and Company
Drug:	Olanzapine (ZYPREXA)
Indication:	Symptoms of Psychotic Disorders
Material Submitted:	Four-month Safety Update
Correspondence Date:	January 12, 1996
Date Received:	January 16, 1996

I. Background

On September 21, 1995, the sponsor submitted NDA 20-592 for the approval of olanzapine, a novel serotonin/dopamine receptor antagonist, in the treatment of symptoms of psychotic disorders. The safety database cutoff dates were 6/30/95 (for deaths and serious adverse events) and 2/14/95 (for other safety data). This submission contains their first four-month safety update to their original submission.

II. Clinical Data

A. Description of Submitted Data

This update consists of safety data from 2/15/95 through 10/31/95 for deaths and serious adverse events and from 2/15/95 through 7/14/95 for all other types of safety data. This data was categorized, in parallel with data in the original submission, into a Primary Safety Database and a Secondary Safety Database.

Primary Safety Database
The Primary Safety Database consists of data from open-label extensions of four Phase 2/3 multicenter trials (HGAD, HGAP, E003, and HGAO), from double-blind and open-label extensions of one Phase 3 multicenter study (HGAJ), and seven open-label Phase 3 trials (HGBB, HGBI, HGBX, HGCA, HGBT, HGBK, and HGCG). These studies are all described in the clinical review of the original NDA submission except for HGBK (Open Label Olanzapine in Treatment-Refractory Schizophrenics) and HGCG (Open Label Experience with Olanzapine).

Data was provided in the form of line listings of patients with the following types of events:

- Deaths
- Dropouts due to Adverse Events
- Serious Adverse Events
- Potentially Clinically Significant (PCS) Adverse Events
- PCS Changes in Vital Signs and Weights
- PCS Changes in Chemistry Analytes
- PCS Changes in Hematology Analytes
- PCS Changes in Urinary Analytes
- PCS Changes in ECG Intervals and Heart Rate

The criteria used to identify these patients was identical to that applied in the original NDA database, with one exception: the criteria for a PCS change in body weight was an increase of 15% or a decrease of 7%.

Individual summaries for listed patients were included for events occurring in the 2/15/96 to 7/14/96 interval; annotations to the line listings are given for some later events.

Secondary Safety Database

The Secondary Safety Database consists of information from nine clinical pharmacology studies (HGAU, HGAW, HGAX, HGCB, HGCC, HGCE, HGCD, E002, and 205E), four open-label studies conducted in Japan (202E, 203E, 204E, and 208E), and six ongoing, blinded Phase 3 studies (HGBA, HGBG, HGBH, HGBJ, HGBL, and HGBU).

Listings were provided for the following patients:

- Deaths
- Serious, unexpected, possibly causally related adverse events ("Alert" events).
- Dropouts due to Adverse Events (clinical pharmacology and Japanese open-label studies only).

Individual summaries for the listed patients were provided for events occurring in the 2/15/96 to 7/14/96 timeframe; annotations to the line listings are given for some later events.

B. Review Methodology

Line listings of COSTART terms were examined for all deaths, serious or "alert" events, or events leading to discontinuation, to detect the occurrence of any adverse events judged to be clinically important. For any such event or any event with a non-specific COSTART term, the corresponding patient summary was reviewed. For cases of serious adverse events of concern without a narrative summary, the corresponding 10-Day Alert Report was located in the Division Document Room to obtain further information. A

judgement was made regarding possible causality to olanzapine.

For potentially clinically significant adverse events in the Primary Database, listings were examined to detect any events not previously observed in the original NDA database.

Line listings of patients with potentially clinically significant changes in laboratory, vital sign, and ECG parameters were not examined in detail for the following reasons. Changes in these parameters were more systematically evaluated in the original NDA database. Data in this update were largely uncontrolled and from long-term use; patient exposure was not known, which did not permit the calculation of even uncontrolled incidence rates. Furthermore, changes in these parameters which were associated with clinical events should have been detected under the reviews of important adverse events. In short, a useful interpretation of the line listings for these variables, as presented in this submission, would not have been possible.

C. Summary of Safety Findings

Deaths

Three deaths were previously considered in the original clinical review of this NDA due to some overlap in the timeframes for including deaths between the original submission and this update (i.e. 2/15/95 through 6/30/95): **HGAJ 315-2896** (suicide attempt), **HGAP 5-1215** (pneumonia and myocardial infarction), and **HGBT 241-2409** (multiple organ failure). No additional substantive information was provided relevant to these cases.

Three new deaths were reported: **HGAJ 1-1423** (cardiac arrest in a 64 y.o. female with breast cancer after 412 days of treatment), **HGAP 6-1262** (heat stroke in a 60 y.o. female after 539 days of treatment), and **HGAJ 322-3008** (associated with epistaxis in a 56 y.o. male). Olanzapine was unlikely to play a role in the first death given the length of treatment prior to death. A causative role is more likely in the second death, given the possibility of thermal dysregulation with antipsychotic agents, although the duration of treatment prior to the event raises the question of non-drug factors. The last case, death associated with epistaxis, could not be further evaluated because of the limited data provided, to include information from the 10-Day Report (FR95101612A submitted 10/17/95).

Serious/"Alert" Adverse Events

There were two cases of cardiomyopathy reported: **HGBB 1-1001** was a 44 y.o. male with a history of heart disease who developed atrial fibrillation 3 weeks after olanzapine was discontinued following 116 days of therapy; shortly

thereafter, he was diagnosed with myocarditis. HGBH 325-3251 was a 59 y.o. male with prestudy PVC's and a history of hypertension and smoking who received olanzapine for 21 days. He experienced acute, severe blood pressure elevation at that time (205/145) and was hospitalized medically for treatment. Subsequent echocardiograms revealed global hypokinesia and apparent low flow. He expired about 3 months later, presumably due to progressive cardiac problems.

A 45 y.o. male (HGAJ 723-5541) was diagnosed with hepatitis and hyperbilirubinemia (apparently without jaundice) after 708 days of olanzapine therapy. Liver ultrasound indicated lipodystrophy and venous congestion. Review of the corresponding updated 10-Day Report (F195105668A submitted 12/12/95) revealed considerable confounding by heavy alcohol use and possibly by cardiac decompensation, resulting in liver congestion.

Patient JE203E 48-1 was a 44 y.o. male who, after 334 days of treatment, experienced hyponatremia (sodium= 110 mEq/L) (attributed to psychogenic polydipsia) accompanied by fever, rigidity, coma, and elevated CPK (>22,000 U/L). He improved after olanzapine discontinuation. Neuroleptic malignant syndrome was suspected, based on a review of the 10-Day Report (JP95091135A submitted on 10/3/95).

Patient J203E 62-2 was a 52 y.o. female treated with olanzapine 15 mg/day for 296 days when she developed hyponatremia and was diagnosed with SIADH. However, it was subsequently judged that her electrolyte imbalance was related to psychogenic polydipsia, according to the 10-Day Report (JP 95100424A) submitted on 10/24/95.

Lastly, patient HGAJ 27-1526 was a 45 y.o. diabetic male who experienced a non-fatal cerebrovascular accident after 183 days of treatment with olanzapine 15 mg/day.

With the exception of possible NMS in Patient JE203E 48-1, these events were not judged to be causally related to olanzapine.

<u>Discontinuations due to Adverse Events</u>
Excluding fatal or other serious/"alert" events which were discussed above, only two events leading to dropout were remarkable:

Patient HGAJ 601-4889 was a 36 y.o. male who was found to have hepatic steatosis after treatment with olanzapine 5 mg/day for 484 days. No etiology was mentioned, to include alcohol use.

Patient HGAJ 74-1357 was a 48 y.o. male with new onset congestive heart failure after receiving olanzapine 20 mg/day

for 254 days. He also had a postural decrease in systolic blood pressure of 34 mmHg.

While a role for olanzapine in these events cannot be entirely ruled out, there certainly are other possible etiologies and, given experience in the larger NDA database, there does not appear to be a pattern of either hepatic steatosis or cardiac failure associated with this drug.

Potentially Clinically Significant Adverse Events

Only three such events were reported: two cases of syncope (occurring after 647 and 466 days of treatment) and one cerebrovascular accident (**HGAJ 57-1061**) after 452 days of therapy, which is described as resolving within one day and not leading to hospitalization. Both cerebrovascular accidents and syncope were reported among patients in the original NDA database.

III. Conclusions and Recommendations

Only two reported adverse events in this update were felt to be clinically important and attributable to olanzapine:

- Possible drug-induced thermal dysregulation (**HGAP 6-1262**).
- Possible neuroleptic malignant syndrome (**JE203E 48-1**).

Both events are known to be associated with other antipsychotic agents and neither changes the previous conclusions regarding the overall safety and approvability of this drug. However, standard statements regarding the potential effects on body temperature regulation and the possible occurrence of NMS with olanzapine should be included in labeling.

Gregory M. Dubitsky, M.D.
July 29, 1996

cc: NDA# 20-592
HFD-120
HFD-120/GDubitsky
PAndreason
TLaughren
SHardeman

7-29-96
I agree with the above assessment. See my memo to file for more detailed comments on the NDA.
Thomas P. Laughren, MD
TL, PDP

Statistical Review and Evaluation

NDA#: 20-592

Applicant: Eli Lilly and Company

Name of Drug: Zyprex (olanzapine)

Documents reviewed: Vols. 1.254, 1.258, 1.265, 1.272, 1.315, 1.323

Medical Officer: Paul Andreason, M.D., HFD-120

Background

The sponsor has submitted four (4) randomized, controlled, double-blind, multicenter, parallel design trials in support of Zyprex's efficacy and safety for the treatment of schizophrenia. Trials HGAP (Zyprex doses of 10.0mg and 1.0 mg) and HGAD (Zyprex doses of 5.0 +/- 2.5mg, 10.0 +/- 2.5 mg, 15.0 +/- 2.5mg, Haldol 15.0 +/- 5.0 mg) were placebo-controlled, while E003 (same Zyprex dose groups as in HGAD) used a very low dose of Zyprex (1.0 mg) as a control, and HGAJ (Zyprex 5-20mg) used Haldol (5-20mg) as a control. All 4 trials used 6 weeks of double blind therapy for the acute phase.

All results of analyses and bar charts were provided by the sponsor. The graphs of cohort 'histories' were provided by the reviewer.

The only supplementary analysis specified in the protocols was the 'responder' analysis.

Trial HGAP

This trial was designed to randomize 120 patients in order to have at least 80% power to show a difference of at least 10 in mean change from baseline BPRS score (0-6 scale) for the LOCF analysis. This calculation assumed a standard deviation of 14.56. Randomization was to continue until at least 4 centers had each randomized at least 15 patients. Twelve (12) US centers randomized patients.

After a 4-9 day placebo lead-in phase used to screen out patients who responded to inpatient hospitalization, 50 patients were randomized to placebo, 50 to Zyprex 10.0 mg/day and 52 to Zyprex 1.0 mg/day. Patients had to have at least 4 on the CGI and a BPRS of at least 24 (0-6 point scale) or 42 (0-7 point scale). Patients were hospitalized for at least 3 weeks. Beginning at the 4th week, patients could qualify to go on open label treatment as outpatients based on performance in the trial and physician judgement.

The **primary analysis** for all variables is ANOVA on the LOCF change from baseline with treatment, investigator and their interaction in the model. This review concentrates on the efficacy variables that the Medical Division has chosen: Total PANSS, negative PANSS, BPRS

'positive' items, and CGI Severity. The sponsor has also done supplementary analyses on 'response' rates, repeated measures, and slopes.

Results

Randomization was well-balanced among and within investigators. Cell sizes ranged from 2 to 7 patients and there were no important baseline differences among treatment groups. **Table 1** displays the patient disposition over time. Dropouts were overwhelming due to lack of efficacy. **Figure 1**'s Kaplan-Meier curves show that placebo patients dropped out more frequently for lack of efficacy than those in the 10.0mg group (p=.03 logrank) for this endpoint.

Table 2 displays the major statistical results for the four endpoints. Note that all p-values against placebo for the 10.0mg dose group are statistically significant. There was no meaningful treatment by center interaction.

Figures 2-5 display the 'histories' of different dropout cohorts during the trial for the 10.0mg and placebo groups. For instance, the **top plot** displays the mean scores at each timepoint for each dropout cohort. Note, for example, that completers (week 6) in the two arms not only did not differ at the end of the trial, but also hardly varied from each other during the whole course of the trial. This is generally true for all four endpoints. Note also the not surprising fact that completers tend to improve earlier in the trial than those who eventually drop out. The **bottom plot** displays the change from baseline for each dropout cohort and completers cohort thus highlighting the effect of the condition of dropouts on the eventual LOCF treatment differences. **Figure 6** displays the cumulative distribution function of the Total PANSS. Note the clear separation of the 10.0mg arm from the other two arms.

Supplementary analyses:

The **'responder'** (a patient in the trial for greater than 3 weeks whose BPRS decreased from baseline to endpoint by at least 40% or whose endpoint BPRS was 18 or less) analysis was statistically significant for the 10.0mg arm (p=.03) with 12/42 (27.9%) responders while the placebo arm had 4/43 (9.5%) responders.

The repeated measures analysis produced a statistically significant difference between 10.0mg and placebo **for average BPRS over time based upon an LOCF imputation for each timepoint.**

The **comparison of average slopes** of BPRS over time, however, was not close to statistical significance (p=.345). The placebo average was -.273 BPRS points/visit while that for 10.0mg was -1.34.

The sponsor also used a supplementary **covariate analysis for the negative PANSS**. It used on-study covariates, viz the change from baseline in positive PANSS, PANSS depression item and parkinsonian symptoms (Simpson-Angus Scale total scores). There were no statistical differences between any of the arms using this adjusted analysis. The effect of the adjustment was to dramatically decrease the treatment difference of almost 4 points in the unadjusted analysis to only 1.5 points in the adjusted.

Table 3 displays the frequency distributions of **baseline-endpoint changes in the CGI Severity** scores. Note a general shift in the marginal totals toward lower final scores in the 10.0mg arm. In addition, the sponsor performed a proportional odds analysis and found an odds ratio of 1.89 with p-value of .088. This means that the odds of finishing lower than any specified CGI Severity value in the 10.0 mg arm is approximately twice that of someone in the placebo arm.

Trial HGAD

This US and Canadian trial was designed to randomize 250 'protocol-qualified' patients in order to have at least 80% power to show a difference of at least 8 in mean change from baseline to visit 7 (week 4) for the BPRS score (0-6 scale) LOCF analysis. This calculation assumed a standard deviation of 11 points. At least twenty-two (22) investigators randomized patients.

After a 4-9 day placebo lead-in phase for neuroleptic washout, 68 patients were randomized to placebo, 65 to Zyprex Low dose (L), 64 to Zyprex Medium dose (M), 69 to Zyprex High dose (H), and 69 to Haldol. Patients had to have at least 4 on the CGI and a BPRS of at least 24 (0-6 point scale). Patients were hospitalized for a least 2 weeks (until Visit 5). Beginning at Visit 5, patients could qualify to go on open label treatment as outpatients based on performance in the trial and physician judgement.

The **primary analysis** for all variables is ANOVA on the LOCF change from baseline with treatment, investigator and their interaction in the model. This review concentrates on the efficacy variables that the Medical Division has chosen: Total BPRS, SANS, BPRS 'positive' items, and CGI Severity. The sponsor has also done supplementary analyses on 'response' rates, repeated measures, and slopes.

Results

There were some cells with no patients. Three investigators (8, 14, and 18) were pooled so that each cell would have at least one patient. Cell sizes then ranged from 1 to 9. There is some degree of imbalance among centers in total enrollment ranging from 5 to 43. Only Total BPRS showed a statistical difference at baseline when all arms were included in the ANOVA among all the treatment groups. For purposes of concentrating on the comparison of High dose (H) to placebo, the placebo mean was 39.69 and that of H was 42.62. **Table 4** displays the patient disposition over time. Dropouts were overwhelming due to lack of efficacy. **Figure 7**'s Kaplan-Meier curves show that placebo patients dropped out more frequently for lack of efficacy than

those in the H arm (p=.003 logrank).

Table 5 displays the major statistical results for the four endpoints. Note that all p-values against placebo for the H dose group are statistically significant.

Figures 8-11 display the 'histories' of different dropout cohorts during the trial for the Zyprex H and placebo groups. Again, the **top plot** displays the mean scores at each timepoint for each dropout cohort. Note, for example, that completers (week 6) in the two arms not only did not differ at the end of the trial, but also hardly varied from each other during the whole course of the trial. This is generally true for all four endpoints. Note also the not surprising fact that completers tend to improve earlier in the trial than those who eventually drop out. The **bottom plot** displays the change from baseline for each dropout cohort and completers cohort thus highlighting the effect of the condition of dropouts on the eventual LOCF treatment differences. **Figure 12** displays the cumulative distribution function of the Total BPRS. Note the clear separation of the Haldol and Zyprex H arms from placebo.

Supplementary analyses:

The **'responder'** (a patient in the trial for greater than 3 weeks whose BPRS decreased from baseline to endpoint by at least 40% or whose endpoint BPRS was 18 or less) analysis was not statistically significant for any pairwise comparison. The H group had 32/65 (49.2%) responders while the placebo arm had 21/62 (33.9%) responders (p=.08).

The repeated measures analysis produced statistically significant differences between botn the Zyprex H and M doses and placebo **for average BPRS over time based upon an LOCF imputation for each timepoint.**

The **comparison of average slopes** of BPRS over time produced significant comparisons from placebo for all doses.

Table 6 displays the frequency distributions of **baseline-endpoint changes in the CGI severity scores**. The difference between the two highest Zyprex doses and placebo appears to be a shift in endpoint from category 6 (very ill) to category 4 (moderate) compared to placebo. In addition, the sponsor performed a proportional odds analysis and found an odds ratio of 1.84 with p-value of .051 for the H dose against placebo.

The sponsor also used a supplementary **covariate analysis for the SANS**. It used on-study covariates, viz the change from baseline in BPRS total, the BPRS depression item and parkinsonian symptoms (Simpson-Angus Scale total scores). There was a statistically significant difference between the Zyprex H group and placebo. The adjustment reduced the treatment difference between the high dose and placebo.

Trial E003

This international trial using 50 study centers was designed to randomized 390 patients in order to have 90% power to show a difference of at least 8 in mean change from baseline in the BPRS. This calculation assumed a standard deviation of 13 points and a dropout rate of 30%. At least 8 countries were required to have at least 5 complete blocks (5 patients/block).

After a 4-7 day placebo lead-in phase to exclude placebo/hospitalization responders, 88 patients were randomized to Zyprex 1.0mg, 87 to Zyprex low dose (L), 86 to Zyprex Medium dose (M), 89 to Zyprex High dose (H), and 81 to Haldol. Patients had to have at least 4 on the CGI and a BPRS of at least 24 (0-6 point scale). Patients were hospitalized for at least 2 weeks, after which they could be in- or out-patients.

The **primary analysis** for all variables is ANOVA on the LOCF change from baseline with treatment, investigator and their interaction in the model. This review concentrates on the efficacy variables that the Medical Division has chosen: Total PANSS, negative PANSS, BPRS 'positive' items, and CGI Severity. The sponsor has also done supplementary analyses on 'response' rates, repeated measures, and slopes.

Results

This trial was poorly administered with respect to patient accrual. Only one country accrued 5 patients/block and there were many cases of zero cells. Most cells had either 0, 1, or 2 patients. Investigators were pooled so that each cell would have at least one patient. There were no important imbalances in baseline values among the treatment groups. **Table 7** displays the patient disposition over time. The modal reason for dropping out was lack of efficacy. **Figure 13**'s Kaplan-Meier curves show that Zyprex H patients dropped out at about the same rate as the Zyprex 1.0mg patients.

Table 8 displays the major statistical results for the four endpoints. Only the Zyprex H group reaches nominal statistical significance against the 'pseudo-control' Zyprex 1.0mg, and that only on the positive BPRS and CGI severity.

Figures 14-17 display the 'histories' of different dropout cohorts during the trial for the Zyprex H and placebo groups. Again, the **top plot** displays the mean scores at each timepoint for each dropout cohort. Note, for example, that completers (week 6) in the two arms not only did not differ at the end of the trial, but also hardly varied from each other during the whole course of the trial. This is generally true for all four endpoints. Note also the not surprising fact that completers tend to improve earlier in the trial than those who eventually drop out. The **bottom plot** displays the change from baseline for each dropout cohort and completers cohort thus highlighting the

effect of the condition of dropouts on the eventual LOCF treatment differences. **Figure 18** displays the cumulative distribution function of the Total PANSS. The largest separation appears to be that of Zyprex H from Zyprex 1.0mg.

Supplementary analyses:

The **'responder'** (a patient in the trial whose BPRS decreased from baseline to endpoint by at least 40% or whose endpoint BPRS was less than 18) analysis was significant for only the Zyprex H group. The H group had 49/85 (57.6%) responders while the placebo arm had 35/83 (42.2%) responders (p=.045).

The repeated measures analysis did not produce any statistically significant comparisons to placebo **for average BPRS over time based upon an LOCF imputation for each timepoint.** The Zyprex comparison, however, was close to statistical significance: p=.07.

The **comparison of average slopes** of BPRS over time, however, was not close to statistical significance for any dose comparison to 1.0 mg. The 1.0mg average was -1.50 BPRS points/visit while that for Zyprex H was -2.82 and that for Zyprex M was -2.36.

The sponsor also used a supplementary **covariate analysis for the negative PANSS.** It used on-study covariates, viz the change from baseline in positive PANSS, PANSS depression item and parkinsonian symptoms (Simpson-Angus Scale total scores). There were no statistical differences between any of the arms using this adjusted analysis.

Table 9 displays the frequency distributions of **baseline-endpoint changes in the CGI severity** scores. There appears to a be a slight shift in the marginal totals toward lower final scores in the Zyprex H arm relative to the 1.0mg arm.

Trial HGAJ

This international trial using 174 study centers in 17 countries was designed to randomize 1500-2500 patients in a 2:1 ratio (Olz:Haldol). The primary reason for the sample size was to treat as many as 2000 patients with olanzapine in doses of at least 5mg/day. According to the sponsor, this size provided 99% power to detect a difference of 8 total BPRS points in mean change from baseline at 6 weeks. This calculation assumed a standard deviation of 11.

After a 4-7 day screening phase for neuroleptic washout, 1336 patients were randomized to Olz and 660 to Haldol. Patients had to have scored at least 18 on the extracted BPRS (0-6 point scale). Patients could be in- or out-patients.

The **primary analysis** for all variables was ANOVA on the LOCF change from baseline with

treatment, investigator and their interaction in the model. This review concentrates on the efficacy variables that the Medical Division has chosen: Total PANSS, negative PANSS, BPRS 'positive' items, and CGI Severity. The sponsor has also done supplementary analyses on 'response' rates, repeated measures, and slopes.

Results

There were no important imbalances in baseline values among the treatment groups. **Table 10** displays the patient disposition over time. The modal reason for dropping out was lack of efficacy. **Figure 19**'s Kaplan-Meier curves show that Zyprex H patients dropped out less often than Haldol patients.

Table 11 displays the major statistical results for the four endpoints. Nominal statistical differences occurred in favor of olanzapine on 3 of the 4 primary endpoints.

Figures 20-23 display the 'histories' of different dropout cohorts during the trial for the Zyprex H and placebo groups. Again, the **top plot** displays the mean scores at each timepoint for each dropout cohort. Note, for example, that completers (week 6) in the two arms not only did not differ at the end of the trial, but also hardly varied from each other during the whole course of the trial. This is generally true for all four endpoints. Note also the not surprising fact that completers tend to improve earlier in the trial than those who eventually drop out. The **bottom plot** displays the change from baseline for each dropout cohort and completers cohort thus highlighting the effect of the condition of dropouts on the eventual LOCF treatment differences. **Figure 24** displays the cumulative distribution function of the Total PANSS.

Supplementary analyses:

The **'responder'** (a patient in the trial for greater than 3 weeks whose BPRS decreased from baseline to endpoint by at least 40% and whose baseline BPRS total was greater than 18) analysis was significantly in favor of the olanzapine group. The olanzapine group had 567/1099 (51.6%) responders while the Haldol arm had 176/514 (34.2%) responders (p= 001).

The repeated measures analysis produced a statistically significant difference in favor of olanzapine compared to Haldol **for average BPRS over time based upon an LOCF imputation for each timepoint.**

The **comparison of average slopes** of BPRS over time, however, was not statistically significant. The olanzapine average was -1.75 BPRS points/visit while that for Haldol was -1.34.

The sponsor also used a supplementary **covariate analysis for the negative PANSS**. It used on-study covariates, viz the change from baseline in positive PANSS, PANSS depression item and parkinsonian symptoms (Simpson-Angus Scale total scores). This adjusted analysis was not statistically significant.

Table 12 displays the frequency distributions of **baseline-endpoint changes in the CGI Severity** scores.

Discussion and Conclusions

Trials HGAP and **HGAD** provide statistical evidence that, on average, olanzapine-treated patients who remain in the trials for up to and including six weeks of treatment attain better scores on standard scales than patients treated with placebo. Review of the figures illustrating dropout cohorts discloses a substantial effect of dropouts, especially in Trial HGAP at 4 weeks when patients had the opportunity of leaving the trial to be on open label medication. **Trial E003** probably suffered from the Zyprex 1.0 mg/day dose being somewhat efficacious.

Nevertheless, quantification of a "treatment effect" is difficult due to the appreciable dropout rates in these trials. One measure could be the 'response rate' difference proposed by the sponsor. However, those depend upon an arbitrary percent decrease of an average on a standard psychiatric scale. Alternatively, we can look at the frequency of patients who improved from baseline with respect to CGI Severity. The table below displays the frequencies of changes from baseline for the highest dose olanzapine groups and placebo in **Trials HGAP, HGAD, and E003**. A **negative** change indicates improvement.

		Change from baseline in CGI Severity								
		-5	-4	-3	-2	-1	0	1	2	Total
HGAD										
	Olz-H	0	1	5	13	24	21	4	0	68
	Placebo	0	0	1	14	10	26	15	2	68
E003	Olz-H	0	7	19	17	17	20	3	2	85
	Olz 1.0 mg/day	0	3	6	17	20	25	10	2	83
HGAP	Olz10.0 mg/day	1	2	4	1	11	24	7	0	50
	Placebo	0	1	0	3	12	21	9	3	49

The underlined numbers in **HGAD** show that the treatment difference arises from numbers of olanzapine patients improving 1 unit on the CGI Severity scale while those on placebo tend to worsen 1 unit. Examination of the baseline distributions reveal that virtually all of the differential movement comes from patients with either 4 or 5 on the CGI Severity Scale at baseline in both arms. The differential movement in trial E003 arises from a somewhat greater differential improvement than in **HGAD** (see underlined entries). In this case, the differential movement arises overwhelmingly from patients with baseline scores of 5 & 6 in contrast to 4 & 5 in **HGAD**.

The average baseline CGI Severity was, in fact, somewhat less in **HGAD** tha
contrast, any differential movement is not as pronounced in **Trial HGAP**.

With respect to a 'minimally effective dose', trial **HGAD** provides evidence t
(10 +/-2.5 mg/day) is effective using either a simple step-up or step-down m
procedure as long as monotonicity of dose response was a reasonable assump
Although there are consistent but slight numerical differences which favor Ol
primary endpoints, Olz-H (15 +/- 2.5 mg/day) is not statistically different fro
HGAD or **E003**. It is clear that the only effective dose in trial **HGAP** is 10.0

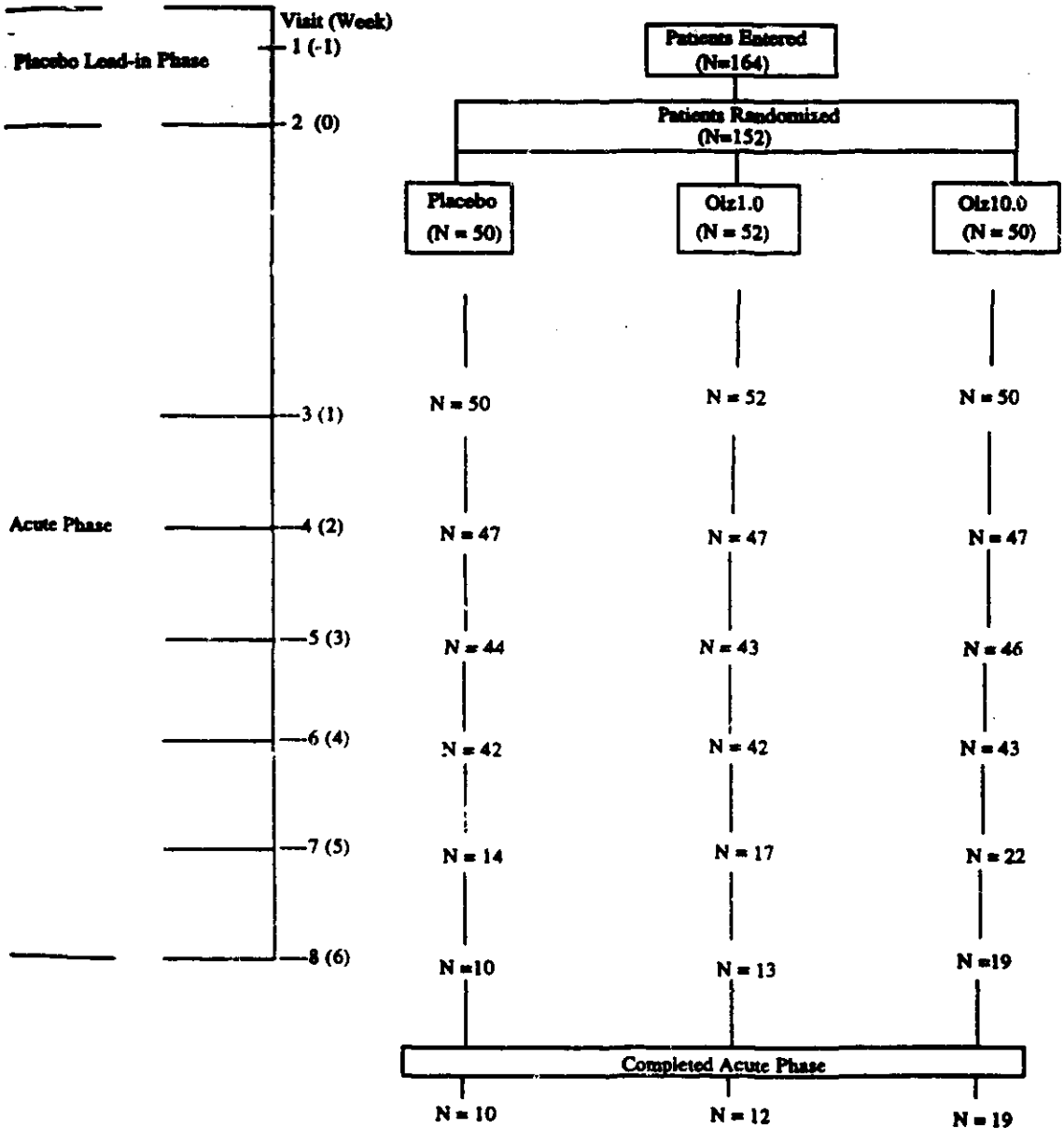
David Hoberman, Ph
Mathematical Statist

concur: Dr. Sahlroot 2-6-96

Dr. Chi 2/14/96

cc:
NDA# 20-592
HFD-701/Dr. Anello
HFD/120/Dr. Leber
HFD-120/Dr. Laughren
HFD-120/Dr. Andreason
HFD-120/Mr. Purvis
HFD-120/Mr. Hardiman
HFD-344/Dr. Lisook
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/Dr. Hoberman
HFD-710/chron
This review consists of 9 pages of text, 12 appended tables and 24 appended f

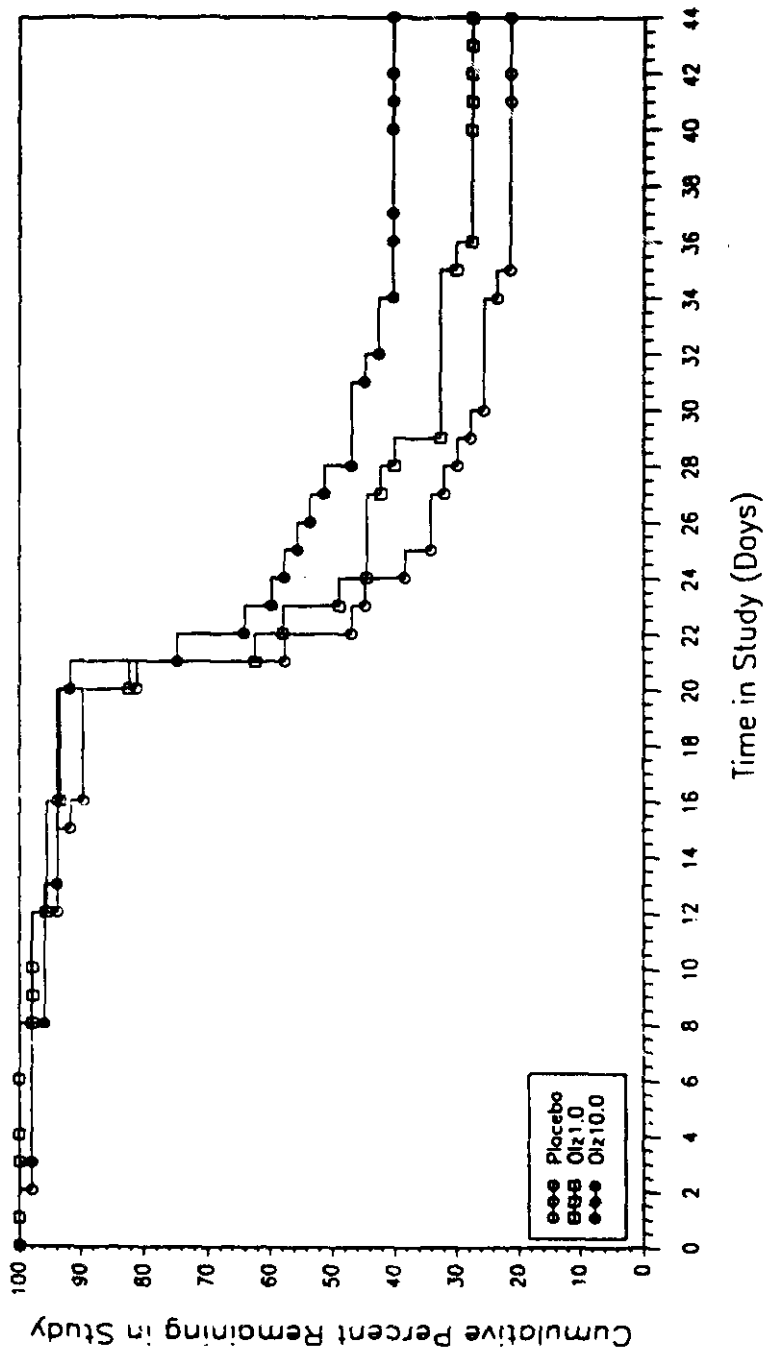
TABLE 1



N = number of patients at designated visit.

Figure HGAP.5.1.1. Overview of Patient Disposition
F1D-MC-HGAP Acute Phase

FIGURE 1



IGAP.5.1.3. Time to Discontinuation for Lack of Efficacy
F1D-MC-HGAP Acute Phase

Table HGAP.6.1.18. PANSS Total Score
Mean Change from Baseline to Endpoint
F1D-MC-HGAP Acute Phase

Variable analyzed: PANSS Total Score (PANSSTOT)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	Placebo	49	95.63	97.00	13.59	98.43	100.00	26.93	2.80	3.00	28.61
2)	Olz1.0	51	100.69	96.00	22.17	98.80	99.00	22.57	-1.88	-1.00	21.47
3)	Olz10.0	49	98.31	95.00	15.90	86.00	83.00	24.05	-12.31	-9.00	21.76

		p-Values			
				Pairwise*3	
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)	vs.(3)
1)	Placebo	.276	.057	.006	.192	.002
2)	Olz1.0	.903				.051
3)	Olz10.0	<.001				

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Table HGAP.6.1.20. PANSS Negative Score
Mean Change from Baseline to Endpoint
F1D-MC-HGAP Acute Phase

Variable analyzed: PANSS Negative Score (PANSSNG)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	Placebo	49	23.92	24.00	5.36	24.96	24.00	8.28	1.04	1.00	6.83
2)	Olz1.0	51	25.14	24.00	7.96	25.18	24.00	7.22	0.04	0.00	5.39
3)	Olz10.0	49	26.39	26.00	6.91	23.57	23.00	6.98	-2.82	-2.00	6.27

		p-Values			
				Pairwise*3	
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)	vs.(3)
1)	Placebo	.260	.501	.020	.411	.007
2)	Olz1.0	.901				.050
3)	Olz10.0	.001				

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Table HGAP.6.1.11. BPRS Positive Score
Mean Change from Baseline to Endpoint
F1D-MC-HGAP Acute Phase

Variable analyzed: BPRS Positive Score (BPRSPS)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	Placebo	49	12.31	13.00	3.31	12.29	12.00	4.96	-0.02	0.00	3.87
2)	Olz1.0	51	13.47	13.00	3.86	12.57	13.00	4.50	-0.90	-1.00	4.00
3)	Olz10.0	49	12.88	13.00	3.50	9.96	10.00	3.17	-2.92	-2.00	4.63

		p-Values			
				Pairwise*3	
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)	vs.(3)
1)	Placebo	.862	.033	.011	.131	.003
2)	Olz1.0	.212				.109
3)	Olz10.0	<.001				

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Table HGAP.6.1.27. CGI Severity Score
Mean Change from Baseline to Endpoint
F1D-MC-HGAP Acute Phase

Variable analyzed: CGI Severity Score (CGISEV)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	Placebo	49	5.00	5.00	0.82	4.88	5.00	1.29	-0.12	0.00	1.13
2)	Olz1.0	51	5.10	5.00	0.92	5.18	5.00	1.09	0.08	0.00	1.13
3)	Olz10.0	49	4.94	5.00	0.80	4.31	5.00	1.34	-0.63	0.00	1.41

		p-Values			
				Pairwise*3	
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)	vs.(3)
1)	Placebo	.561	.002	.013	.439	.036
2)	Olz1.0	.397				.004
3)	Olz10.0	.002				

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

FIGURE 2

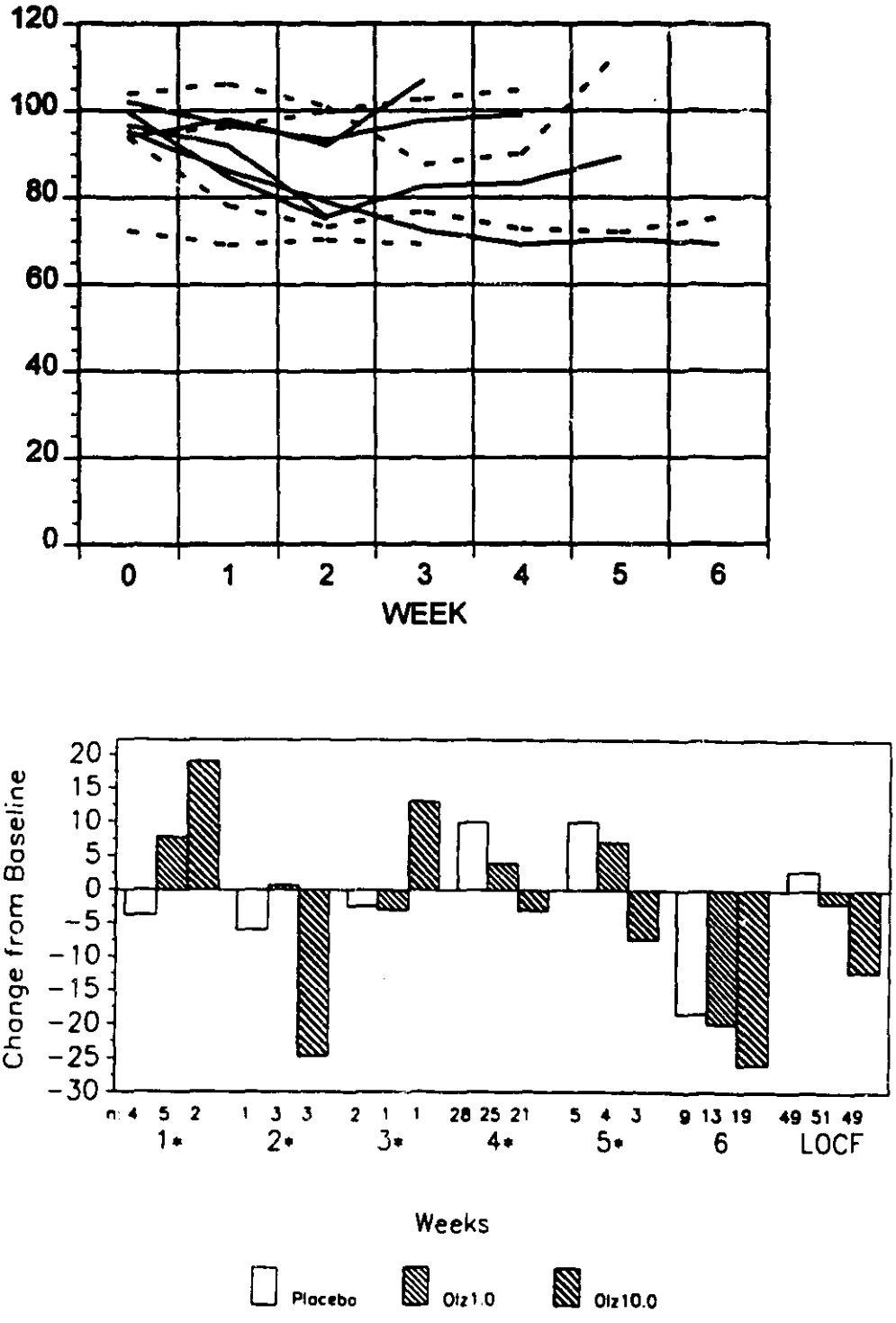

PANSS TOTAL
120
100
80
60
40
20
0
0 1 2 3 4 5 6
WEEK
Change from Baseline
20
15
10
5
0
-5
-10
-15
-20
-25
-30
n: 4 5 2 1 3 3 2 1 1 28 25 21 5 4 3 9 13 19 49 51 49
1* 2* 3* 4* 5* 6 LOCF
Weeks
Placebo
Olz1.0
Olz10.0

FIGURE 3

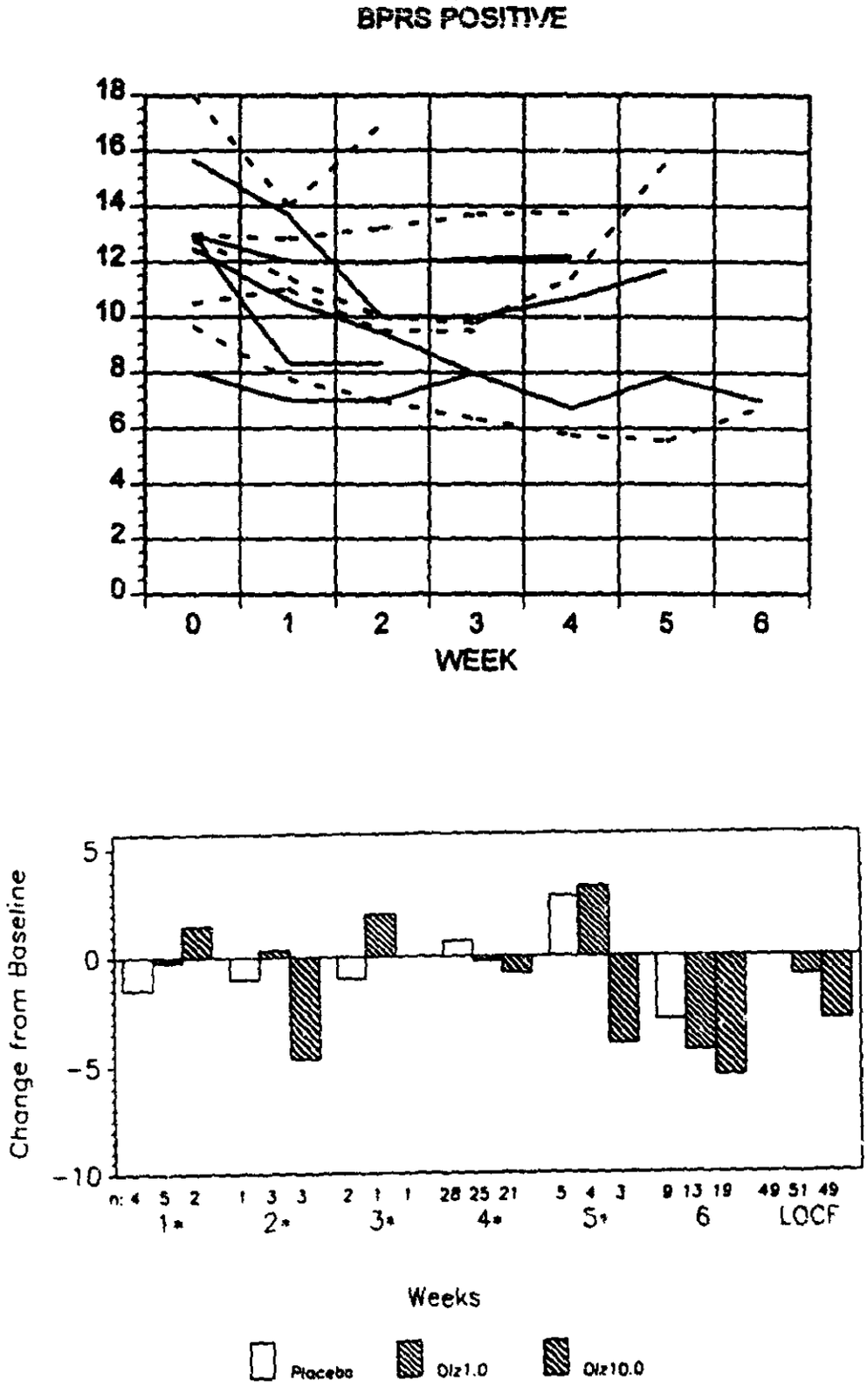

BPRS POSITIVE
18
16
14
12
10
8
6
4
2
0
0 1 2 3 4 5 6
WEEK
Change from Baseline
5
0
-5
-10
n: 4 5 2 1 3 3 2 1 1 28 25 21 5 4 3 9 13 19 49 51 49
1* 2* 3* 4* 5* 6 LOCF
Weeks
Placebo
Olz1.0
Olz10.0

FIGURE 4

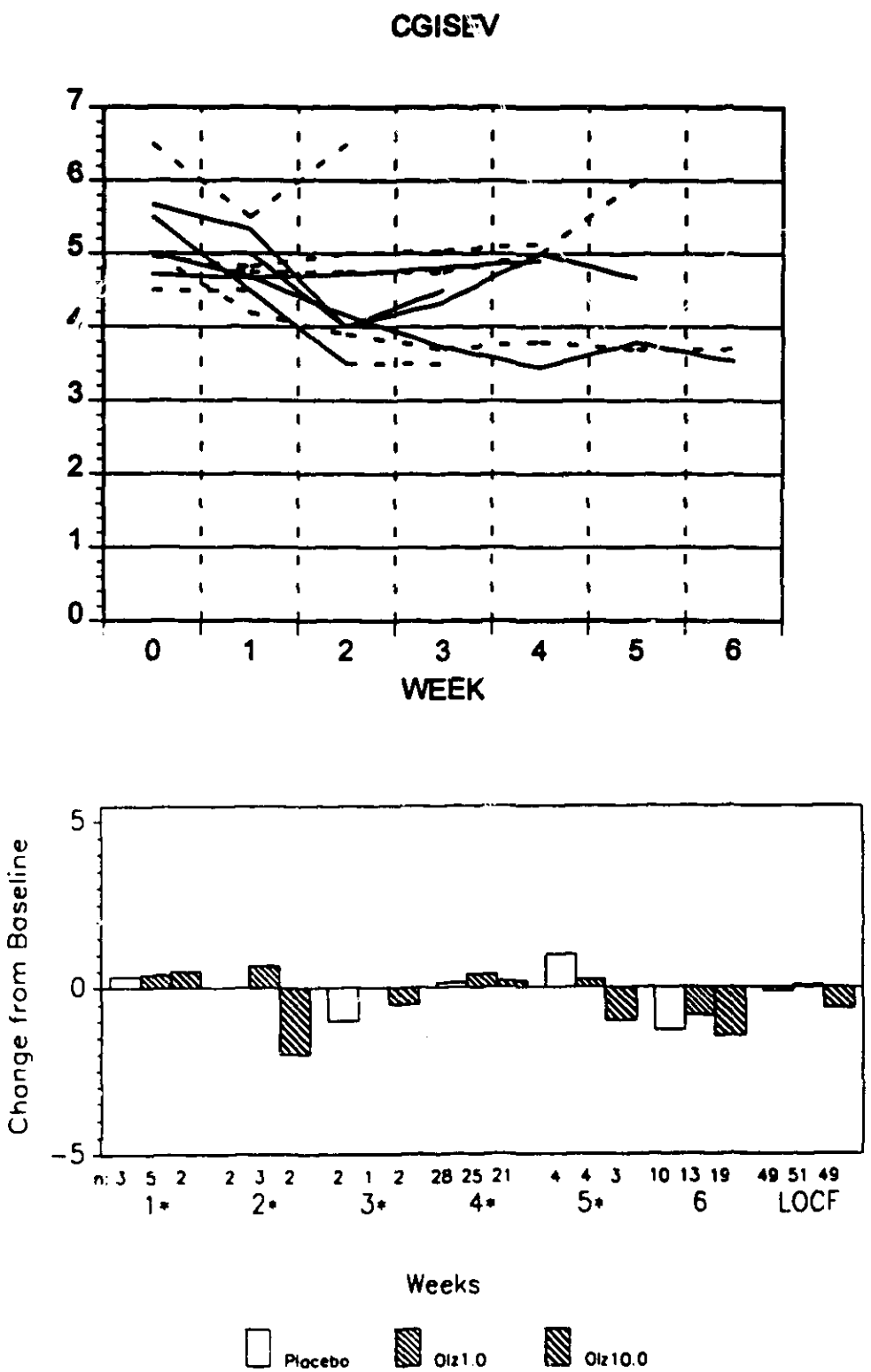
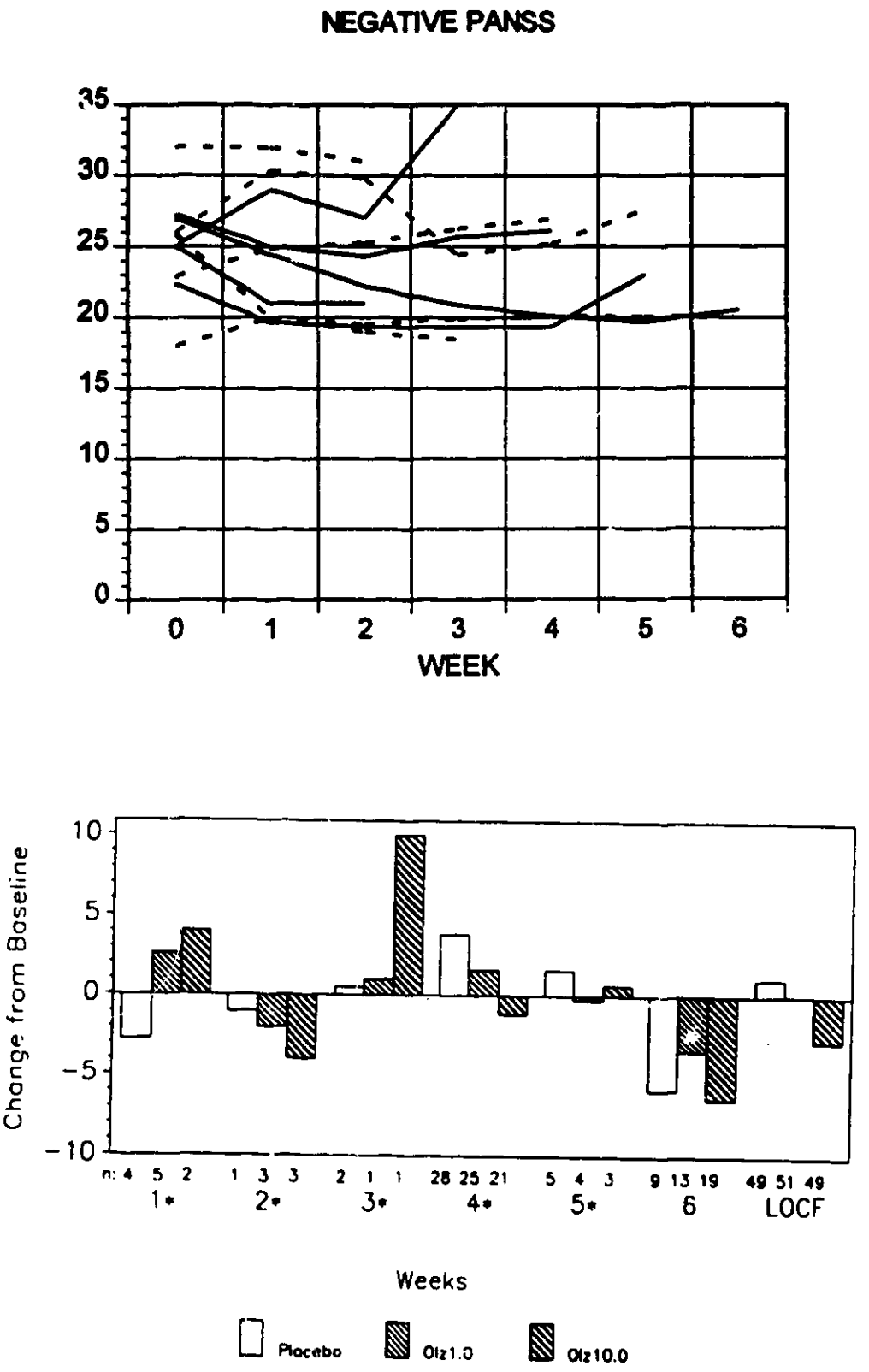

CGISEV
7
6
5
4
3
2
1
0
0 1 2 3 4 5 6
WEEK
Change from Baseline
5
0
-5
n: 3 5 2 2 3 2 2 1 2 28 25 21 4 4 3 10 13 19 49 51 49
1* 2* 3* 4* 5* 6 LOCF
Weeks
Placebo
Olz1.0
Olz10.0

FIGURE 5


NEGATIVE PANSS
35
30
25
20
15
10
5
0
0 1 2 3 4 5 6
WEEK
Change from Baseline
10
5
0
-5
-10
n: 4 5 2 1 3 3 2 1 1 28 25 21 5 4 3 9 13 19 49 51 49
1* 2* 3* 4* 5* 6 LOCF
Weeks
Placebo
Olz1.0
Olz10.0

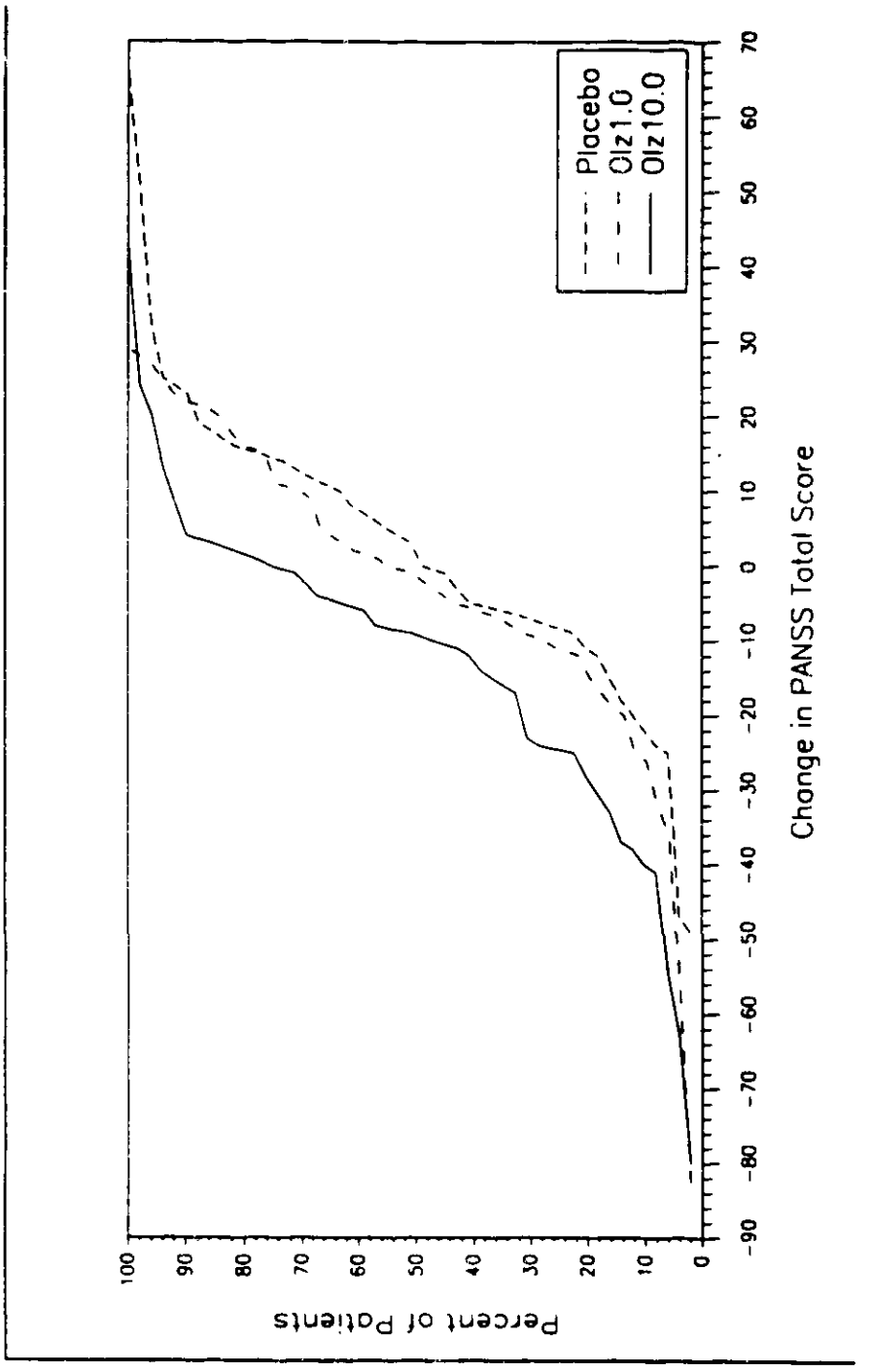


Figure HGAP.6.1.42. PANSS Total Score
Cumulative Distribution of Change
F1D-MC-HGAP Acute Phase

Table HGAP.6.1.29. CGI Severity Score, Baseline to Endpoint F1D-MC-HGAP Acute Phase

Treatment Group	Baseline Score	Endpoint Score[a] 1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	Total
Placebo	4	0	0	5 (33%)	5 (33%)	3 (20%)	2 (13%)	0	15
	5	0	0	1 (5%)	6 (30%)	9 (45%)	3 (15%)	1 (5%)	20
	6	0	1 (8%)	0	2 (15%)	1 (8%)	5 (38%)	4 (31%)	13
	7	0	0	0	0	0	0	1 (100%)	1
	Total	0	1	6	13	13	10	6	49
Olz1.0	4	0	0	2 (13%)	6 (40%)	6 (40%)	1 (7%)	0	15
	5	0	0	0	1 (5%)	8 (40%)	10 (50%)	1 (5%)	20
	6	0	0	1 (8%)	2 (17%)	3 (25%)	5 (42%)	1 (8%)	12
	7	0	0	1 (25%)	0	0	0	3 (75%)	4
	Total	0	0	4	9	17	16	5	51
Olz10.0	3	0	1 (100%)	0	0	0	0	0	1
	4	1 (7%)	0	2 (14%)	6 (43%)	5 (36%)	0	0	14
	5	0	2 (10%)	0	5 (24%)	13 (62%)	1 (5%)	0	21
	6	1 (8%)	2 (15%)	1 (8%)	1 (8%)	3 (23%)	4 (31%)	1 (8%)	13
	Total	2	5	3	12	21	5	1	49

Abbreviations Olz1.0 = olanzapine 1.0 mg/day; Olz10.0 = olanzapine 10.0 mg/day.

[a] Table entries are frequencies; row percents = frequency divided by row total.

Table 4

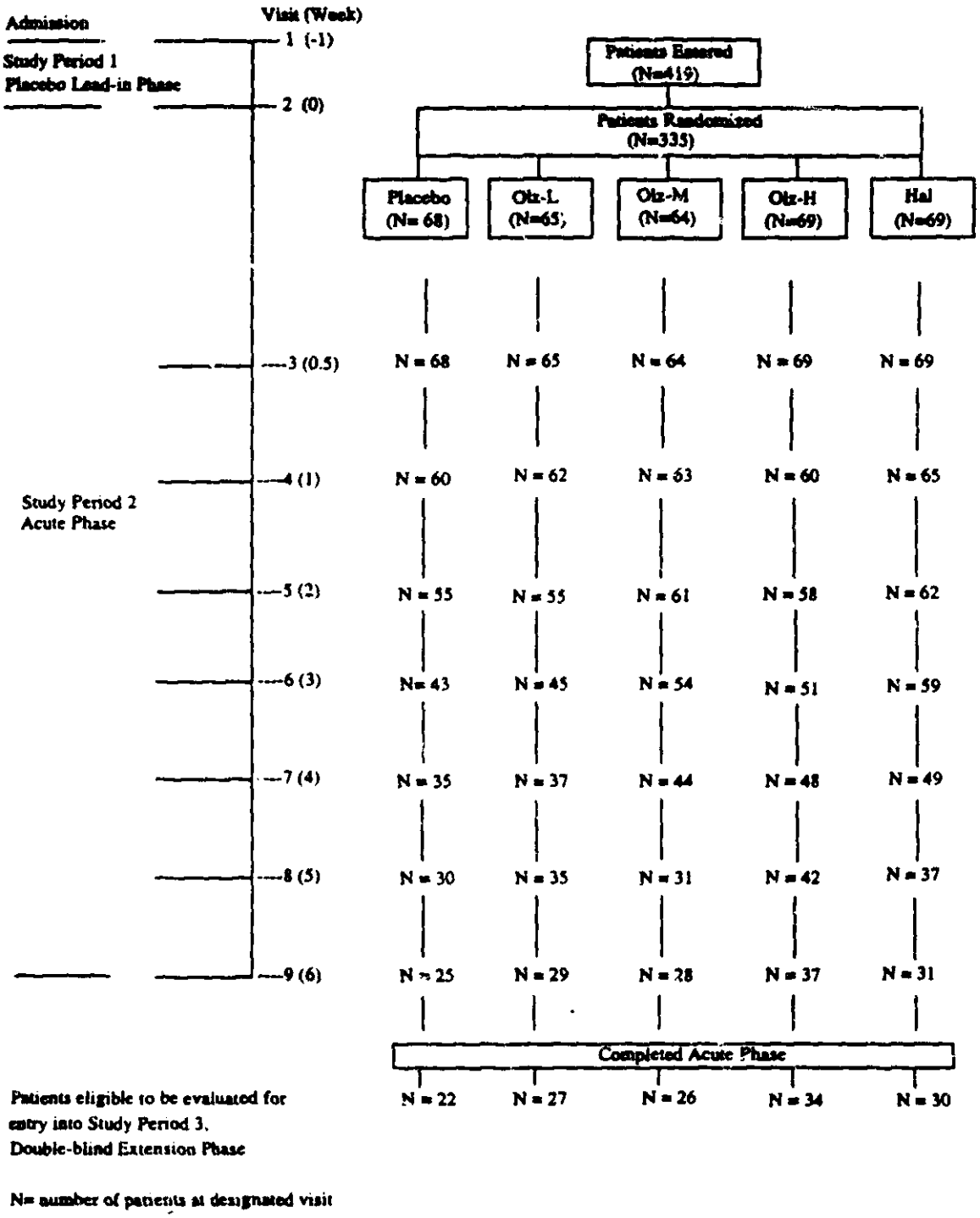
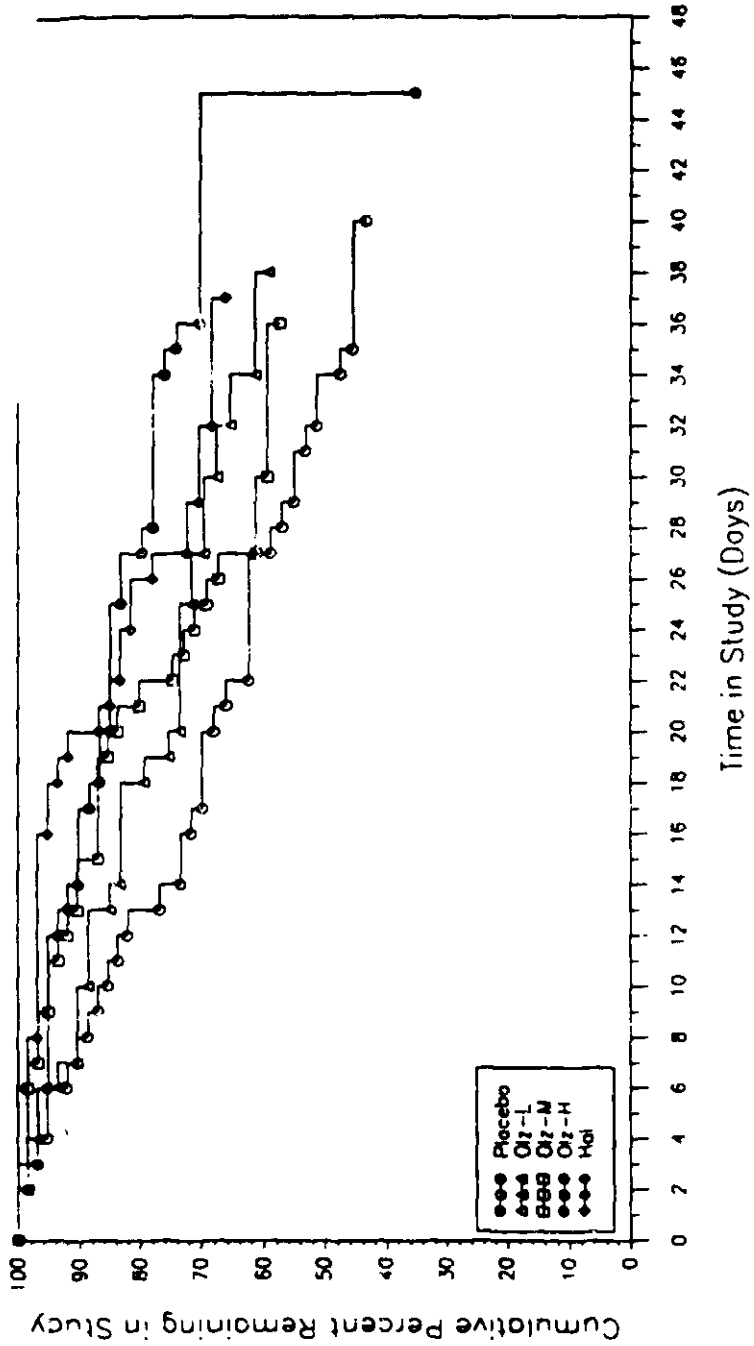


Figure HGAD.5.1.1. Overview of Patient Disposition F1D-MC-HGAD Acute Phase.

Figure 7



HGAD.5.1.3. Time to Discontinuation for Lack of Efficacy
F1D-MC-HGAD Acute Phase

Table HGAD.6.1.11. BPRS Total Score
Mean Change from Baseline to Endpoint
F1D-MC-HGAD Acute Phase

Variable analyzed: BPRS Total Score (BPRSTOT)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	Placebo	62	39.69	38.50	10.47	36.00	32.50	20.50	-3.69	-4.00	18.06
2)	Ola-L	64	40.70	39.00	12.14	34.30	35.50	17.36	-6.41	-7.50	13.48
3)	Ola-M	62	42.84	42.50	10.03	30.63	26.00	18.47	-12.21	-13.50	16.10
4)	Ola-H	65	42.62	42.00	10.88	27.43	24.00	17.38	-15.18	-14.00	16.09
5)	Hal	68	41.79	41.00	11.42	28.99	26.00	15.86	-12.81	-15.00	13.79

		p-Values					
					Pairwise*3		
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)	vs.(3)	vs.(4)	vs.(5)
1)	Placebo	.108	.644	.002	.118	.003	<.001	.004
2)	Ola-L	<.001				.186	.027	.212
3)	Ola-M	<.001					.442	.824
4)	Ola-H	<.001						.396
5)	Hal	<.001						

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction..
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.
Investigators 8, 14, and 18 are pooled for this analysis.

Table HGAD.6.1.12. BPRS Positive Score
Mean Change from Baseline to Endpoint
F1D-MC-HGAD Acute Phase

Variable analyzed: BPRS Positive Score (BPRSPOS)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	Placebo	63	13.02	13.00	3.70	11.29	11.00	6.90	-1.73	-2.00	5.79
2)	Ola-L	64	12.92	12.50	4.38	10.28	9.50	5.45	-2.64	-3.00	4.64
3)	Ola-M	63	14.05	14.00	3.69	9.67	10.00	6.08	-4.38	-5.00	5.66
4)	Ola-H	65	13.75	14.00	4.35	9.13	8.00	6.21	-4.63	-4.00	5.78
5)	Hal	68	13.15	13.00	3.94	8.59	8.50	5.32	-4.56	-5.00	5.04

		p-Values					
					Pairwise*3		
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)	vs.(3)	vs.(4)	vs.(5)
1)	Placebo	.021	.292	.021	.338	.010	.004	.047
2)	Ola-L	<.001				.106	.057	.326
3)	Ola-M	<.001					.798	.469
4)	Ola-H	<.001						.331
5)	Hal	<.001						

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.
Investigators 8, 14, and 18 are pooled for this analysis.

Table HGAD.6.1.19. SANS Summary Score
Mean Change from Baseline to Endp
F1D-MC-HGAD Acute Phase

Variable analyzed: SANS Summary Score (SANSCLS)

			Baseline			Endpoint			
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	M
1)	Placebo	65	13.11	13.00	5.53	12.40	11.00	6.95	-0
2)	Ols-L	65	14.40	14.00	5.13	11.95	12.00	5.67	-2
3)	Ols-M	63	12.94	13.00	4.77	11.03	10.00	6.32	-1
4)	Ols-H	65	13.42	14.00	5.08	9.32	8.00	5.39	-4
5)	Mal	68	13.22	14.00	4.59	11.22	11.50	4.80	-2

		p-Values			
				Pairwise*3	
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)	vs.(3)	vs.(
1)	Placebo	.321	.643	.024	.041	.155	.0
2)	Ols-L	<.001				.549	.2
3)	Ols-M	.006					.0
4)	Ols-H	<.001					
5)	Mal	<.001					

*1 The significance of a location shift from zero of the chan
within a treatment group is tested by the Wilcoxon Signed
*2 Type III Sums of Squares from an analysis of variance (ANC
model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using
for error.
Note: Each investigator has at least one patient in each trea
Investigators 14, and 18 are pooled for this analysis.

Table HGAD.6.1.24. CGI Severity Score
Mean Change from Baseline to End
F1D-MC-HGAD Acute Phase

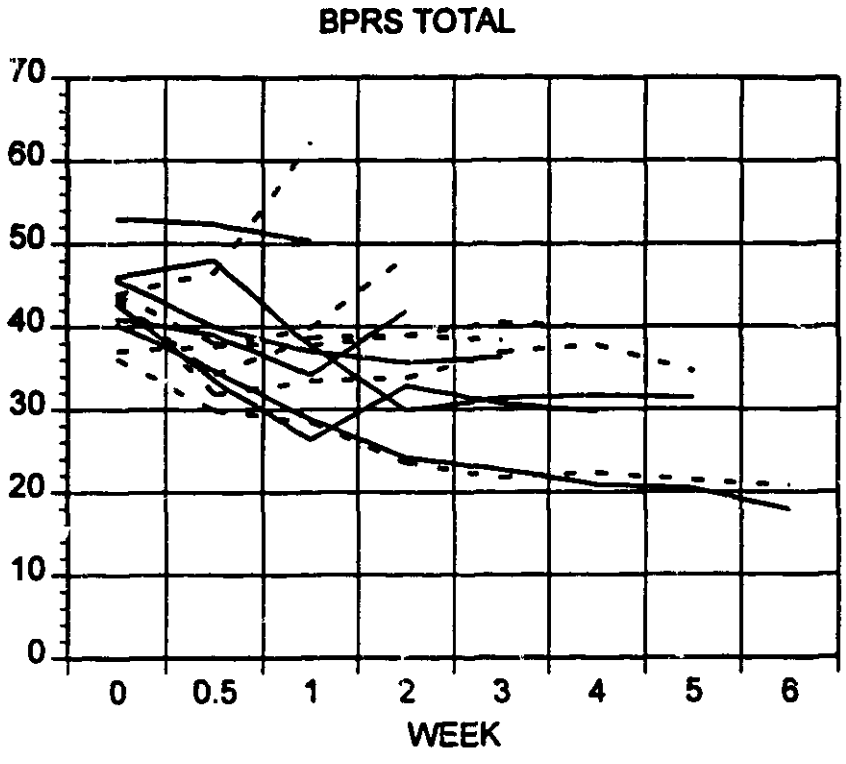
Variable analyzed: CGI Severity Score (CGISEV)

			Baseline			Endpoint		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD
1)	Placebo	66	4.88	5.00	0.81	4.55	5.00	1.51
2)	Ols-L	65	4.85	5.00	0.83	4.45	4.00	1.21
3)	Ols-M	63	5.08	5.00	0.87	4.13	4.00	1.40
4)	Ols-H	66	5.05	5.00	0.85	4.06	4.00	1.30
5)	Mal	68	4.85	5.00	0.70	3.91	4.00	1.16

		p-Values				
					Pairwis	
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)	vs.(3)	v
1)	Placebo	.813	.314	.921	.423	.003	
2)	Ols-L	.002				.048	
3)	Ols-M	<.001					
4)	Ols-H	<.001					
5)	Mal	<.001					

*1 The significance of a location shift from zero of the c
within a treatment group is tested by the Wilcoxon Sign
*2 Type III Sums of Squares from an analysis of variance
model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA m
for error.
Note: Each investigator has at least one patient in each
Investigators 8, 14, and 18 are pooled for this analysis.

Figure 8


BPRS TOTAL
70
60
50
40
30
20
10
0
0
0.5
1
2
3
4
5
6
WEEK

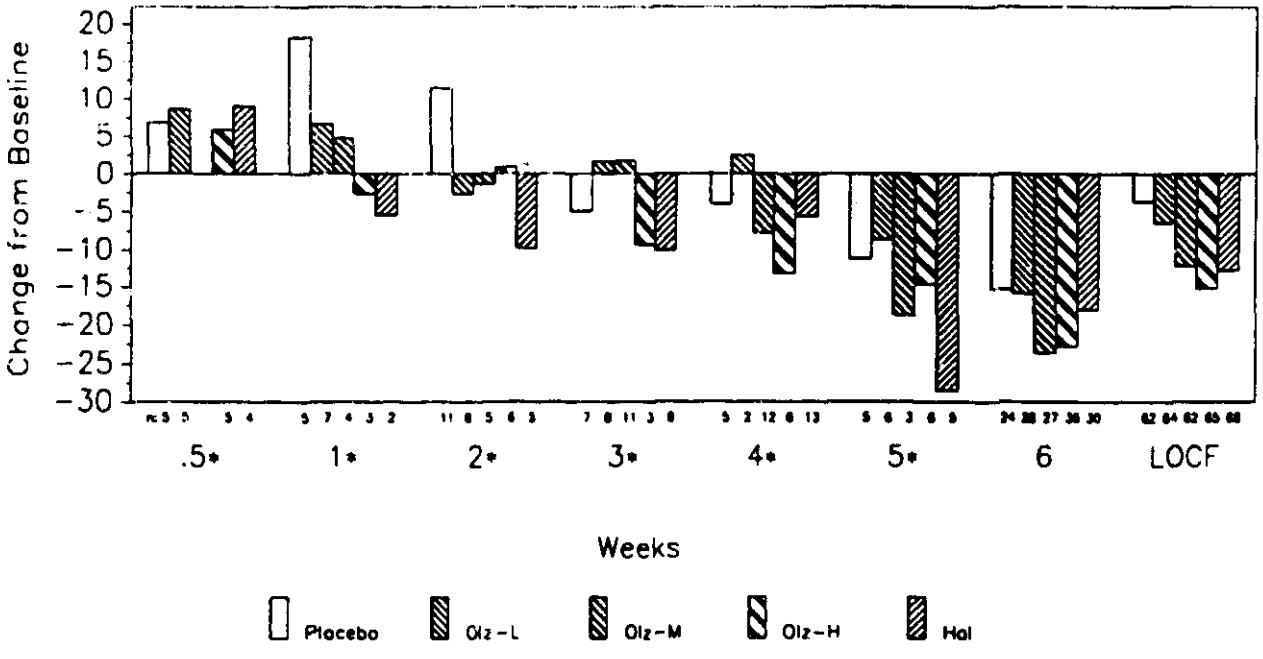
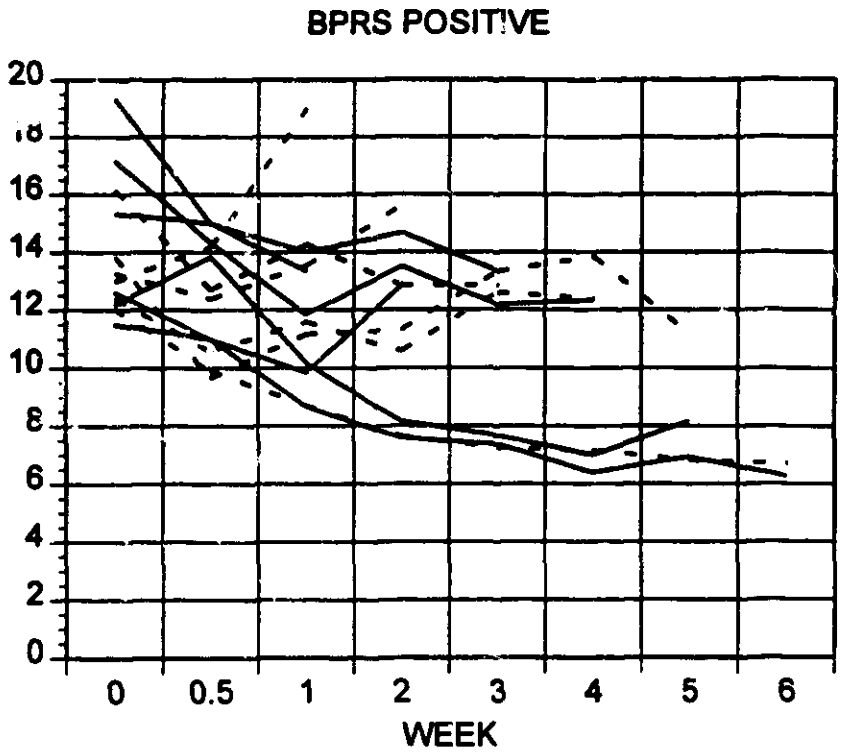

Change from Baseline
20
15
10
5
0
-5
-10
-15
-20
-25
-30
.5*
1*
2*
3*
4*
5*
6
LOCF
Weeks
Placebo
Olz-L
Olz-M
Olz-H
Hal

Figure 9


BPRS POSITIVE
20
16
14
12
10
8
6
4
2
0
0
0.5
1
2
3
4
5
6
WEEK

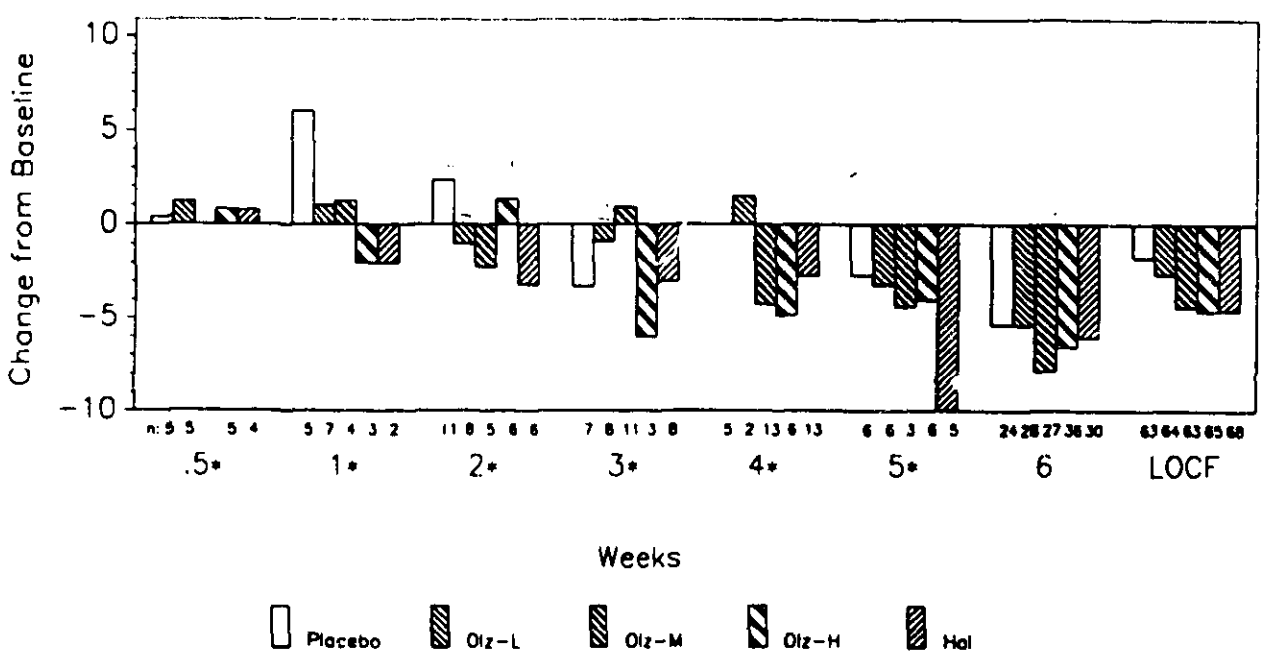
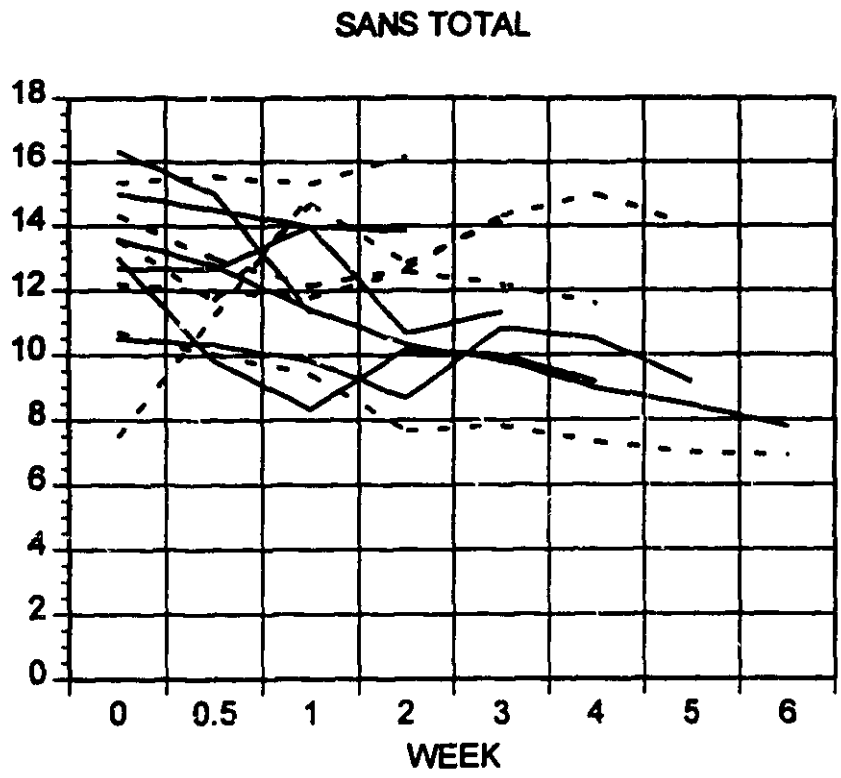

Change from Baseline
10
5
0
-5
-10
n: 9 5 5 4 5 7 4 3 2 11 8 5 6 6 7 8 11 3 8 5 2 13 6 13 6 6 3 6 5 24 26 27 36 30 63 64 63 65 60
.5*
1*
2*
3*
4*
5*
6
LOCF
Weeks
Placebo
Olz-L
Olz-M
Olz-H
Hal

Figure 10


SANS TOTAL
18
16
14
12
10
8
6
4
2
0
0
0.5
1
2
3
4
5
6
WEEK

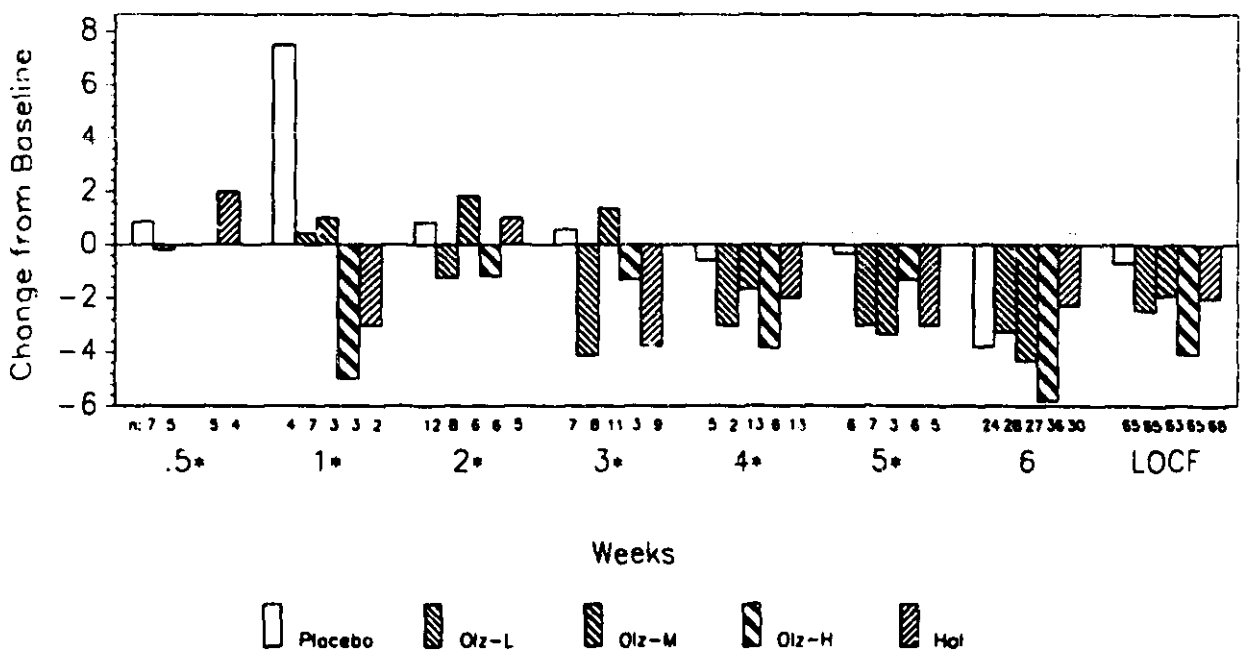
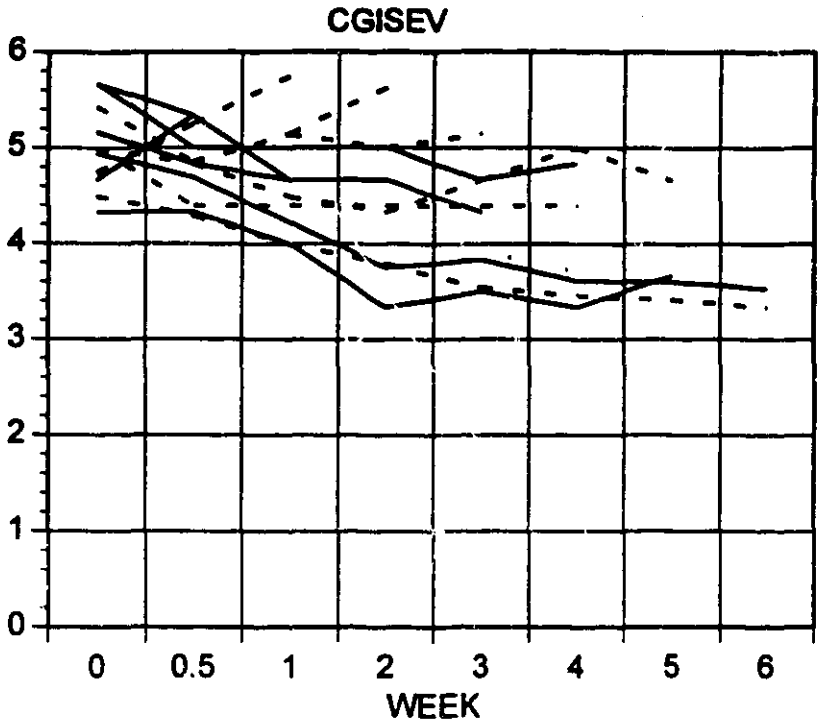

Change from Baseline
8
6
4
2
0
−2
−4
−6
n: 7 5 5 4 4 7 3 3 2 12 8 6 6 5 7 8 11 3 9 5 2 13 8 13 8 7 3 6 5 24 28 27 36 30 65 65 63 65 68
.5*
1*
2*
3*
4*
5*
6
LOCF
Weeks
Placebo
Olz-L
Olz-M
Olz-H
Hal

Figure 11


CGISEV
6
5
4
3
2
1
0
0
0.5
1
2
3
4
5
6
WEEK

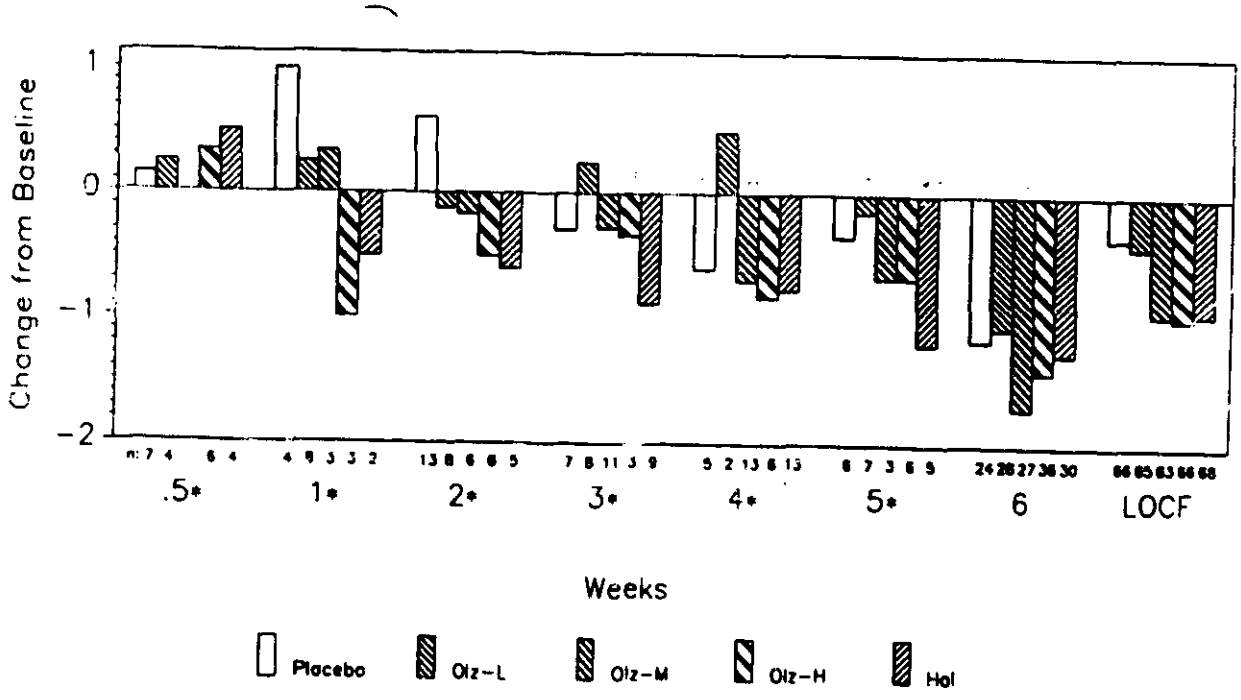

Change from Baseline
1
0
-1
-2
.5*
1*
2*
3*
4*
5*
6
LOCF
Weeks
Placebo
Olz-L
Olz-M
Olz-H
Hal

Figure 12

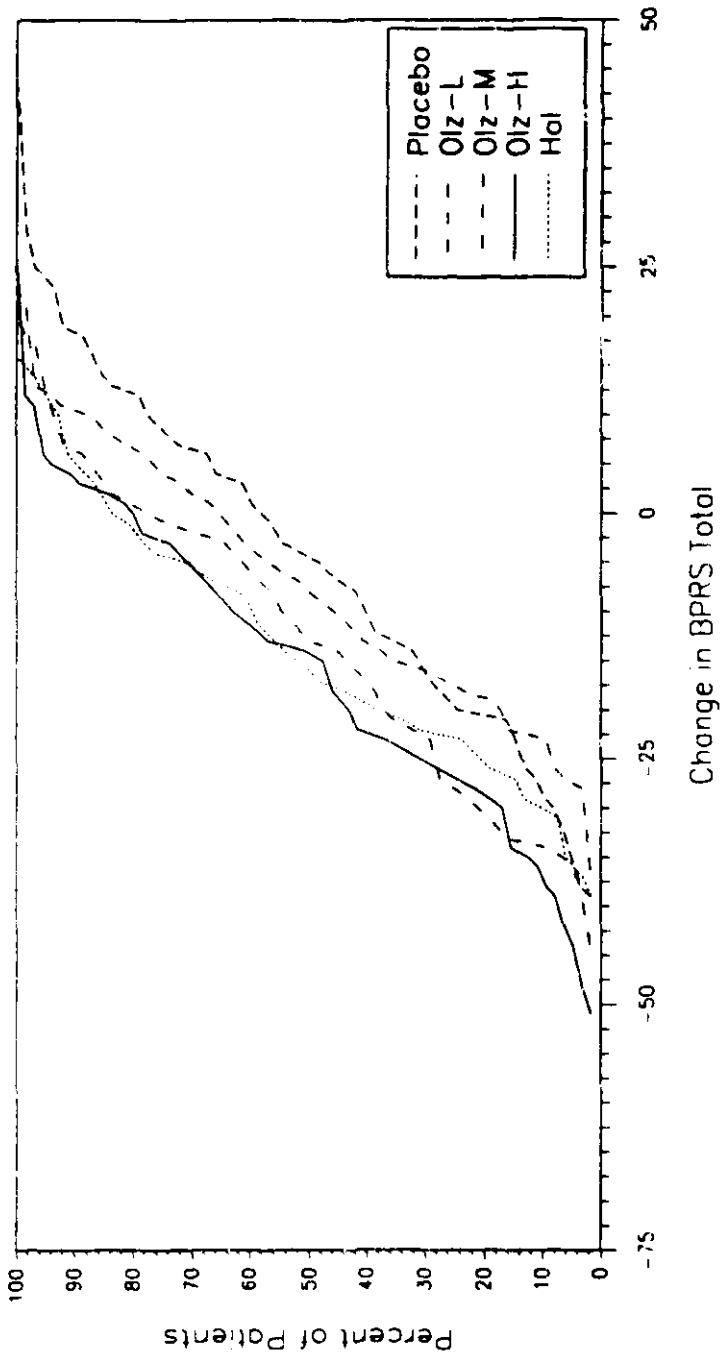


Figure HGAD.6.1.19. BPRS Total Score
Cumulative Distribution of Change (LOCF)
F1D-MC-HGAD Acute Phase

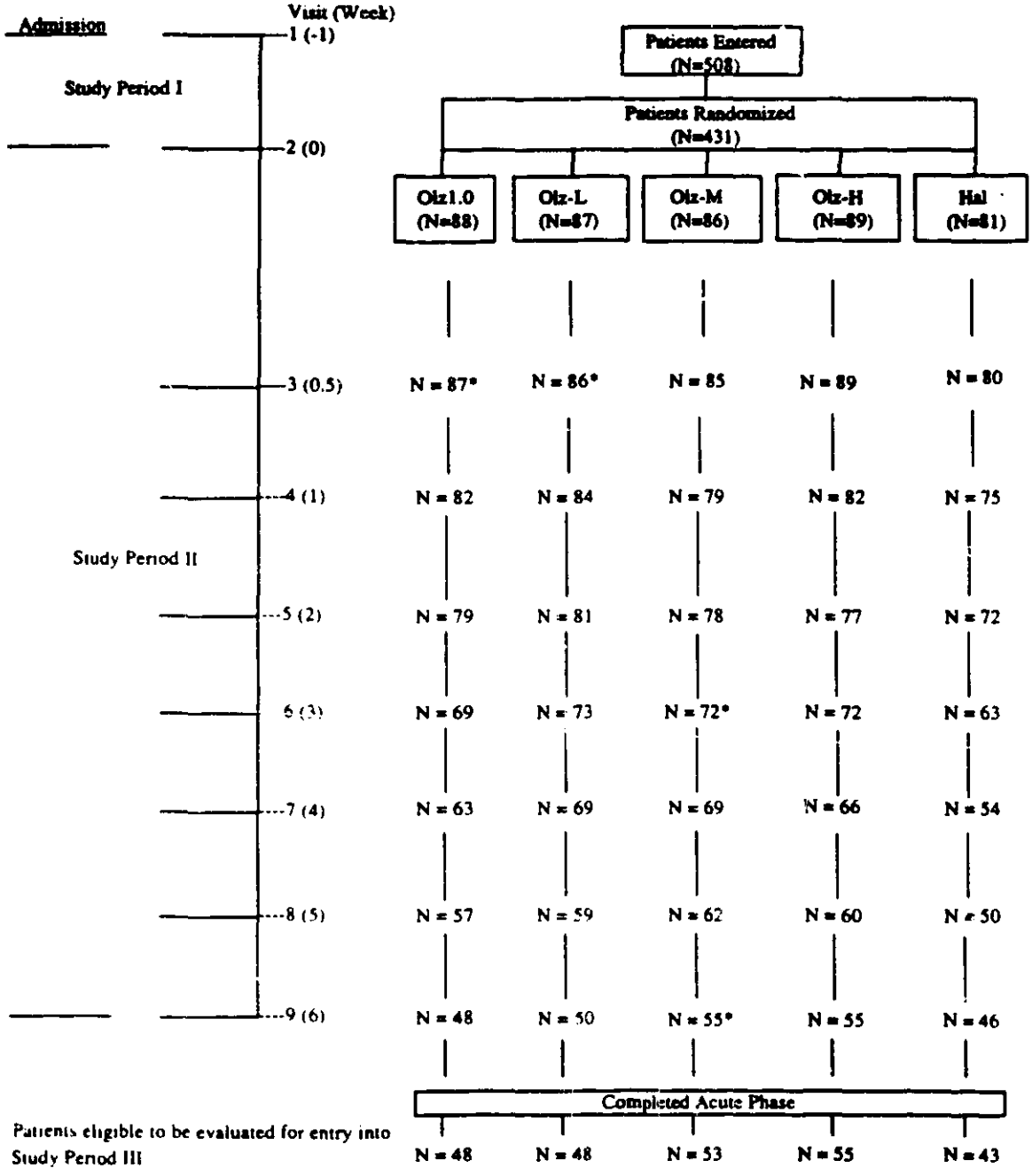
ble HGAD.6.1.26. CGI Severity Score
Baseline to Endpoint
F1D-MC-HGAD Acute Phase

atment up	Baseline Score	Endpoint Score[a] 1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	Total
ebo	3	0	0	1 (100%)	0	0	0	0	1
	4	0	7 (32%)	5 (23%)	5 (23%)	3 (14%)	2 (9%)	0	22
	5	0	1 (4%)	6 (21%)	4 (14%)	6 (21%)	11 (39%)	0	28
	6	0	0	0	1 (7%)	1 (7%)	11 (79%)	1 (7%)	14
	7	0	0	0	0	0	0	1 (100%)	1
	Total	0	8	12	10	10	24	2	66
L	3	0	0	0	0	0	0	0	0
	4	0	3 (12%)	7 (27%)	10 (38%)	6 (23%)	0	0	26
	5	0	0	5 (20%)	5 (20%)	8 (32%)	6 (24%)	1 (4%)	25
	6	0	0	1 (8%)	2 (17%)	3 (25%)	6 (50%)	0	12
	7	0	0	0	0	0	2(100%)	0	2
	Total	0	3	13	17	17	14	1	65
M	3	0	0	0	0	0	0	0	0
	4	1 (6%)	3 (17%)	9 (50%)	3 (17%)	2 (11%)	0	0	18
	5	0	3 (12%)	5 (20%)	7 (28%)	8 (32%)	2 (8%)	0	25
	6	0	0	1 (6%)	4 (24%)	2 (12%)	9 (53%)	1 (6%)	17
	7	0	1 (33%)	0	0	1 (33%)	1 (33%)	0	3
	Total	1	7	15	14	13	12	1	63
H	3	1 (100%)	0	0	0	0	0	0	1
	4	0	4 (24%))	9 (53%)	4 (24%)	0	0	0	17
	5	0	3 (11%)	3 (11%)	11 (39%)	7 (25%)	4 (14%)	0	28
	6	0	1 (6%)	2 (11%)	5 (28%)	4 (22%)	6 (33%)	0	18
	7	0	0	0	0	0	0	2 (100%)	2
	Total	1	8	14	20	11	10	2	66
	3	0	0	0	0	0	0	0	0
	4	0	5 (24%)	8 (38%)	3 (14%)	5 (24%)	0	0	21
	5	0	1 (3%)	13 (35%)	10 (27%)	12 (32%)	1 (3%)	0	37
	6	0	0	2 (22%)	2 (22%)	1 (11%)	3 (33%)	1 (11%)	9
	7	0	0	0	1 (100%)	0	0	0	1
	Total	0	6	23	16	18	4	1	68

reviations: Olz-L = olanzapine 5.0 ± 2.5 mg/day; Olz-M = olanzapine 10.0 ± 2.5 mg/day;
Olz-H = olanzapine 15.0 ± 2.5 mg/day; Hal = haloperidol 15.0 ± 5.0 mg/day

Table entries are frequencies; row percents = frequency divided by row total.

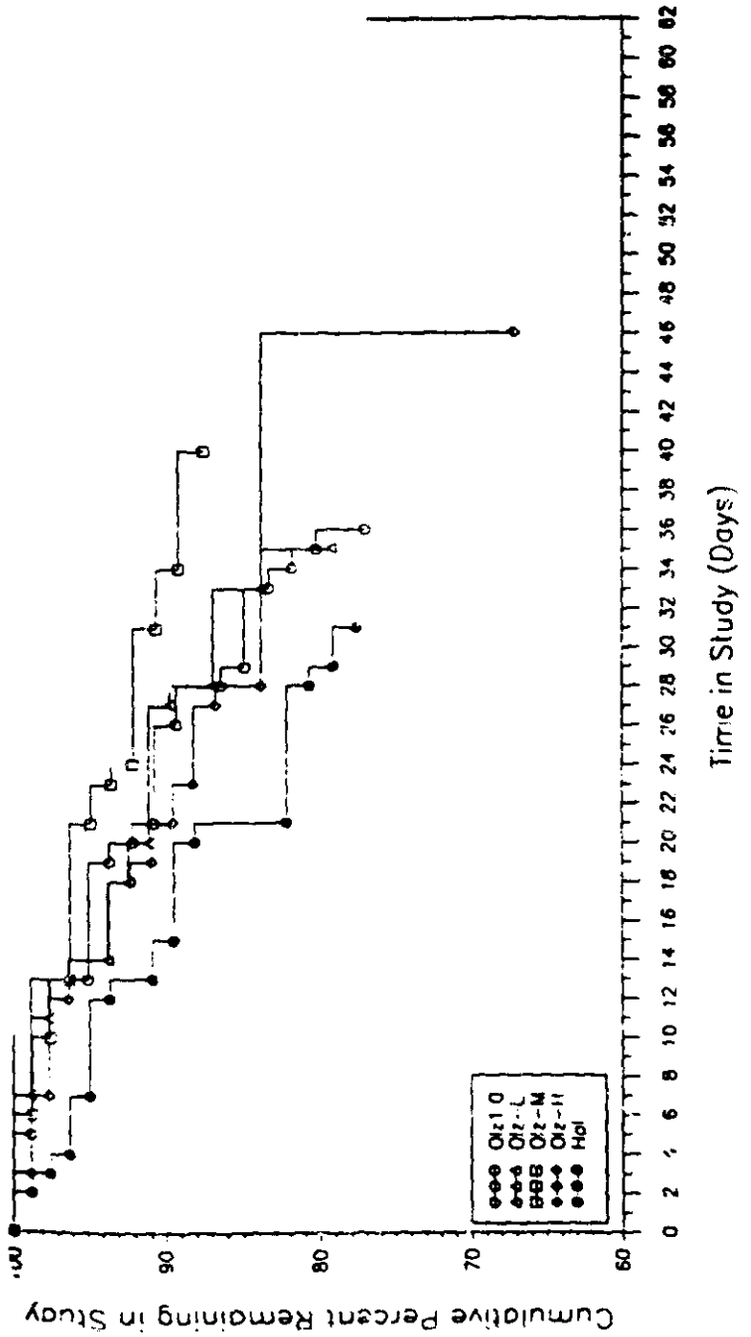
Table 7



*Patient 304-3062 in the Olz-L treatment group and Patients 742-7434 and 242-2428 in the Olz1.0 treatment group did not have a Visit 3. They are included in the total because they returned for Visit 4. Patient 104-1003 in the Olz-M treatment group did not have a Visit 6, but is included in the total because he returned for Visit 7. Patient 606-6132 in the Olz-M treatment group had a patient summary at Visit 9 but did not appear for Visit 9; he was lost to follow-up.
N = Number of patients per designated visit

Figure E003.5.1.1. Overview of Patient Disposition
F1D-EW-E003 Acute Phase

Figure 13



3.5.1.3. Time to Discontinuation for Lack of Efficacy F1D-EW-E003 Acute Phase

Table E003.6.1.19. PANSS Total Score
Mean Change from Baseline to Endpoint
F1D-EW-E003 Acute Phase

Variable analyzed: PANSS Total Score (PANSSTOT)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	Olz1.0	83	100.86	102.00	17.91	84.02	82.00	30.15	-16.83	-16.00	28.67
2)	Olz-L	85	102.73	99.00	19.38	81.29	80.00	26.07	-21.44	-21.00	25.19
3)	Olz-M	83	102.22	102.00	16.91	79.48	73.00	27.97	-22.73	-23.00	29.21
4)	Olz-H	85	105.60	105.00	18.92	78.93	73.00	28.62	-26.67	-28.00	23.69
5)	Hal	79	105.25	104.00	18.49	85.22	82.00	25.60	-20.04	-20.00	25.92

		p-Values					
					Pairwise*3		
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)	vs.(3)	vs.(4)	vs.(5)
1)	Olz1.0	<.001	.163	.466	.327	.532	.097	.863
2)	Olz-L	<.001				.715	.512	.424
3)	Olz-M	<.001					.296	.647
4)	Olz-H	<.001						.163
5)	Hal	<.001						

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.
GEOCODE is substituted for inv. in this analysis.

Table E003.6.1.21. PANSS Negative Score
Mean Change from Baseline to Endpoint
F1D-EW-E003 Acute Phase

Variable analyzed: PANSS Negative Score (PANSSNG)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	Olz1.0	83	25.59	25.00	6.79	21.24	21.00	7.78	-4.35	-4.00	8.23
2)	Olz-L	85	27.08	26.00	7.28	22.04	21.00	8.13	-5.05	-4.00	7.46
3)	Olz-M	83	26.14	26.00	7.35	20.72	20.00	8.15	-5.42	-3.00	7.95
4)	Olz-H	85	27.87	28.00	7.72	21.24	21.00	8.25	-6.64	-6.00	6.89
5)	Hal	79	27.89	27.00	7.07	23.08	23.00	6.13	-4.81	-4.00	6.29

		p-Values					
					Pairwise*3		
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)	vs.(3)	vs.(4)	vs.(5)
1)	Olz1.0	<.001	.687	.667	.562	.746	.187	.962
2)	Olz-L	<.001				.786	.466	.597
3)	Olz-M	<.001					.306	.786
4)	Olz-H	<.001						.208
5)	Hal	<.001						

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.
GEOCODE is substituted for inv. in this analysis.

Table E003.6.1.12. BPRS Positive Score Mean Change from Baseline to Endpoint F1D-EW-E003 Acute Phase

Variable analyzed: BPRS Positive Score (BRPRSPS)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	Olz1.0	83	11.98	12.00	3.63	8.90	9.00	5.54	-3.07	-3.00	4.92
2)	Olz-L	85	12.66	13.00	3.59	8.15	8.00	4.50	-4.51	-4.00	4.60
3)	Olz-M	83	12.19	12.00	3.29	7.94	7.00	4.99	-4.25	-4.00	5.29
4)	Olz-H	85	13.18	13.00	3.51	7.87	7.00	4.89	-5.32	-5.00	4.61
5)	Hal	79	12.73	12.00	3.66	7.91	7.00	4.74	-4.82	-4.00	5.12

		p-Values					
					Pairwise*3		
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)	vs.(3)	vs.(4)	vs.(5)
1)	Olz1.0	<.001	.192	.068	.038	.367	.008	.090
2)	Olz-L	<.001				.217	.600	.724
3)	Olz-M	<.001					.070	.394
4)	Olz-H	<.001						.379
5)	Hal	<.001						

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.
GEOGROUP [illegible] investigators for two in this analysis.

Table E003.6.1.28. CGI Severity Score Mean Change from Baseline to Endpoint F1D-EW-E003 Acute Phase

Variable analyzed: CGI Severity Score (CGISEV)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	Olz1.0	83	5.19	5.00	0.79	4.35	4.00	1.52	-0.84	-1.00	1.35
2)	Olz-L	85	5.28	5.00	0.80	4.29	4.00	1.25	-0.99	-1.00	1.12
3)	Olz-M	83	5.14	5.00	0.73	3.93	4.00	1.30	-1.22	-1.00	1.23
4)	Olz-H	85	5.49	6.00	0.72	3.98	4.00	1.52	-1.52	-2.00	1.48
5)	Hal	79	5.33	5.00	0.71	4.23	4.00	1.31	-1.10	-1.00	1.33

		p-Values					
					Pairwise*3		
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)	vs.(3)	vs.(4)	vs.(5)
1)	Olz1.0	<.001	.036	.048	.130	.055	.003	.238
2)	Olz-L	<.001				.701	.160	.755
3)	Olz-M	<.001					.266	.487
4)	Olz-H	<.001						.077
5)	Hal	<.001						

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Figure 14

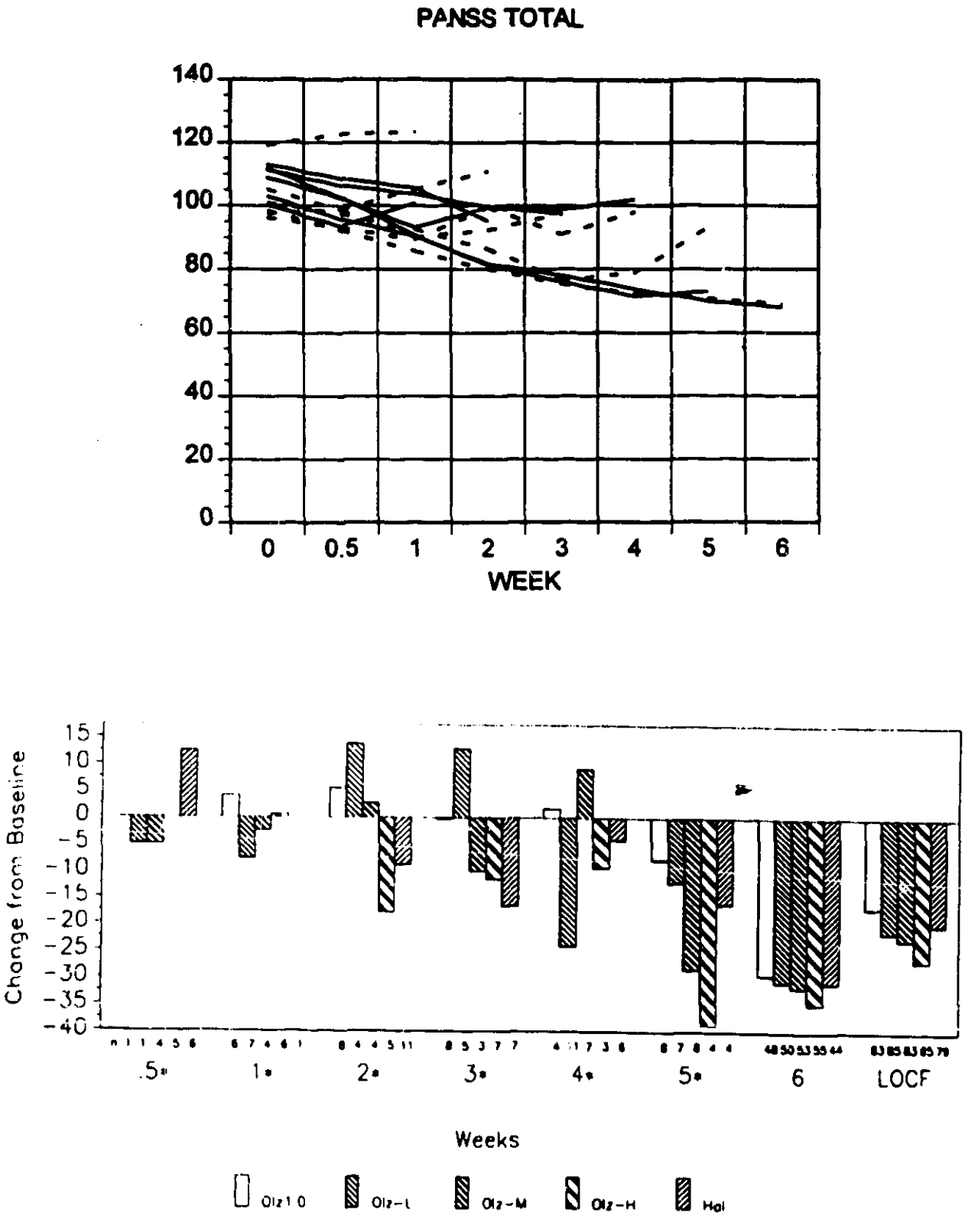
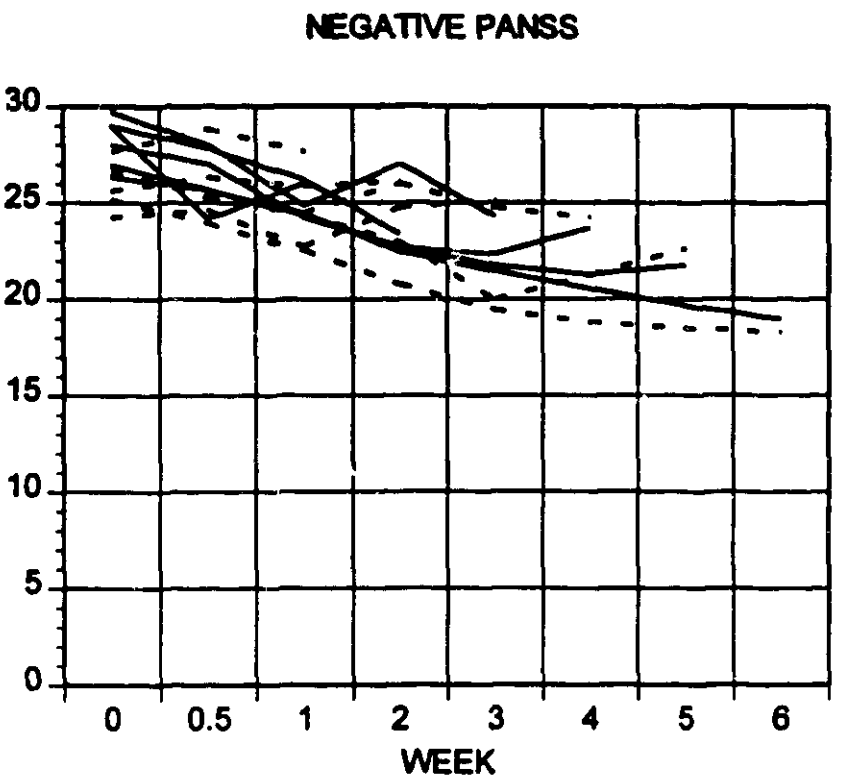

PANSS TOTAL
140
120
100
80
60
40
20
0
0
0.5
1
2
3
4
5
6
WEEK
Change from Baseline
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
.5*
1*
2*
3*
4*
5*
6
LOCF
Weeks
Olz10
Olz-L
Olz-M
Olz-H
Hal

Figure 15


NEGATIVE PANSS
30
25
20
15
10
5
0
0
0.5
1
2
3
4
5
6
WEEK

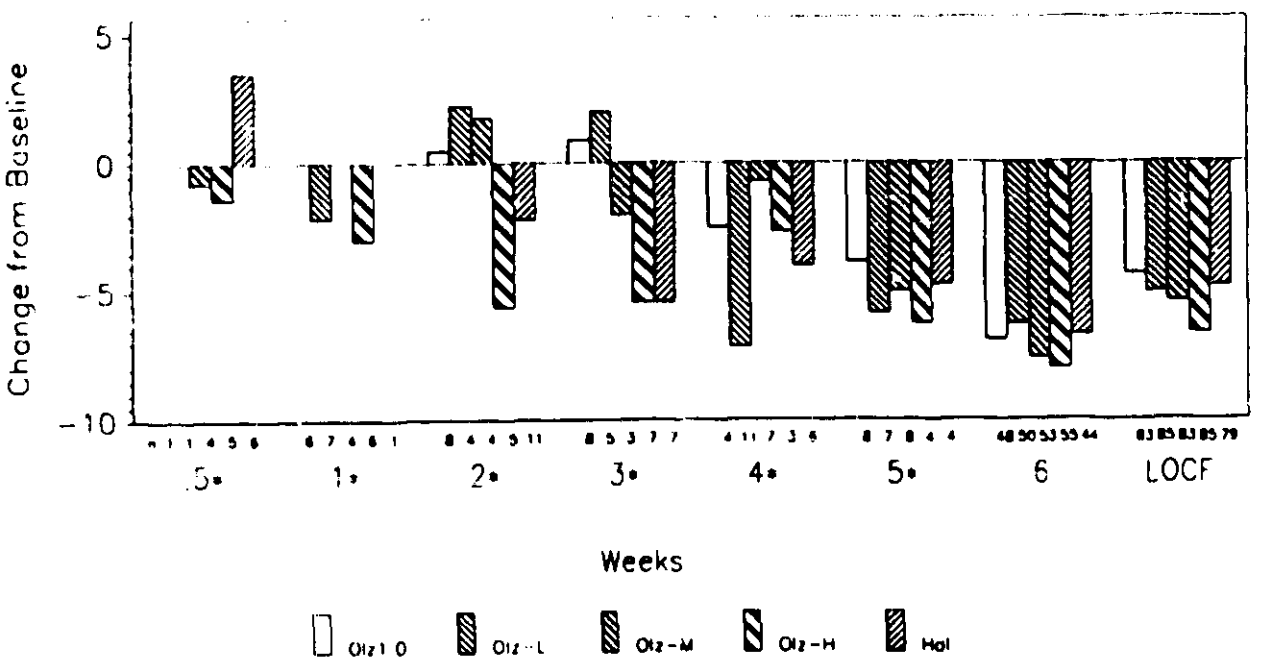
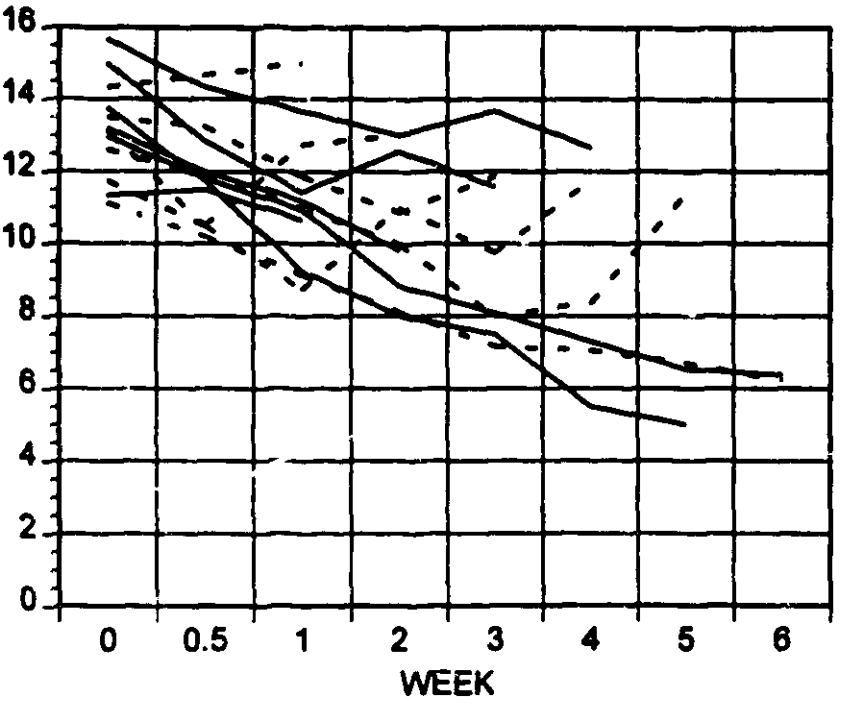

Change from Baseline
5
0
-5
-10
.5*
1*
2*
3*
4*
5*
6
LOCF
Weeks
Olz1 0
Olz-L
Olz-M
Olz-H
Hal

Figure 16


BPRS POSITIVE
16
14
12
10
8
6
4
2
0
0
0.5
1
2
3
4
5
6
WEEK

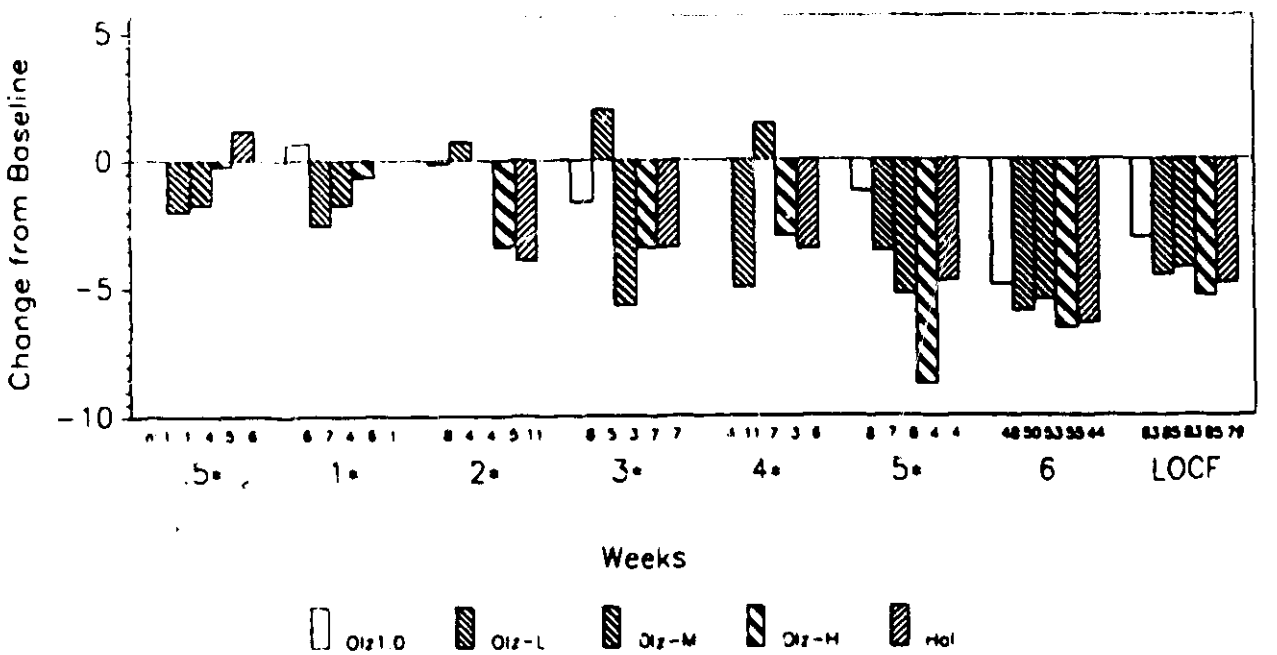
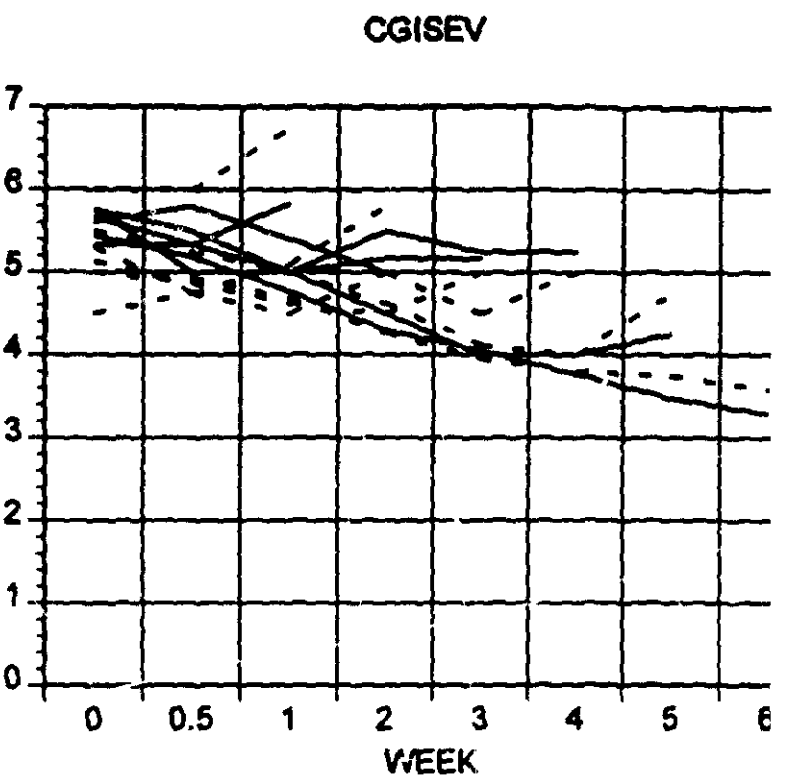

Change from Baseline
5
0
-5
-10
.5*
1*
2*
3*
4*
5*
6
LOCF
Weeks
Olz1.0
Olz-L
Olz-M
Olz-H
Hal

Figure 17


CGISEV
7
6
5
4
3
2
1
0
0
0.5
1
2
3
4
5
WEEK

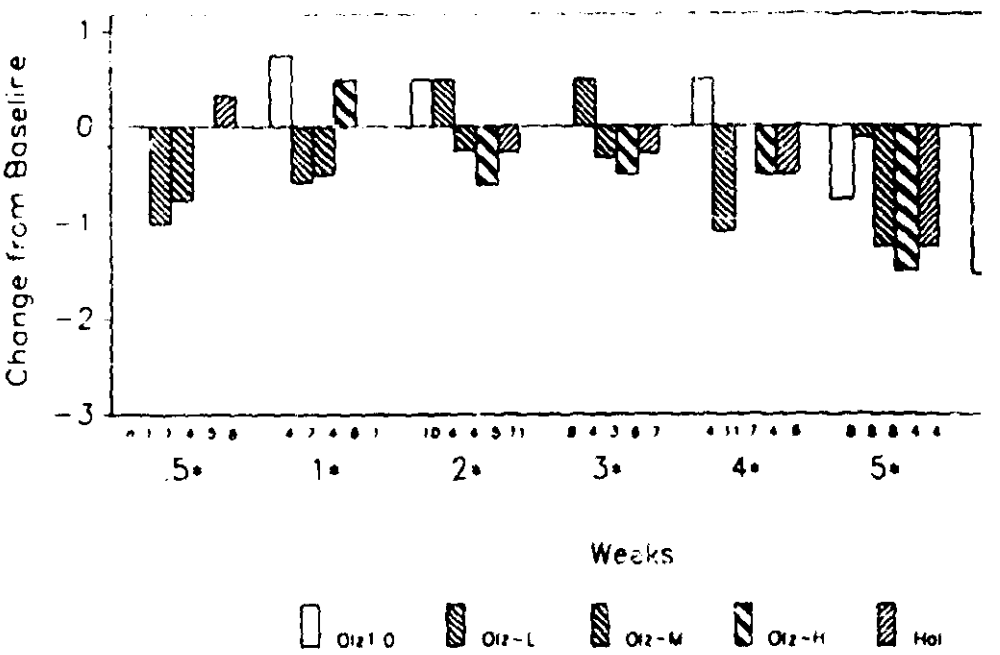
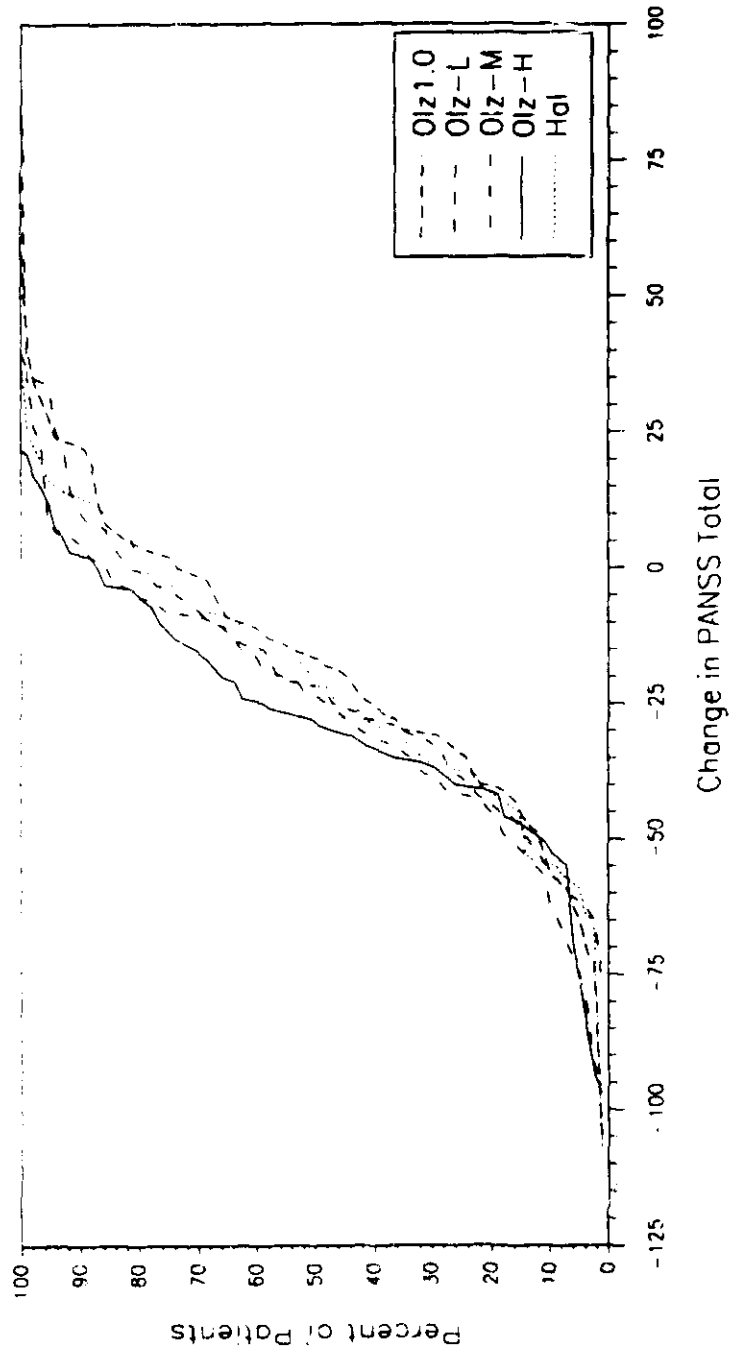

Change from Baseline
1
0
-1
-2
-3
5*
1*
2*
3*
4*
5*
Weeks
Oiz1 0
Oiz-L
Oiz-M
Oiz-H
Hol

Figure 18



E003.6.1.24. PANSS Total Score, Cumulative Distribution of Change, F1D-EW-E003 Acute Phase

Table E003.6.1.30. CGI Severity Score, Baseline to Endpoint F1D-EW-E003 Acute Phase

Treatment Group	Baseline Score	Endpoint Score[a] 1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	Total
Olz1.0	4	0	7 (41%)	5 (29%)	2 (12%)	1 (6%)	2 (12%)	0	17
	5	0	3 (9%)	6 (17%)	11 (31%)	11 (31%)	4 (11%)	0	35
	6	0	2 (7%)	3 (10%)	4 (14%)	3 (10%)	12 (41%)	5 (17%)	29
	7	0	0	1 (50%)	0	0	1 (50%)	0	2
	Total	0	12	15	17	15	19	5	83
Olz-L	4	0	2 (17%)	3 (25%)	6 (50%)	1 (8%)	0	0	12
	5	0	4 (9%)	14 (33%)	12 (28%)	7 (16%)	4 (9%)	2 (5%)	43
	6	0	0	0	8 (33%)	9 (38%)	7 (29%)	0	24
	7	0	0	0	1 (17%)	2 (33%)	2 (33%)	1 (17%)	6
	Total	0	6	17	27	19	13	3	85
Olz-M	4	0	4 (25%)	5 (31%)	5 (31%)	1 (6%)	1 (6%)	0	16
	5	1 (3%)	6 (15%)	8 (20%)	15 (38%)	9 (23%)	1 (3%)	0	40
	6	0	2 (8%)	4 (15%)	7 (27%)	5 (19%)	7 (27%)	1 (4%)	26
	7	0	0	0	0	0	1 (100%)	0	1
	Total	1	12	17	27	15	10	1	83
Olz-H	4	0	1 (17%)	2 (33%)	1 (17%)	0	2 (33%)	0	6
	5	0	11 (31%)	9 (25%)	9 (25%)	5 (14%)	2 (6%)	0	36
	6	0	6 (16%)	7 (18%)	7 (18%)	4 (11%)	13 (34%)	1 (3%)	38
	7	0	0	1 (20%)	1 (20%)	0	2 (40%)	1 (20%)	5
	Total	0	18	19	18	9	19	2	85
Hal	4	0	3 (38%)	2 (25%)	3 (38%)	0	0	0	8
	5	0	2 (5%)	10 (25%)	10 (25%)	13 (33%)	4 (10%)	1 (3%)	40
	6	0	2 (7%)	4 (14%)	8 (29%)	6 (21%)	6 (21%)	2 (7%)	28
	7	0	1 (33%)	0	1 (33%)	0	1 (33%)	0	3
	Total	0	8	16	22	19	11	3	79

Abbreviations: Olz1.0 = olanzapine 1.0 mg/day; Olz-L = olanzapine 5.0 ± 2.5 mg/day; Olz-M = olanzapine 10.0 ± 2.5 mg/day; Olz-H = olanzapine 15.0 ± 2.5 mg/day; Hal = haloperidol 15.0 ± 5.0 mg/day.

[a] Table entries are frequencies; row percents = frequency divided by row total.

Table 10

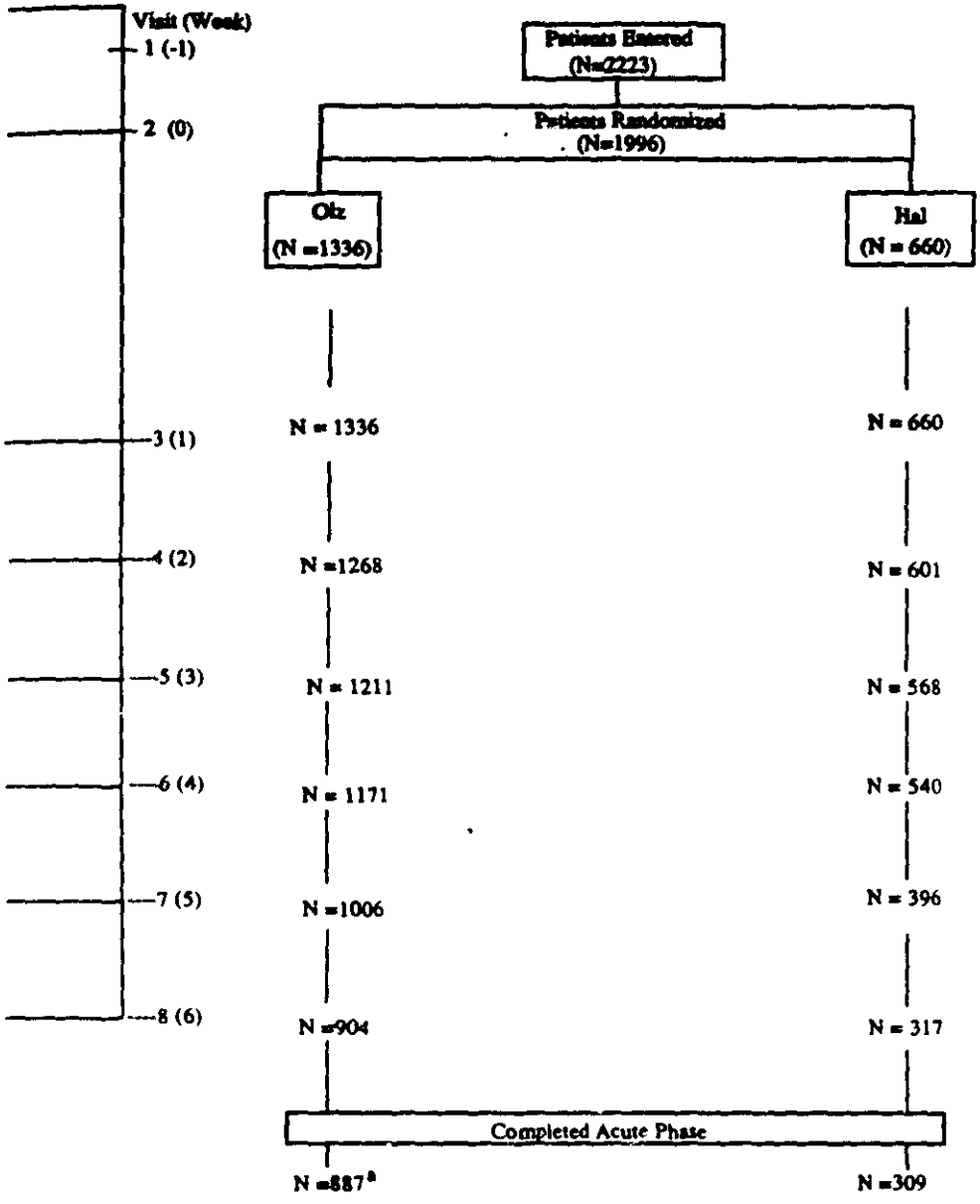
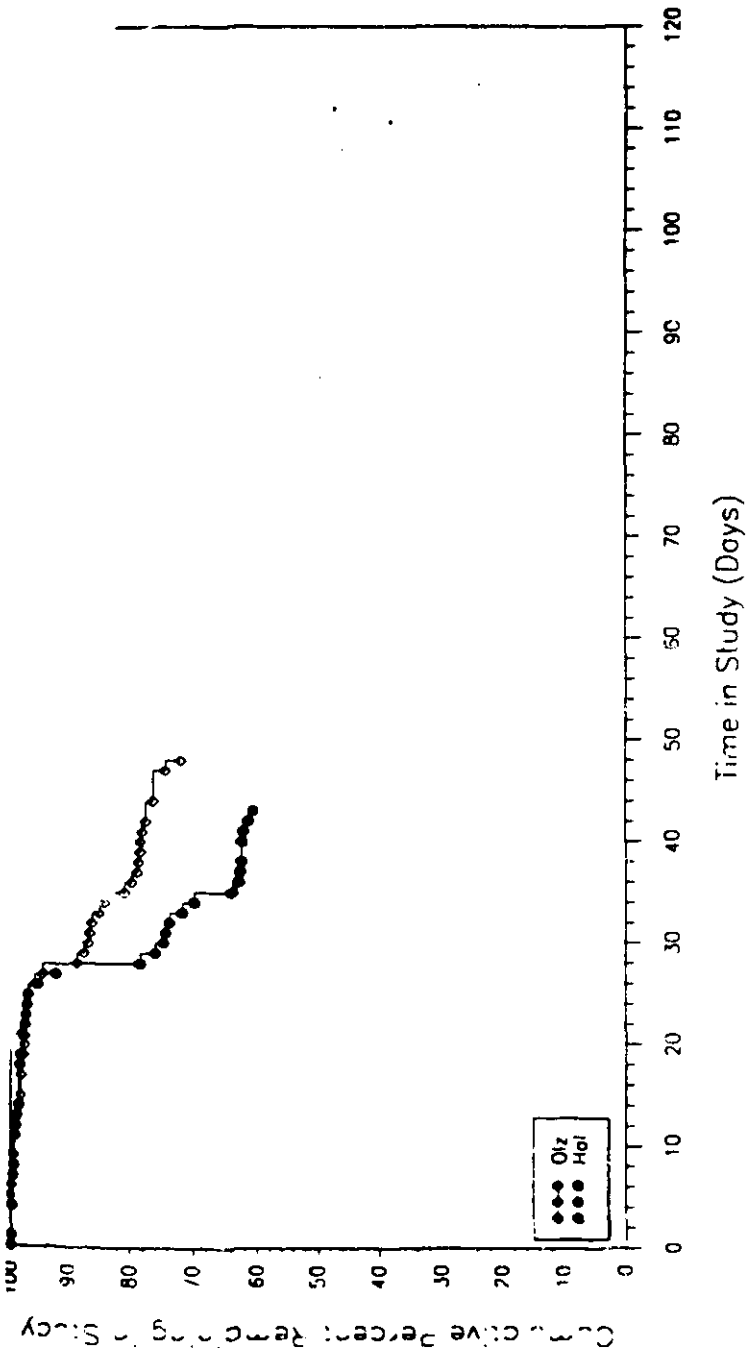

Visit (Week)
1 (-1)
2 (0)
3 (1)
4 (2)
5 (3)
6 (4)
7 (5)
8 (6)
Patients Entered
(N=2223)
Patients Randomized
(N=1996)
Olz
(N =1336)
Hal
(N = 660)
N = 1336
N = 660
N =1268
N = 601
N = 1211
N = 568
N = 1171
N = 540
N =1006
N = 396
N =904
N = 317
Completed Acute Phase
N =887[a]
N =309

Figure 19



Time to Discontinuation for Lack of Efficacy
F1D-MC-HGAJ Acute Phase

Table HGAJ.6.1.14. BPRS Positive Score
Mean Change from Baseline to Endpoint
F1D-MC-HGAJ Acute Phase

Variable analyzed: BPRS Positive Score (BRPRSPS)

No.	Therapy	n	Baseline Mean	Baseline Median	Baseline SD	Endpoint Mean	Endpoint Median	Endpoint SD	Change Mean	Change Median	Change SD
1)	Olz	1312	10.24	10.00	4.05	6.83	6.00	4.66	-3.41	-3.00	4.30
2)	Hal	636	10.43	10.00	4.13	7.61	7.00	4.54	-2.82	-2.00	3.97

No.	Therapy	p-Values Within Group*1	Inter-action*2	Overall*2	Pairwise*3 vs.(2)
1)	Olz	<.001	.674	.117	.117
2)	Hal	<.001			

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.

Table HGAJ.6.1.33. CGI Severity Score
Mean Change from Baseline to Endpoint
F1D-MC-HGAJ Acute Phase

Variable analyzed: CGI Severity Score (CGISEV)

No.	Therapy	n	Baseline Mean	Baseline Median	Baseline SD	Endpoint Mean	Endpoint Median	Endpoint SD	Change Mean	Change Median	Change SD
1)	Olz	1318	4.68	5.00	0.93	3.71	3.00	1.21	-0.97	-1.00	1.23
2)	Hal	640	4.73	5.00	0.93	4.05	4.00	1.14	-0.68	-1.00	1.09

No.	Therapy	p-Values Within Group*1	Inter-action*2	Overall*2	Pairwise*3 vs.(2)
1)	Olz	<.001	.230	.029	.029
2)	Hal	<.001			

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.

Table HGAJ.6.1.21. PANSS Total Score
Mean Change from Baseline to Endpoint
F1D-MC-HGAJ Acute Phase

Variable analysed: PANSS Total Score (PANSSTOT)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	Olz	1312	90.11	88.00	19.15	72.41	69.00	23.50	-17.70	-17.00	21.79
2)	Hal	636	92.10	90.00	19.99	78.73	78.00	22.92	-13.37	-12.00	20.60

	p-Values			
				Pairwise*3
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)
1)	Olz	<.001	.466	.051	.051
2)	Hal	<.001			

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.

Table HGAJ.6.1.23. PANSS Negative Score
Mean Change from Baseline to Endpoint
F1D-MC-HGAJ Acute Phase

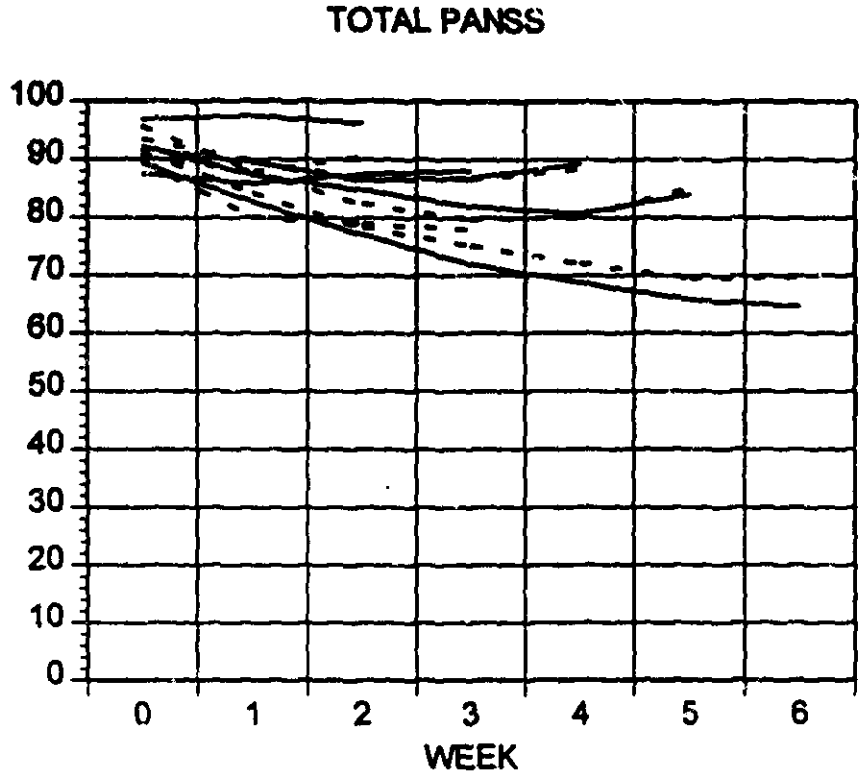
Variable analysed: PANSS Negative Score (PANSSNEG)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	Olz	1312	24.02	24.00	6.83	19.57	19.00	6.92	-4.46	-4.00	6.26
2)	Hal	636	24.47	24.00	7.11	21.29	21.00	6.87	-3.18	-2.00	6.11

	p-Values			
				Pairwise*3
No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs.(2)
1)	Olz	<.001	.242	.032	.032
2)	Hal	<.001			

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.

Figure 20


TOTAL PANSS
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
WEEK

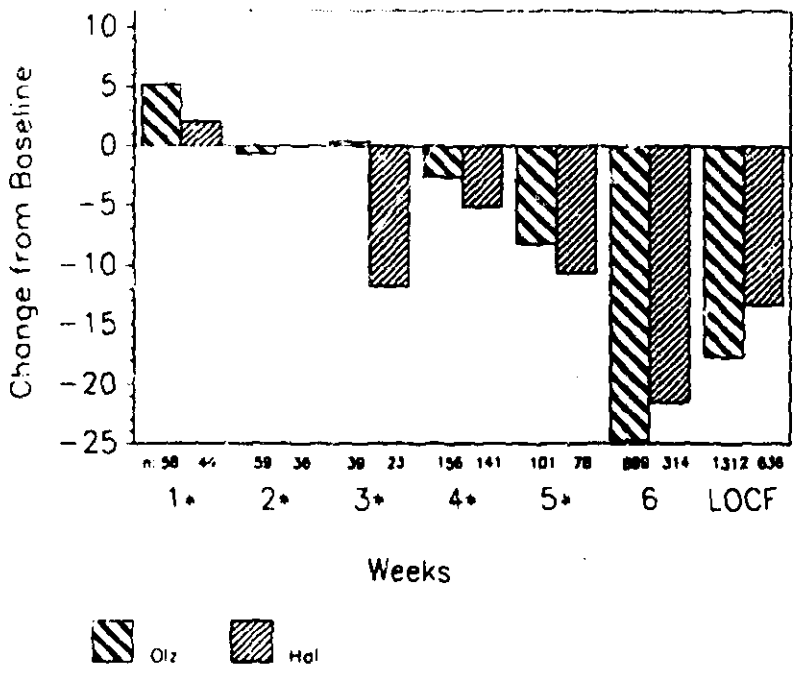
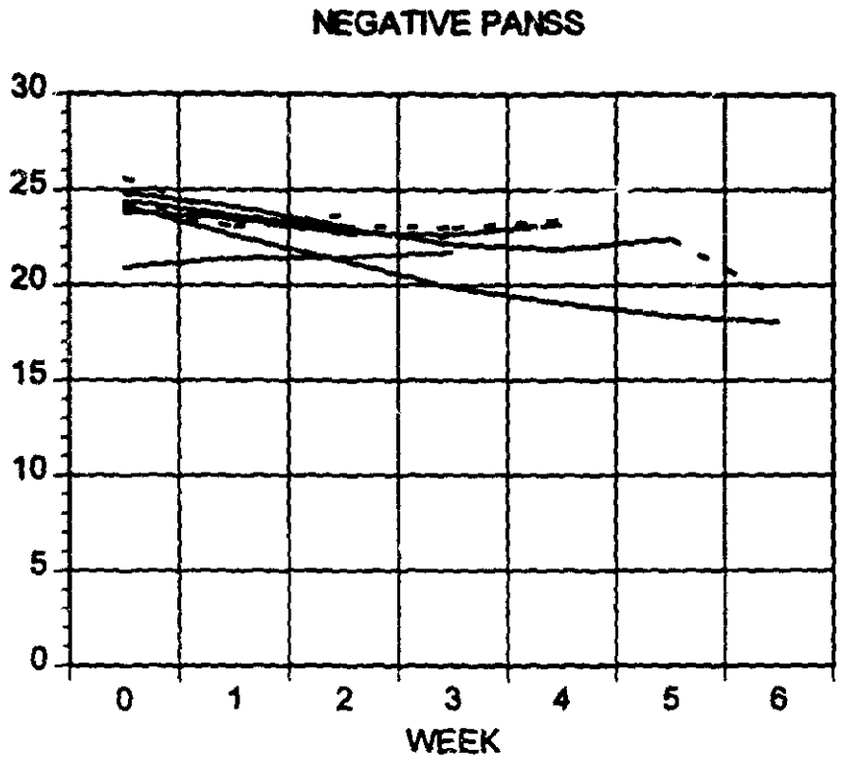

Change from Baseline
10
5
0
-5
-10
-15
-20
-25
1*
2*
3*
4*
5*
6
LOCF
Weeks
Olz
Hal

Figure 21


NEGATIVE PANSS
30
25
20
15
10
5
0
0
1
2
3
4
5
6
WEEK

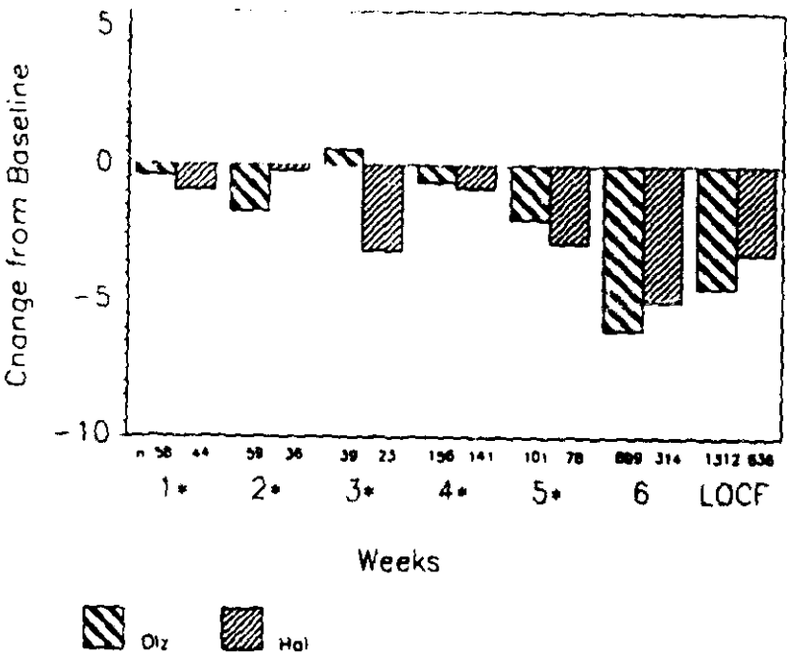
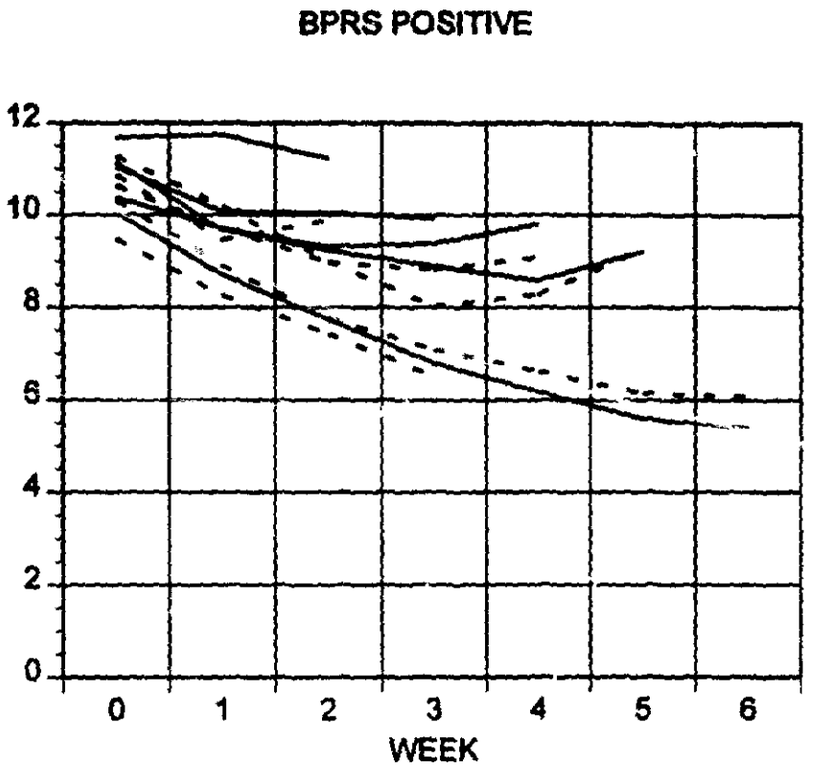

Change from Baseline
5
0
-5
-10
n 58 44 58 36 39 23 156 141 101 78 889 314 1312 636
1* 2* 3* 4* 5* 6 LOCF
Weeks
Olz
Hal

Figure 22


BPRS POSITIVE
12
10
8
6
4
2
0
0
1
2
3
4
5
6
WEEK

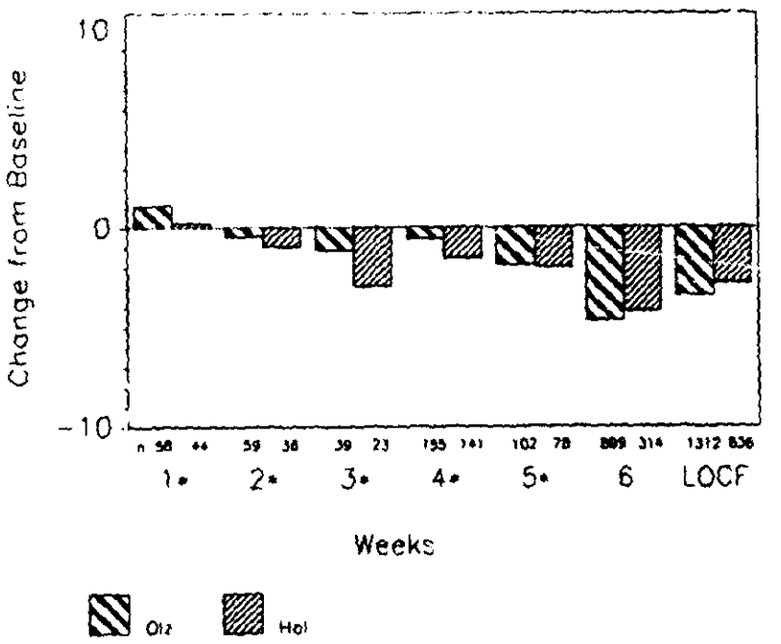
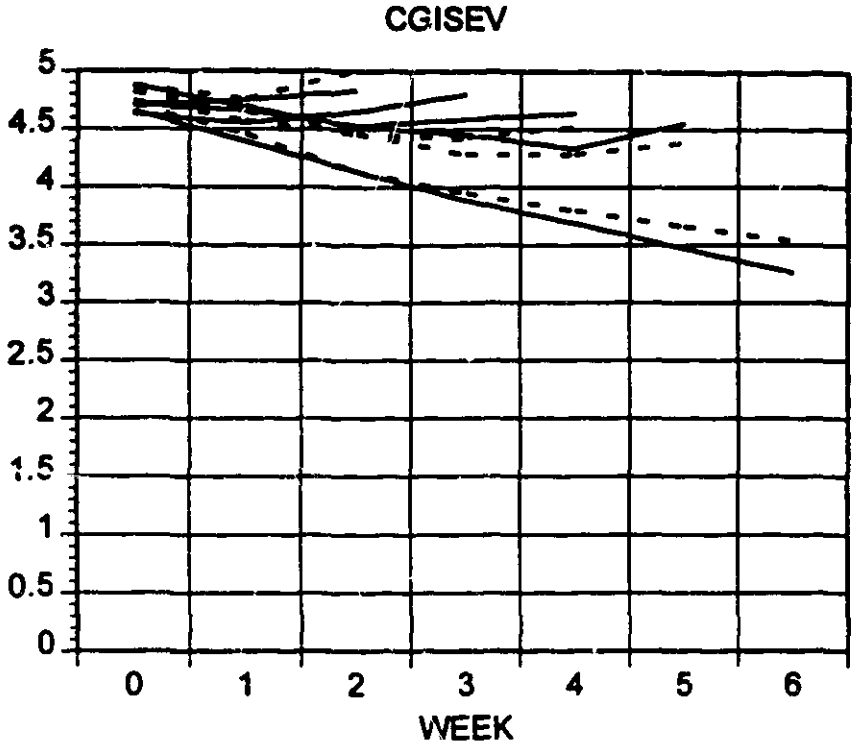

10
0
-10
Change from Baseline
n 58 44 59 36 39 23 155 141 102 78 889 314 1312 836
1* 2* 3* 4* 5* 6 LOCF
Weeks
Olz
Hal

Figure 23


CGISEV
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
1
2
3
4
5
6
WEEK

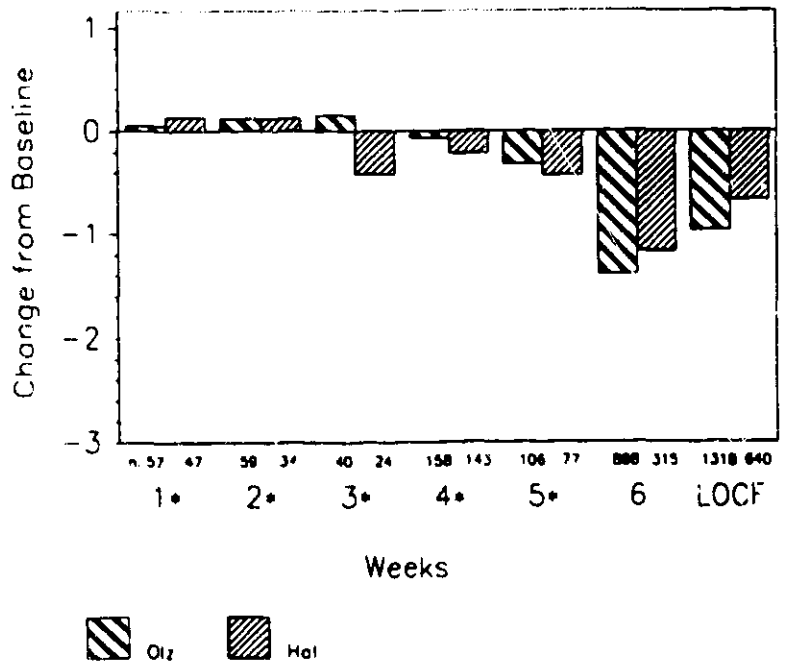
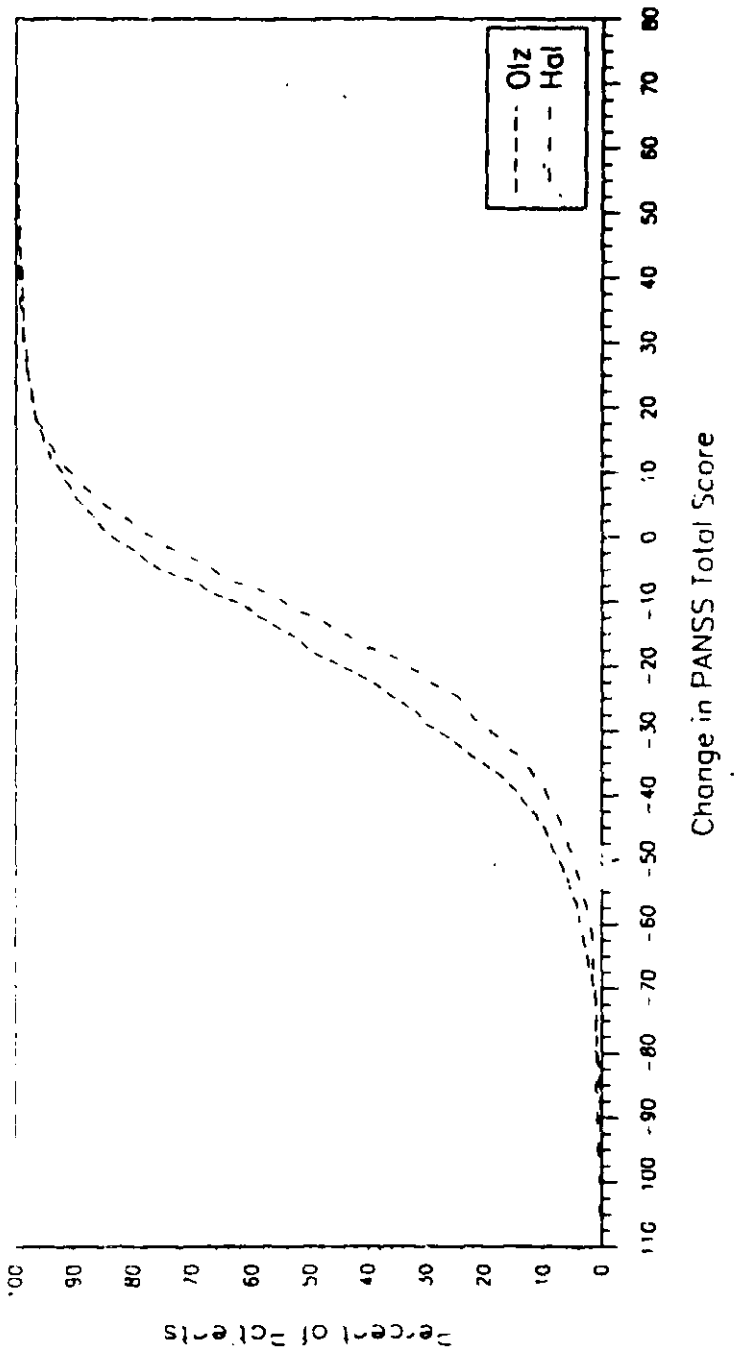

Change from Baseline
1
0
-1
-2
-3
n. 57 47 58 34 40 24 158 143 106 77 888 315 1318 640
1*
2*
3*
4*
5*
6
LOCF
Weeks
Olz
Hal

Figure 24



PANSS Total Score
Cumulative Distribution of Change (LOCF)
F1D-MC-HGAJ Acute Phase

Table 12

CGI Severity Score
Baseline to Endpoint
F1D-MC-HGAJ Acute Phase

Treatment Group	Baseline Score	Endpoint Score 1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	Total
Olz	1	1 (33%)	0[a]	0	2 (67%)	0	0	0	3
	2	2 (33%)	4 (67%)	0	0	0	0	0	6
	3	4 (5%)	12 (16%)	43 (58%)	10 (14%)	3 (4%)	1 (1%)	1 (1%)	74
	4	6 (1%)	69 (13%)	228 (43%)	175 (33%)	41 (8%)	10 (2%)	1 (<1%)	530
	5	7 (2%)	42 (9%)	161 (35%)	98 (22%)	111 (24%)	34 (7%)	2 (<1%)	455
	6	3 (1%)	11 (5%)	64 (30%)	42 (19%)	38 (18%)	51 (24%)	7 (3%)	216
	7	0	1 (3%)	3 (9%)	10 (29%)	4 (12%)	7 (21%)	9 (26%)	34
	Total	23	139	499	337	197	103	20	1318
Hal	1	0	0	0	0	0	0	0	0
	2	3 (43%)	2 (29%)	1 (14%)	1 (14%)	0	0	0	7
	3	1 (3%)	4 (11%)	23 (66%)	4 (11%)	3 (9%)	0	0	35
	4	0	20 (9%)	60 (27%)	113 (50%)	25 (11%)	7 (3%)	0	225
	5	1 (<1%)	11 (4%)	61 (25%)	75 (31%)	81 (33%)	15 (6%)	1 (<1%)	245
	6	0	3 (3%)	20 (18%)	14 (13%)	40 (36%)	34 (30%)	1 (<1%)	112
	7	0	0	0	4 (25%)	1(6%)	6 (38%)	5 (31%)	16
	Total	5	40	165	211	150	62	7	640

Abbreviations Olz = olanzapine 5, 10, 15, or 20 mg/day; Hal = haloperidol 5, 10, 15, or 20 mg/day.

Table entries are frequencies; row percents = frequency divided by row total.

Table 12

CGI Severity Score
Baseline to Endpoint
F1D-MC-HGAJ Acute Phase

Treatment Group	Baseline Score	Endpoint Score 1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	Total
Olz	1	1 (33%)	0[a]	0	2 (67%)	0	0	0	3
	2	2 (33%)	4 (67%)	0	0	0	0	0	6
	3	4 (5%)	12 (16%)	43 (58%)	10 (14%)	3 (4%)	1 (1%)	1 (1%)	74
	4	6 (1%)	69 (13%)	228 (43%)	175 (33%)	41 (8%)	10 (2%)	1 (<1%)	530
	5	7 (2%)	42 (9%)	161 (35%)	98 (22%)	111 (24%)	34 (7%)	2 (<1%)	455
	6	3 (1%)	11 (5%)	64 (30%)	42 (19%)	38 (18%)	51 (24%)	7 (3%)	216
	7	0	1 (3%)	3 (9%)	10 (29%)	4 (12%)	7 (21%)	9 (26%)	34
	Total	23	139	499	337	197	103	20	1318
Hal	1	0	0	0	0	0	0	0	0
	2	3 (43%)	2 (29%)	1 (14%)	1 (14%)	0	0	0	7
	3	1 (3%)	4 (11%)	23 (66%)	4 (11%)	3 (9%)	0	0	35
	4	0	20 (9%)	60 (27%)	113 (50%)	25 (11%)	7 (3%)	0	225
	5	1 (<1%)	11 (4%)	61 (25%)	75 (31%)	81 (33%)	15 (6%)	1 (<1%)	245
	6	0	3 (3%)	20 (18%)	14 (13%)	40 (36%)	34 (30%)	1 (<1%)	112
	7	0	0	0	4 (25%)	1(6%)	6 (38%)	5 (31%)	16
	Total	5	40	165	211	150	62	7	640

Abbreviations Olz = olanzapine 5, 10, 15, or 20 mg/day; Hal = haloperidol 5, 10, 15, or 20 mg/day.

Table entries are frequencies; row percents = frequency divided by row total.

APR 29 1996

CLINICAL PHARMACOLOGY AND BIOPHARMAC

NDA 20-592 Submission Dat
SPONSOR: Eli Lilly and Company
Indianapolis, IN
DRUG: Zyprex (Olanzapine, 2.5, 5, 7.5 and 10 mg tablets)
INDICATION: Psychosis
TYPE OF SUBMISSION: NME
REVIEWER: Robert Harris, Ph.D.

SYNOPSIS:

Olanzapine is an antipsychotic agent that has a pharmacological profil clozapine. It appears to be have a wide therapeutic range. The dosing administered once daily, and the recommended starting dose is 10 mg. marketing 2.5, 5, 7.5, and 10 mg tablets.

Olanzapine is well absorbed and reaches peak concentrations in approx relative oral bioavailability of olanzapine tablet in comparison to an or is eliminated significantly by first pass metabolism, with approximatel metabolized before reaching systemic circulation. Food does not signi or extent of olanzapine absorption.

Olanzapine is extensively distributed throughout the body, having a vo approximately 1000 L. It is 93% bound to plasma proteins, binding pri α-acid glycoprotein. Olanzapine does not extensively bind to red bloo

Following a single oral dose of ^{14}C labeled olanzapine, approximately was recovered in the urine and feces respectively. Only 7 percent of a recovered as unmetabolized drug, indicating that olanzapine is highly m urinary metabolites have been identified, the major being the 10-N-glu accounted for 13% of the dose. In the plasma, olanzapine accounted fo AUC for total radioactivity, indicating that there is significant exposure multiple dosing, the major metabolites identified in plasma were the 1 N-desmethyl olanzapine. However, it is possible that there is extensive metabolites.

Direct glucuronidation and cytochrome P-450 (CYP) mediated oxidati metabolic pathways. In vitro studies suggest that CYP1A2 is involved N-desmethyl and 7-hydroxy olanzapine, and the flavin-containing mon involved in the formation of the 4'-N-oxide metabolite. CYP2D6 is in of 2-hydroxymethyl olanzapine, although this appears to be a minor m

vivo as evidenced by the fact that the clearance of olanzapine is not reduced in subjects who are deficient in CYP2D6.

Olanzapine displays linear kinetics over the clinical dosing range. The apparent clearance (CL/f) and half life are approximately 25 L/hr and 30 hr respectively. Administration of olanzapine once daily leads to steady-state concentrations in about 1 week which are approximately 2-fold higher than single dose concentrations. The pharmacokinetics of olanzapine show a large amount of inter-subject variability. The clearance varies approximately four-fold within the population. The clearance of olanzapine is, on average, approximately 30% lower in women than in men, 40% higher in smokers compared to non-smokers, and 30% lower in the elderly than in the young. A cross study comparison between data obtained in Japan compared to data obtained in the US, suggests that exposure to olanzapine may be about two fold greater in the Japanese. Differences in olanzapine pharmacokinetics may be partially attributable to differences in CYP1A2 or glucuronyl transferase activity, both of which have been show to be affected by smoking and gender. Preliminary results suggest that olanzapine clearance is not significantly altered in hepatically or renally impaired subjects. In addition, olanzapine is not removed by the dialysis process. It is possible, however, that hepatic and renal impairment may alter the elimination of olanzapine metabolites.

A number of clinical drug interaction studies have been performed. Co-administered charcoal caused a 50% decrease in olanzapine exposure (as measured by AUC) and a 60% decrease in Cmax, presumably due to decreased absorption. Neither antacid nor cimetidine appeared to affect olanzapine absorption. Carbamazepine caused a 33% decrease in olanzapine exposure and a 25% decrease in Cmax, presumably due to enzyme induction. Imipramine caused a 19% increase in olanzapine exposure, although this increase was not statistically significant. Ethanol did not have a significant effect on olanzapine kinetics nor did olanzapine have a significant effect on ethanol kinetics. Warfarin did not affect olanzapine pharmacokinetics. In addition, olanzapine did not appear to have a significant effect on the pharmacokinetics of imipramine or its active metabolite, desipramine (potential markers of CYP2D6), diazepam or N-desmethyldiazepam (potential markers of CYP3A4), warfarin (potential marker of CYP2C9), lithium, biperiden or ethanol. It should be noted that two of the interaction studies (imipramine; warfarin) were performed in subjects who received a single olanzapine dose and thus had lower olanzapine concentrations than would be expected during normal clinical dosing. Therefore, lack of an apparent interaction is not conclusive. In vitro data suggest that olanzapine, at concentrations normally observed in vivo, should not significantly inhibit the activity of CYPs 3A4, 2D6, 1A2, 2C9, and 2C19.

The sponsor has adequately linked the to be marke ed tablets to the capsules used in the clinical trials. The dissolution methodology and specification submitted by the sponsor are acceptable.

RECOMMENDATION:

The submission (NDA 20,592) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and has been found to be acceptable. Comment 1 is for the medical officer. Please convey Comments 2-5 to the firm.

COMMENTS:

1. The medical officer is requested to verify the following statement that the sponsor has placed in the Special Population subsection of the Clinical Pharmacology section of labeling:

'...clinical trial safety and efficacy data did not suggest clinically significant differences among Caucasian patients, patients of African descent, and a third pooled category including Asian and Hispanic patients. Dosage modifications are not routinely recommended.'

2. The sponsor is requested to adopt the following dissolution methodology and specification for **all** tablet strengths:

Specification: not less than (Q)

3. The sponsor is requested to incorporate the labeling as provided at the end of the Summary section of this review on page 10.

4. If possible the sponsor should determine whether the population PK database provides any information regarding drug interactions.

5. The sponsor should be commended for providing the NDA on CD ROM. This greatly facilitated the review process. In addition, the analysis based upon the reference data base was informative. The sponsor is encouraged to continue this type of analysis whenever possible.

TABLE OF CONTENTS

SUMMARY

ABSORPTION

Rate: After administration of olanzapine, the time to reach maximal plasma concentration is approximately 6 hours (studies HGAT, HGAN, HGAH, and reference data base).

Extent: The absolute bioavailability of olanzapine has not been determined. After administration of ^{14}C radiolabeled drug to 6 male volunteers, an average of 57% of the dose was recovered in the urine and 30% was recovered in the feces, suggesting that at least 57% of the dose is absorbed (study HGAI). However, the percentage of absorbed dose is likely to be considerably higher than 57% because unmetabolized olanzapine in the feces accounted for only 2% of the dose, and 2/3 of the fecal radioactivity was recovered more than 48 hours postdose (study HGAI). Approximately 40% of an olanzapine dose is eliminated via first pass hepatic elimination (calculation by reviewer in Appendix). The relative bioavailability of olanzapine tablets compared to drug in solution is 100% (study HGBW).

Food effect: There does not appear to be a significant food effect. In six healthy subjects, 15 mg of olanzapine was administered in both the fasting state, and 30 minutes following a standard high fat breakfast (HGAH). Food did not affect the extent of absorption, although the absorption may have been slightly faster when olanzapine was administered with food (Tmax = 4.7±1.4 hr fed versus 5.8±1.3 hr fasted).

DISTRIBUTION

Volume of distribution: The apparent volume of distribution is large ($V\beta/F$ = 1000 L) indicating that olanzapine distributes extensively into tissues (HGAU, HGAW, population PK studies).

Protein and red blood cell binding: Olanzapine is about 93% bound to plasma proteins (HGAW). The protein binding is concentration-independent over the range of 7-1140 ng/mL (olanzapine Cmax values rarely exceed 40 ng/mL). Binding is primarily to albumin and α-1-acid glycoprotein. Because olanzapine is a low extraction ratio compound with a high volume of distribution, drug interactions mediated by protein binding should not occur. Olanzapine does not extensively bind to red blood cells (HGAI).

METABOLISM & ELIMINATION

In vivo: Olanzapine is highly metabolized. Only about 2 and 7% of an olanzapine dose is recovered as unmetabolized drug in the feces and urine respectively (HGAI). Olanzapine metabolites appear to be eliminated via both urinary (57% of dose) and biliary (up to 30% of dose) excretion (HGAI). Direct glucuronidation appears to be one of the major pathways of

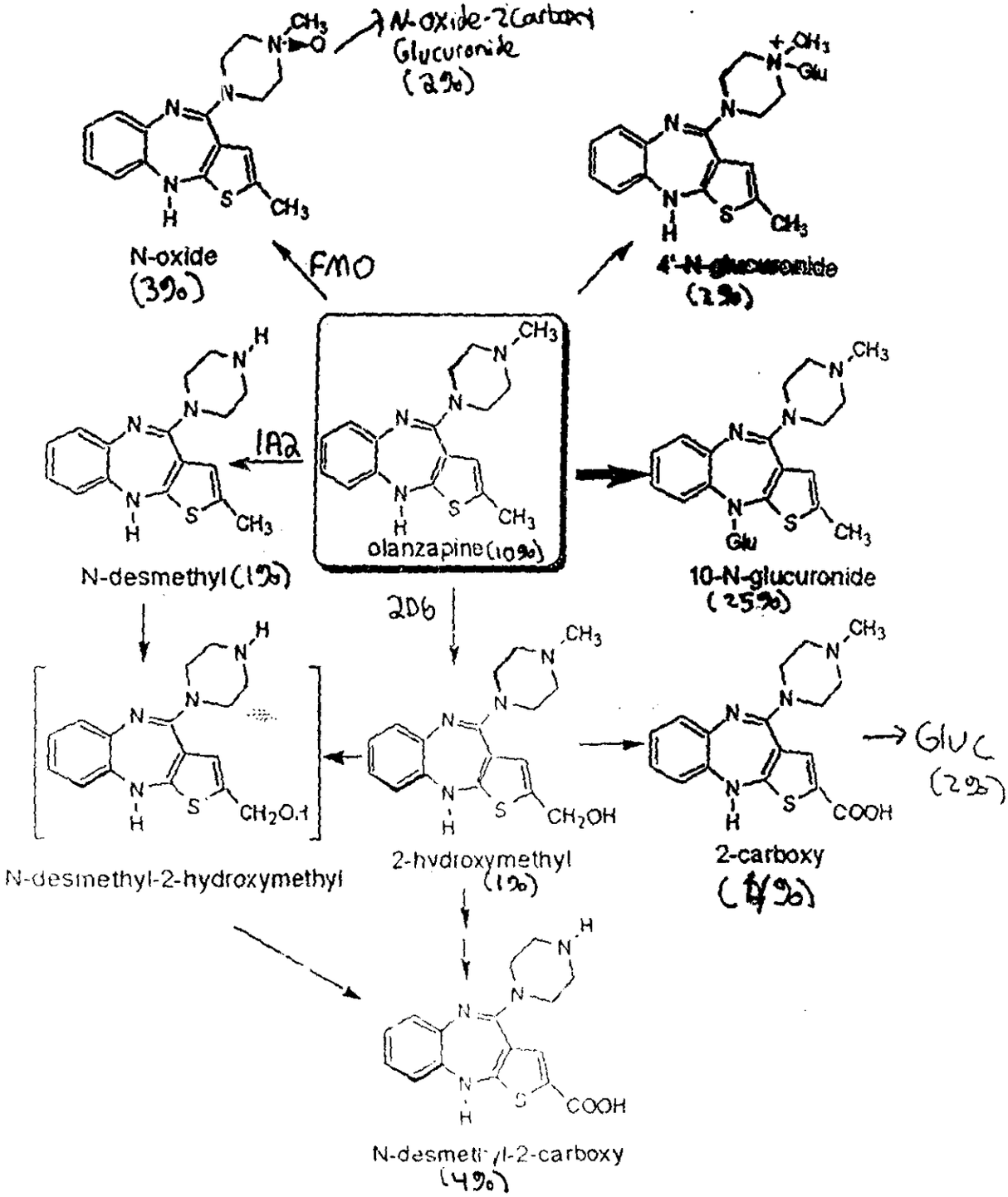


Figure Metabolic pathways of OLZ in humans. The compound in brackets has not yet been identified. Glu stands for glucuronic acid. Bold arrow indicates the major pathway.

elimination. In the feces, the major metabolite recovered is the 10-N-glucuronide, which accounts for 12% of the dose (HGAI). In urine, the 10-N glucuronide is also the major metabolite accounting for 13% of the dose. Nine other urinary metabolites have also been identified including N-desmethyl-2-carboxy olanzapine (3.8%), 2-carboxy olanzapine (3.5%) and olanzapine N-oxide (3.4% of dose; HGAI).

In plasma, after administration of radiolabeled drug, unmetabolized olanzapine accounted for only 12% of the AUC for total radioactivity, indicating that there is significant exposure to metabolites (HGAI). Metabolites found in the plasma include the 10-N-glucuronide, N-oxide, N-desmethyl, and 2-hydroxymethyl olanzapine (analysis of samples from HGAP). The sponsor has not reliably determined the exposure to metabolites at a quantitative level. Analysis of samples from subjects who were at steady state showed that the plasma levels of 10-N-glucuronide and N-desmethyl olanzapine were each approximately half that of olanzapine (HGAJ). It is possible that there may be significant exposure to metabolites other than the 10-N glucuronide and the N-desmethyl compound.

In vitro: CYP and flavin-contain monooxygenase (FMO) systems have been shown to be involved in the metabolism of olanzapine in vitro. Studies utilizing specific inhibitors, pure enzymes, and correlation techniques suggest that CYP1A2 is the primary enzyme involved in N-desmethyl formation, CYP2D6 is the major enzyme involved in 2-hydroxymethyl formation, and FMO is responsible for N-oxide formation. While each of these metabolites has been observed in vivo (see above), none can be considered a major metabolite. Thus, a decrease in the activity of a single enzyme should not have a large affect on olanzapine elimination. Consistent with this, the elimination of olanzapine was not reduced in subjects who were deficient in CYP2D6 (reference data base). For more information on in vitro metabolism see the Drug Interaction section below.

GENERAL PHARMACOKINETICS

Clearance and half life: The apparent clearance (CL/F) and half-life are approximately 25±12 L/hr and 30±10 hr respectively (reference data base).

Dose proportionality: Olanzapine displays linear kinetics (for clearance, volume and half life) over the dosing range of 2.5-20 mg (HGBY, HGAH, HGAM and population analysis).

Multiple vs single dose kinetics: The concentration of olanzapine is approximately doubled after multiple once daily dosing compared to single dose administration (MS-E001). This doubling is what would be predicted based upon olanzapine's half life of approximately 30 hours.

SPECIAL POPULATIONS

General approach: The sponsor utilizes three approaches to determine the kinetics in special populations: 1. Analysis of individual small scale classical PK studies; 2. Analysis of a pooled data set (Reference Data Base) consisting of all of the data from the classical PK studies; 3. Population pharmacokinetic analysis of data obtained in clinical trials.

Smoking, gender, and age: All three approaches lead to the conclusion that olanzapine clearance is increased (and thus steady state drug levels are decreased) by about 40% in smokers compared to nonsmokers and increased by about 30% in men compared to women (population analysis of HGAJ and reference data base). Because smoking and male gender have been shown to cause increased CYP1A2 activity, the sponsor attributes these effects to CYP1A2 differences. There are also literature reports that suggest that glucuronidation is increased in men and in smokers, so it is likely that the direct glucuronidation of olanzapine is also increased in these populations. The clearance of olanzapine also appears to be 30% higher in the young compared to the elderly (HGAM, HGCC).

Hepatic and renal impairment: Preliminary results based on 6 subjects with cirrhosis suggest that hepatic disease does not appear to affect olanzapine clearance (HGAU). This study was confounded by the fact that 4 of the 6 cirrhotic subjects were smokers. It appears, at least, that this type of liver impairment does not cause large changes in the elimination rate of olanzapine. Similarly, renal status, as measured by creatinine clearance, did not appear to affect olanzapine clearance (HGAW). This is expected because olanzapine is highly metabolized, with only 7% excreted unchanged in the urine (HGAI). In addition, no drug is lost during the dialysis process. The effects of renal impairment on the elimination of olanzapine metabolites has not been examined.

Race: No specific pharmacokinetic study was conducted to investigate the effects of race. A cross study comparison between data obtained in Japan compared to data obtained in the US, suggests that exposure to olanzapine may be about two fold greater in the Japanese when equivalent doses are administered.

DRUG INTERACTIONS

Effects of drugs on olanzapine metabolism in vivo: Co-administered charcoal (1 g) caused a 50% decrease in olanzapine exposure (as measured by AUC) and a 60% decrease in Cmax, presumably due to decreased absorption. Neither antacid nor cimetidine (800 mg single dose) appeared to affect olanzapine absorption (HGAT). Carbamazepine (200 mg b.i.d. for 18 days) caused a 33% decrease in olanzapine exposure and a 25% decrease in Cmax (HGBC), presumably due to enzyme induction. Because carbamazepine is known to increase the activity of a number of enzyme systems, the decrease in olanzapine levels cannot be attributed to an increase in the activity of a specific enzyme. Imipramine (75 mg single dose), a potential inhibitor of CYP2D6 caused a 19% increase in olanzapine exposure, although this

increase was not statistically significant (HGAQ). As described in the In Vitro Metabolism section, olanzapine elimination is not impaired in people deficient in CYP2D6, which suggests that CYP2D6 inhibitors should not significantly alter the pharmacokinetics of this drug. Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine kinetics (HGAN). Also, Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics.

Effects of olanzapine on the metabolism of other drugs in vivo: Olanzapine did not appear to have a significant effect on the pharmacokinetics of imipramine or its active metabolite desipramine (potential markers of CYP2D6; olanzapine dose = 5 mg single dose; HGAQ), diazepam or N-desmethyldiazepam (potential markers of CYP2C19 and CYP3A4; olanzapine dose = 12.5 mg/day for 9 days; HGAE), warfarin (potential marker of CYP2C9; olanzapine dose = 10 mg single dose; HGBE), ethanol (olanzapine dose = 10 mg/day for 7 days; HGAN), lithium (olanzapine dose = 10 mg/day for 8 days; MS-E001), or biperiden (olanzapine dose =10 mg for 7 days; E002). It should be noted that two of these studies (HGAQ-imipramine and HGBE-warfarin) were performed in subjects who received a single olanzapine dose and thus had lower olanzapine concentrations than would be expected during normal clinical dosing. Therefore, lack of an apparent interaction is not necessarily conclusive.

in vitro studies: Olanzapine is a moderate inhibitor of CYP enzymes (ADME report 38): Ki = 491 μM for CYP3A4 catalyzed formation of 1'=hydroxy midazolam; Ki = 89 μM for CYP2D6 catalyzed formation of 1'-hydroxy bufuralol; Ki = 715 μM for CYP2C9 catalyzed formation of 4-hydroxy tolbutamide; Ki = 920 μM for CYP2C19 catalyzed formation of 4'-hydroxy S-mephenytoin; Ki = 36 μM for CYP1A2 catalyzed acetaminophen formation. These results suggest that olanzapine has the greatest potential of inhibiting CYP1A2 in vivo. However, because the total concentration of olanzapine in plasma does not typically exceed 50 ng/mL (160 nM), the chances of CYP1A2 inhibition in vivo seem low. To investigate the possibility, the sponsor is currently running a clinical study investigating the interaction between theophylline and olanzapine.

Because CYP1A2 is involved in the metabolism of olanzapine (see Metabolism section above), it is possible that CYP1A2 inhibitors could impair olanzapine elimination in vivo. However, because olanzapine is metabolized by a number of pathways, this effect is likely to be small. The theophylline-olanzapine interaction study that is currently in progress should provide pertinent information regarding this potential interaction.

BIOEQUIVALENCE

One large pivotal definitive bioequivalence study has been performed (HGBY, see Appendix for details). This study utilized 5, 7.5, and 10 mg 'to be marketed' tablets (Puerto Rico) and 5, 10, and 15 mg clinical capsules (Basingstoke, UK). Stepwise, 5 x 1 mg and 1 x 5 mg tablets linked to the 5 mg clinical capsule; the 10 mg tablet to the 10 mg capsule; and 2 x 7.5 mg tablets to the 15 mg capsule. The 5 mg tablet was present in all three stages of the

study providing a common link. All comparisons made in this study passed the Agency's criteria for bioequivalence. Thus, the study adequately linked the 'to be marketed' tablets to the capsules used in the clinical studies. It also demonstrated equivalence between strengths. It should be noted that the 2.5 mg tablet strength, a formulation that may be marketed, was not examined in this study. However, a Japanese study (JE-205E) demonstrated that 2 x 2.5 mg tablets are bioequivalent to 1 x 5 mg tablet. Further, because the 1 and 5 mg tablet strengths were studied, dissolution/formulation data could also be used to link this strength to the other strengths.

In addition, the sponsor illustrated that a granule formulation was equivalent to the capsule formulation and to the to be marketed tablet formulation (HGBW). Because the granule formulation is mixed in water before administration, it is equivalent to drug in solution. Although the sponsor has not requested that this formulation be approved for marketing, this study was reviewed because it provided information regarding the relative bioavailability of the olanzapine tablet (approximately 100%).

ANALYTICAL

The sponsor utilized several analytical techniques, (e.g. GC-EC, GC-MS, HPLC-EC) for the measurement of olanzapine in biological fluids. Overall, all of the assays have been validated.

DISSOLUTION

Olanzapine is only very slightly soluble in purified water. The sponsor determined the dissolution characteristics of the tablets in four different media (water; 0.1N HCl; pH 4.5 buffer; pH 6.8 buffer) using the highest (10 mg) strength. Because the solubility in 0.1N HCl is somewhat higher (see Appendix for solubility and dissolution profiles), and because 0.1N HCl is close to the physiological conditions of the stomach, this medium was chosen for the dissolution method. The following dissolution methodology and specification submitted by the sponsor are satisfactory and apply to **all** tablet strengths.

Specification: not less than (Q)

REVISED LABELING

The sponsor is requested to incorporate the following labeling:

CLINICAL PHARMACOLOGY:

Pharmacokinetics

Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism as approximately 40% of the dose is metabolized before reaching systemic circulation. Food does not affect the rate or extent of olanzipine absorption.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr, cv=30%), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr, cv = 45%). Administration of olanzapine once daily leads to steady-state concentrations in about one week which are approximately 2-fold higher than single dose concentrations. Over time and dosage range, pharmacokinetic parameters within an individual are very consistent. However, plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age (see Special Populations).

Olanzapine is extensively distributed throughout the body, having a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α-1-acid glycoprotein.

Metabolism and elimination

Following a single oral dose of ^{14}C labeled olanzapine, 7 percent of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating that there is significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide and 4'-N-desmethyl olanzapine, both of which lack pharmacological activity at the concentrations observed.

Direct glucuronidation and cytochrome P-450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Special Populations

Renal Impairment--Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, suggesting that dosage adjustment based upon the degree of renal impairment may not be required. In addition, olanzapine is not removed by the dialysis process. Multiple-dose studies in patients with renal failure have not been performed, and the effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment--The effect of impaired liver function was evaluated in subjects with clinically significant (Childs Pugh Classification A and B) cirrhosis. Pharmacokinetic assessment indicated that cirrhosis had little effect on the pharmacokinetics of olanzapine. Although the presence of hepatic impairment may reduce the clearance of olanzapine, based upon the available pharmacokinetic data, a dosage reduction for patients with impaired hepatic function is not uniformly indicated.

Age--In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (>65 years) than in non-elderly subjects (≤65 years). However, the pharmacokinetic variability among the elderly was within the variability of their non-elderly counterparts. Caution should be used in dosing to the elderly, although dosage modifications are not routinely recommended in the absence of other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity (see DOSAGE AND ADMINISTRATION).

Gender--Pharmacokinetic screening of healthy subjects and patients s that the clearance of olanzapine is approximately 30% lower in women than in men. However, dosage modifications based on gender are not routinely recommended.

Smoking Status--Pharmacokinetic screening of healthy subjects and patients showed that olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race--No specific pharmacokinetic study was conducted to investigate the effects of race. A cross study comparison between data obtained in Japan compared to data obtained in the US, suggests that exposure to olanzapine may be about two fold greater in the Japanese when equivalent doses are administered.

[Medical Officer: Please see Comment 1 of this review]

Combined effects--The combined effects of age, smoking and gender suggest that the clearance in young smoking males may be 3 times higher than that in elderly nonsmoking

females. This difference in olanzapine clearance is likely related to differences in CYP1A2 and glucuronyl transferase activity. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine (See DOSAGE AND ADMINISTRATION).

PRECAUTIONS

Drug Interactions

The Effect of Other Drugs on ZYPREX-- Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 (e.g. theophylline and caffeine) could potentially inhibit olanzapine elimination. However, because olanzapine is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease olanzapine clearance.

Charcoal: The administration of activated charcoal (1 g) reduced the Cmax and AUC of olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

Cimetidine and Antacids: Single-doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacid did not affect the oral bioavailability of olanzapine.

Carbamazepine: Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Imipramine: Imipramine (75 mg single dose), a potential inhibitor of CYP2D6 caused a 19% increase in olanzapine exposure, although this increase was not statistically significant. Olanzapine elimination is not impaired in people deficient in CYP2D6 which suggests that CYP2D6 inhibitors should not significantly alter the pharmacokinetics of this drug.

Ethanol: Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics.

Warfarin: Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics.

Effect of ZYPREX on Other Drugs--In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam and its active metabolite N-desmethyldiazepam, lithium, ethanol or biperiden. The ability of olanzapine to inhibit the elimination of a CYP1A2 substrate (e.g. theophylline) has not been investigated in clinical studies.

Olanzapine has the potential to inhibit the metabolism of drugs which are eliminated via direct glucuronidation including AZT, lorazepam, valproic acid, and lamotrigine. Caution should be exercised when olanzapine is coadministered with these drugs.

DOSAGE AND ADMINISTRATION

Dosage in Special Populations--Consideration should be given to a lower starting dose in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g. non-smoking female patients >65 years of age) or who may be more pharmacodynamically sensitive to olanzapine (see CLINICAL PHARMACOLOGY; see Drug Interactions under PRECAUTIONS). When indicated, dose escalation should be performed with caution in these patients.

Biopharm Day: April 3, 1996

Robert Z. Harris, Ph.D.
Division of Pharmaceutical Evaluation I

FT initiated by Raman Baweja, Ph.D.

cc: NDA 20,592, HFD-120, HFD-860 (Harris, Baweja, Malinowski), HF
(Viswanathan), Chron, Reviewer, Drug (Clarence Bott HFD-870, PKLN
19 (FOI).

APPENDIX I

INTRODUCTION

B.1. Pharmacologic Class

Olanzapine is a potent antipsychotic agent displaying receptor affinity in vitro at serotonin 5-$HT_{2A/2C}$, 5-HT_3, 5-HT_6, dopamine $D_4/D_3/D_1/D_2$, and muscarinic cholinergic (M_1-M_5), α_1-adrenergic and histamine H_1 receptors. While exhibiting distinct structural and metabolic differences, the compound has a pharmacological profile of activity similar to that of the atypical agent, clozapine. This profile is especially distinct from the typical antipsychotic agents (eg, haloperidol). On the basis of these findings, it would be predicted that olanzapine would have a unique profile highlighted by a wider range of efficacy than typical agents and a much lower incidence of undesirable side effects than either class, eg, extrapyramidal symptoms, hematoxicity, etc.

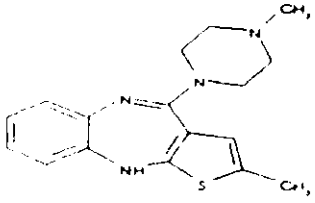
D.1. Drug Substance

D.1.1. Description Including Physical and Chemical Characteristics and Stability

D.1.1.1 Names

Chemical Name (USAN):	1. 2-Methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine or 2. 10*H*-thieno[2,3-*b*][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)-
International Non-proprietary Name (INN)	Olanzapine
Proprietary (Brand) Name:	Zyprex
Synonyms:	None
Lilly Compound Number:	LY170053
Chemical Abstracts Number:	132539-06-1

D.1.1.2 Physical and Chemical Characteristics

Empirical Formula:	$C_{17}H_{20}N_4S$
Molecular Weight:	312.43
Structural Formula:	
Description:	Olanzapine is a yellow crystalline solid
pK_a:	5.00 and 7.40 in Dimethylformamide/Water (60:40, v/v)
Melting Point:	195 ± 2°C

Solubility Profile:

Medium	Solubilities at Room Temperature pH of Medium at Saturation	Solubility (mg/mL)	Solubility Classification
Acetonitrile	–	11.5	sparingly soluble
Buffer pH 2	5.87	2.5	slightly soluble
Buffer pH 4	5.97	11.0	sparingly soluble
Buffer pH 6	6.04	4.3	slightly soluble
Buffer pH 7	7.08	0.4	very slightly soluble
Buffer pH 10	9.92	0.1	very slightly soluble
Ethanol, anhydrous	–	7.0	slightly soluble
Ether	–	7.6	slightly soluble
0.1N HCl	5.38	20.6	sparingly soluble
Methanol	–	4.5	slightly soluble
0.1N NaOH	12.83	0.3	very slightly soluble
n-Propanol	–	43.9	soluble
Propylene Glycol: H_2O (1:5)	–	0.1	very slightly soluble
Water	–	<0.1	practically insoluble

ABSORPTION-FOOD EFFECT

CLINICAL REPORT SYNOPSIS: PROTOCOL

Protocol No.	F1D LC HGAH
Title:	LY170053: DOSE PROPORTIONALITY AND EFFECT OF FEEDING ON BIOAVAILABILITY
Principal Investigator:	D. P. Henry, M. D.
Study Centers:	Lilly Laboratory for Clinical Research; single site.
Clinical Phase:	I
Objectives:	(1) To examine the proportionality of pharmacokinetic parameters to administered single dose of LY170053 in the fasting state (5, 10, 15 mg); (2) To examine the effect of food (breakfast) on the bioavailaibility of LY170053.
Methodology:	Single blind, randomized Crossover study.
Number of Patients:	Six adult male volunteers signed informed consent and 6 completed the study.
Entry Criteria:	Normal adult male volunteers between the ages of 21 and 55 years, inclusive.
CT MATERIALS /ADMINISTRATION:	LY170053, 10 mg capsules (CT00069) LY170053, 2.5 mg capsules (CT00068)
Duration of Treatment:	Four single doses with washout of at least 96 hours between doses.

HGAH

Subject	Body Wt (kg)	Dose (mg/kg)	Cmax (ng/ml)	Cmax' ($L^{-1}x10^{-3}$)	Cmax' (kg/L)	Tmax (hr)	β (hr^{-1})	t ½ (hr)
Mean	75.6	0.201	13.3	0.92	0.0675	5.8	0.0316	22.2
Std Dev	10.5	0.026	2.6	0.18	0.0136	1.3	0.0042	2.7
C.V. %	13.8	12.7	19.9	19.5	29.1	22.8	13.2	11.9

15 mg Fasting

Subject	AUCo-t (ng·hr/ml)	AUC'o-t (kg·hr/L)	AUCo-∞ (ng·hr/ml)	AUC'o-∞ (kg·hr/L)	Cls/FF* (L/hr)	Cls/FF* (ml/min)	Cls/FF* (L/kg/hr)	Vβ/FF* (L)	Vβ/FF* (L/kg)
Mean	325.7	1.65	357.8	1.82	43.2	719.7	0.586	1369	18.4
Std Dev	54.6	0.39	67.5	0.53	8.0	133.9	0.161	215	3.9
C.V. %	16.8	23.7	18.9	29.2	18.6	18.6	27.5	16	21.1

Subject	Body Wt (kg)	Dose (mg/kg)	Cmax (ng/ml)	Cmax' ($L^{-1}x10^{-3}$)	Cmax' (kg/L)	Tmax (hr)	β (hr^{-1})	t ½ (hr)
Mean	76.3	0.199	13.8	0.88	0.0695	4.7	0.0268	26.2
Std Dev	9.6	0.023	2.7	0.18	0.0112	1.4	0.0031	3.2
C.V. %	12.6	11.5	19.5	19.9	16.1	29.3	11.5	12.2

Subject	AUCo-t (ng·hr/ml)	AUC'o-t (kg·hr/L)	AUCo-∞ (ng·hr/ml)	AUC'o-∞ (kg·hr/L)	Cls/FF* (L/hr)	Cls/FF* (ml/min)	Cls/FF* (L/kg/hr)	Vβ/FF* (L)	Vβ/FF* (L/kg)
Mean	325.0	1.65	365.4	1.86	42.3	704.3	0.559	1597	20.9
Std Dev	60.8	0.39	64.5	0.42	8.3	138.1	0.106	404	4.1
C.V. %	18.7	23.6	17.7	22.6	19.6	19.6	19.0	25.3	19.5

15 mg Fed

* normalized for Dose
* normalized for Dose and Bodyweight

A 5

Food Effect in Japanese Subjects
JE-205E

Step 1: Statistical Outcome of Fasting versus Fed N=16 Males

Pharmacokinetic Variable		Contrast	Mean Difference	Contrast P-Value	Ratio of Means	90 % Confidence Interval ‡
C_{max}*	(ng/mL)	Fed vs Fasting	-2.2%	0.589	0.98	0.93 - 1.04 P
Tmax	(hr)	Fed vs Fasting	-0.13† hr	0.619	na	na
AUC_{0-t}*	(ngxhr/mL)	Fed vs Fasting	-0.1%	0.947	1.00	0.95 - 1.05 P
$AUC_{0-\infty}$*	(ngxhr/mL)	Fed vs Fasting	1.5%	0.571	1.01	0.97 - 1.06 P

* Analysis performed on the log-transformed variables.
† Absolute difference. na = not applicable.
‡ Lower and Upper bound. P=pass F=fail Bioequivalence Criterion 0.80 - 1.25

Step 1: Mean Olanzapine Bioavailability After a 5-mg Olanzapine Tablet Given Fasting or Fed

Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ngxhr/mL)	$AUC_{0-\infty}$ (ngxhr/mL)
Fasting	**10.5**	**4.8**	**279**	**313**
CV%	21.0	24.9	31.0	35.7
Fed	**10.3**	**4.6**	**279**	**318**
CV%	20.7	30.4	31.2	34.9

n = 16 Subjects.
Abbreviations: Cmax = maximum plasma concentration; Tmax = time of maximum concentration; AUC = area under the curve; CV = coefficient of variation.

These results are from Japanese study JE-205E (See bioequivalence appendix for details of this study). They illustrate that, as was observed in Americans, food does not appear to have a large effect on olanzapine pharmacokinetics.

CLINICAL STUDY SYNOPSIS: Study F1D-EW-HGBW

Title:	A Bioequivalence Study of 10 mg Capsule (Lilly) vs 10 mg Granules (Lilly) vs 10 mg Tablets (Lilly) of Olanzapine
Investigator:	
Study Centres:	
Dates of Study:	December 1994 through February 1995
Clinical Phase:	Phase 1
Objectives:	To determine the bioequivalence between olanzapine capsule 10 mg (Lilly), olanzapine granules 10 mg (Lilly) and olanzapine tablets 10 mg (Lilly).
Methodology:	Three-period, balanced, randomised, cross-over study.
Number of Subjects:	Olanzapine: Male 20, Female 0, Total 20;
Diagnosis and Inclusion Criteria.	Male volunteers, aged 18 - 45 years, body weight 60 - 90 kg.
Dosage and Administration:	Reference Product A Olanzapine capsules: 10 mg single dose 56346: olanzapine capsules, 10 mg Test Product B Olanzapine tablet: 10 mg single dose CT03822: olanzapine tablets, 10 mg Test Product C Olanzapine granules: 10 mg single dose B0445: olanzapine granules, 10 mg
Duration of Treatment:	Olanzapine: Three 10 mg doses
Criteria for Evaluation:	Bioequivalence-- Plasma olanzapine assay

Study Material Identifier	Formulation Type	Dose	Lot #	Expiry Date
Reference drug A	Olanzapine capsule (Lilly)	10 mg	56346	1st Sept. 1996
Test drug B	Olanzapine tablet (Lilly)	10 mg	CT03822	1st May 1995
Test drug C	Olanzapine granules (Lilly)	10 mg	B0445	1st April 1995

A: one (1) olanzapine capsule 10 mg OR
B. one (1) olanzapine tablet 10 mg OR
C: olanzapine granules equivalent to 10 mg (dissolved in demineralised water, see Attachment 5 of the study protocol)

HGBW

Table HGBW.6.5.1. Mean Olanzapine Bioavailability

Treatment	C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-t} (ng×hr/ml)	$AUC_{0-\infty}$ (ng×hr/ml)
	10 mg Dose (n=18 Subjects)			
A: Capsule	14.2	5.0	458	491
CV%	31.2	55.5	28.7	31.3
B: Tablet	13.3	4.8	437	470
CV%	33.6	36.9	32.8	35.9
C: Granule	12.9	4.6	417	448
CV%	33.2	39.5	33.9	36.7

Abbreviations: Cmax = maximum plasma concentration; Tmax = time of maximum plasma concentration; AUC = area under the curve; CV = coefficient of variation.

Table HGBW.6.5.2. Confidence Intervals on Bioavailability Variables Tablet vs Capsule

Bioavailability Variable		Ratio of Means	90% Confidence Lower Limit	90% Confidence Upper Limit	Bioequivalence Criteria† Pass/Fail
C_{max}	(ng/ml)	0.93	0.87	0.98	Pass
AUC_{0-t}	(ng×hr/ml)	0.94	0.91	0.97	Pass
$AUC_{0-\infty}$	(ng×hr/ml)	0.94	0.91	0.97	Pass

† Bioequivalence Range: 0.80 to 1.25; 90% Confidence Interval constructed in log domain.

Granule vs Capsule

Bioavailability Variable		Ratio of Means	90% Confidence Lower Limit	90% Confidence Upper Limit	Bioequivalence Criteria† Pass/Fail
C_{max}	(ng/ml)	0.90	0.85	0.95	Pass
AUC_{0-t}	(ng×hr/ml)	0.90	0.87	0.92	Pass
$AUC_{0-\infty}$	(ng×hr/ml)	0.90	0.87	0.93	Pass

† Bioequivalence Range: 0.80 to 1.25; 90% Confidence Interval constructed in log domain.

Bioequivalence-absorption conclusions: Olanzapine is similarly absorbed when given as a tablet or capsule compared to a suspension. There is not a significant effect of food on the absorption of olanzapine, although it is possible that food slightly increases the rate of absorption and Cmax in some individuals.

Study HGBW also demonstrates that the 10 mg tablet is bioequivalent to the 10 mg capsule used in the clinical studies. This result supports the conclusions of bioequivalence made in the pivotal bioequivalence study (HGBY).

DETERMINATION OF OLANZAPINE FIRST PASS METABOLISM

Assume that all drug is absorbed from gut.

eq. 1 Fmax = 1 - CL/Q = 1 - CL/90L/hr. Where CL = blood clearance

eq. 2 CL/F = 57 L/hr. (Empirical observation of apparent blood CL of olanzapine*)

If **F = Fmax** (i.e. only hepatic first pass metabolism occurring)
then eq 1 and eq 2 can be combined:

F = 1-(57*F/90). Rearranging and solving: **F = 0.61.**

Thus Extraction ratio **ER = 1- F = 0.39**. **CL = F * 57 = 22 L/hr**.

If **F < Fmax** then even more drug is eliminated before reaching the systemic circulation.
Thus **ER > 0.39, and CL < 22 L/hr**.

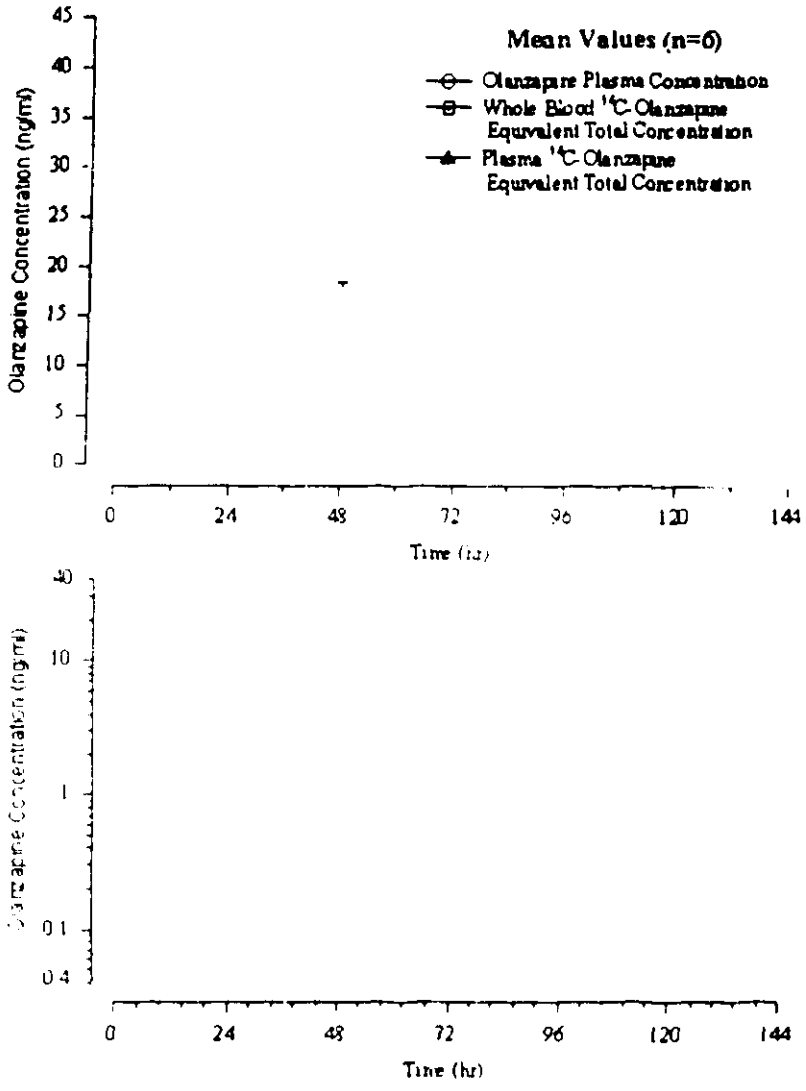
*CLplasma/F = 34 L/hr. Since olanzapine does not significantly partition into red blood cells, CLblood/Vblood = CLplasma/Vplasma. CLblood = CLplasma/(1-H), where H = hemacrit. CLblood = CLplasma /(1-0.4) = 57

^{14}C ADME STUDY / IN VITRO METABOLISM/PROTEIN BINDING

CLINICAL STUDY SYNOPSIS. Study F1D-LC-HGAI

Title:	The Disposition of ^{14}C-LY170053 In Man
Investigators:	
Study Centers:	This was a single-center study.
Dates of Study:	October 19, 1991 through February 11, 1992
Clinical Phase:	Phase 1
Objectives:	The object of this study was to determine the metabolic disposition of ^{14}C-LY170053 in healthy volunteers.
Methodology:	Open-label, single-blind, single-dose study.
Number of Subjects:	Six male subjects were entered and completed the study. Six subjects received olanzapine.
Diagnosis and Inclusion Criteria:	Healthy male subjects
Dosage and Administration:	Test Product Olanzapine Single nominal doses of 12.5 mg capsule (CT00541) with nominal dose of 100 uCi radiocarbon Reference Therapy None
Duration of Treatment:	Test drug name: Olanzapine, single dose once
Criteria for Evaluation:	Efficacy-- Not applicable Pharmacokinetics: Plasma drug concentrations of olanzapine were measured and standard pharmacokinetic and bioavailability indices were calculated. Metabolism: The metabolic profile of ^{14}C-olanzapine was defined. Safety-- Safety parameters included vital signs, electrocardiograms, and clinical laboratory tests.
Statistical Methods	Paired t-tests

Figure HGAI 4 2 Mean plasma concentrations of olanzapine and radioactivity following a single oral dose of [^{14}C]olanzapine to 6 normal subjects



HGAI

Reviewer note: Unmetabolized olanzapine accounts for only approximately 12% of the AUC for total radioactivity. Thus, there is significant exposure to metabolites. This study does not adequately address the question of which metabolites are present in plasma. However, the sponsor does claim that exposure to N-desmethyl olanzapine and the 10-N-glucuronide of olanzapine, which are reported to be the two major circulating metabolites, is approximately 44 and 31% that of olanzapine respectively (supporting figure follows results of this study). Thus, olanzapine and its two major circulating metabolites together may account for only about 20% of the total AUC. The ratio of radioactivity in blood compared to plasma equals about 0.6, suggesting that only a small amount of drug goes into red blood cells.

H6AI

^{14}C-equivalents of OLZ (ng equiv./ml) in Red Blood Cells Volunteer ID: NES[a]

Time after dose (hr)	Plasma	Whole blood	RBC[b]
predose			
0.33			
0.67			
1			
2			
2.5			
3			
3.5			
4			
4.5			
5			
6			
8			
12			
16			
24			
36			
48			
72			
96			
120			
144			

[a] Hematocrit = 0.400

[b] Radioactivity/ml RBC = $\frac{\text{(14C equiv./ml in whole blood) - [(14C equiv./ml in plasma) (- hematocrit)]}}{\text{hematocrit}}$

[c] ND = not detected

Note: This table, which shows the partitioning of radioactivity into the blood components of a representative subject, illustrates that olanzapine and its metabolites only minimally partition into red blood cells. This conclusion is consistent with the average concentration vs time profiles in blood and plasma shown on the previous page.

A 13

Table HGAI 4.14 Noncompartmental Pharmacokinetic Analysis of Plasma Radiocarbon N=6

	Dose(mg)	Wt (kg)	Cmax (ngeq/ml)	Tmax (hr)	β (hr^{-1})	t½ (hr)
Mean	12.5	77.8	39.0	4.92	0.0120	58.7
SD		8.4	14.2	0.66	0.0015	7.1
CV		10.8	36.4	13.5	12.9	12.1

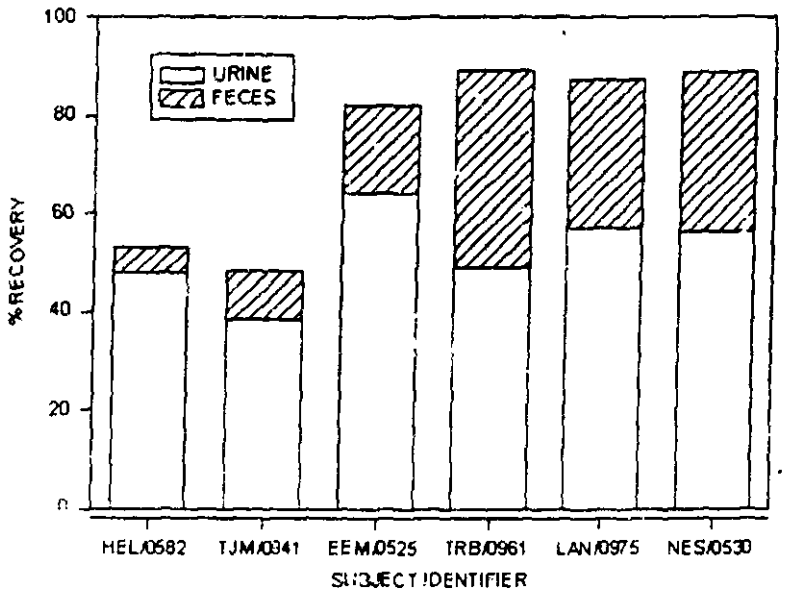
	AUCo-t (ngeq·hr/ml)	AUCo-∞ (ngeq·hr/ml)	Cls/FF* (L/hr)	Cls/FF* (L/kg/hr)	Vβ/FF* (L)	Vβ/FF* (L/kg)
Mean	1961	2398	5.37	0.0692	447	5.73
SD	495	618	1.44	0.0189	84	0.91
CV	25.2	25.8	26.9	27.4	18.8	15.9

Table HGAI 4.15 Noncompartmental Pharmacokinetic Analysis of Whole Blood Radiocarbon

	Dose (mg)	Wt (kg)	Cmax (ngeq/ml)	Tmax (hr)	β (hr^{-1})	t½ (hr)
Mean	12.5	77.8	23.6	4.67	0.0110	63.8
SD		8.4	6.4	1.21	0.0014	7.6
CV		10.8	27.0	26.0	12.6	11.9

	AUCo-t (ngeq·hr/ml)	AUCo-∞ (ngeq·hr/ml)	Cls/FF* (L/hr)	Cls/FF* (L/kg/hr)	V/FF* (L)	V/FF* (L/kg)
Mean	1197	1499	8.42	0.108	780	9.89
SD	267	314	1.80	0.016	209	1.65
CV	22.3	21.0	21.4	14.4	26.9	16.6

Figure HGAI 4.3. Recovery of Radioactivity in Urine and Feces.



Samples were collected up to 21 days after a single dose of [^{14}C] Olanzapine.

Table HGAI 4.16 Total Radioactivity Percent-of-dose Recovery in Urine and Feces

	Overall		Urine				Feces			
	Total 0-21†	Total 0-∞††	0-24 hr	0-48 hr	Total 0-21†	Total 0-∞††	Day 0-2	Day 0-3	Total 0-21†	Total 0-∞††
All 6 subjects MEAN	74.8	74.8	18.1	28.0	52.2	52.2	8.8	14.0	22.6	22.6
SD	18.8	18.8	2.5	4.4	8.9	8.9	7.4	9.7	13.8	13.8
CV	25.1	25.1	14.0	15.8	17.0	17.0	84.6	69.4	60.9	60.9
4 subjects MEAN‡	86.7	86.7	18.8	29.8	56.6	56.6	12.4	18.8	30.2	30.2
SD	3.1	3.1	2.8	4.3	6.2	6.2	6.5	7.9	9.1	9.1
CV	3.6	3.6	14.7	14.5	10.9	10.9	52.4	41.8	30.0	30.0

† Total collected over 21 to 22 days

†† Total is estimate of excretion to infinity

‡ Mean, SD and CV calculated omitting Subjects 0582 and 0941

Note: The sponsor believes that subjects 0582 and 0941 did not collect all of their feces during this study (which would explain why these two subjects have low recovery of radioactivity in the feces). Thus, mean recovery data is presented for all six subjects and for only four subjects.

Table HGAI.4.17. Estimation of Metabolite Recovery in Urine[a]

Compound	% Dose
10-N-glucuronide[b]	13.2
N-desmethyl-2-carboxy olanzapine[c]	3.8
2-carboxy olanzapine[b]	3.5
N-oxide olanzapine[b]	3.4
N-oxide-2-carboxy olanzapine glucuronide[c,d]	2.3
4'-N-glucuronide[c,e]	2.1
2-carboxy olanzapine glucuronide[c,d]	2.1
2-hydroxymethyl olanzapine[c]	1.4
N-desmethyl olanzapine[b]	0.6
Olanzapine[b]	7.3
Total	39.7

[a] Based on total urinary recovery of ~ 52%

[b] Mean value determined from urine samples from 2 subjects (Subjects 0525, 8-16 hr and 0941, 4-8 hr)

[c] Based on urine samples from 3 subjects (0975, 16-72 hr, 0525, 24-48 hr and 0941, 24-72 hr)

[d] Tentative structural assignment

[e] The amounts of 4'-N-glucuronide and 2-carboxy olanzapine (OLZ) glucuronide were estimated following separation on an Inertsil C_{18} analytical column with a mobile phase of 1% acetic acid and acetonitrile.

Estimation of 10-N-Glucuronide and OLZ in Fecal Extracts[a]

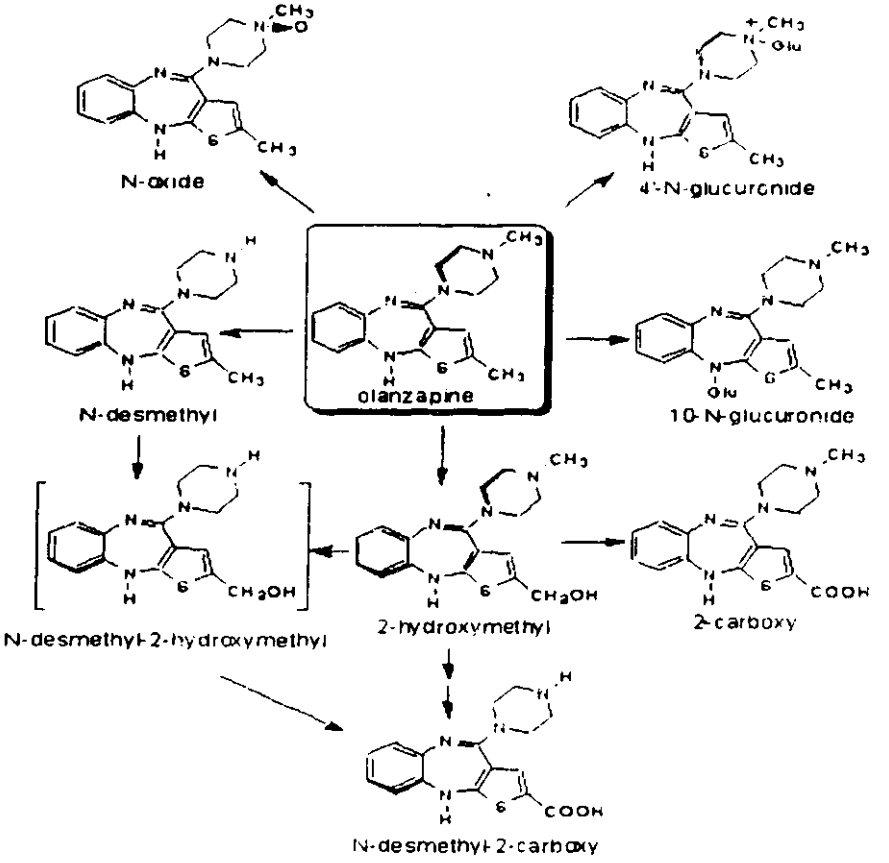
Fecal Sample	% 10-N-glucuronide	% OLZ
EEM 24-48 hr	69.1	8.4
EEM 48-72 hr	48.8	9.5
EEM 72-96 hr	32.3	12.8
HEL 48-72 hr	40.7	2.3
HEL 96-120 hr	36.6	1.2
TJM 24-48 hr	37.2	14.8
TJM 48-72 hr	24.9	9.4
TJM 72-96 hr	31.3	5.3
Mean ± SD	40.1 ± 13.7	8.0 ± 4.8

[a] % of extracted fecal radioactivity

OLZ: (8% fecal radioact = OLZ) · (≈30% of Dose excreted in feces) ⇒ 2.4% of dose excreted as unchanged drug in feces.

10-N-Gluc: (40% = 10-N-Gluc) · (30% dose in feces) ⇒ 12% 10-N-glucuronide in feces

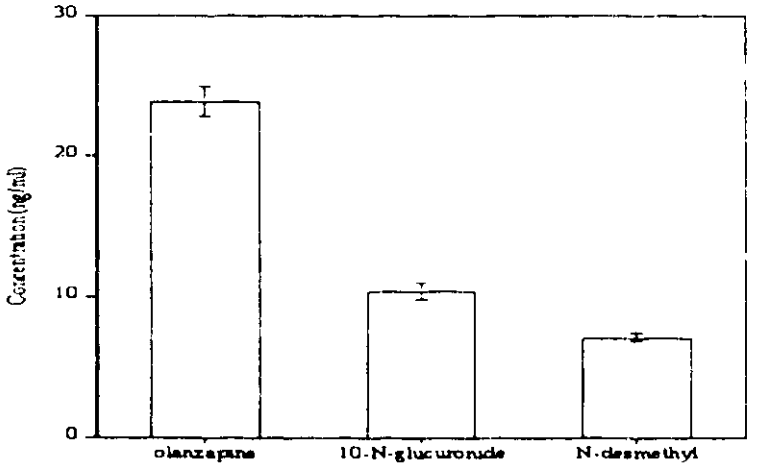
HGAP



major metabolite in urine and feces (13% and 12% of dose respectively)

Figure 24 Proposed metabolic pathways of olanzapine in humans. The compound in brackets has not yet been identified. Glu stands for glucuronic acid

Figure is derived from an analysis of random samples from protocol F1D-MC-HGAP, a study that compared the efficacy of olanzapine vs placebo in patients. In plasma, parent compound, the 10-N glucuronide, N-oxide, N-desmethyl, and 2-hydroxymethyl olanzapine were detected using LC-MS. In addition to the plasma metabolites, N-desmethyl-2-carboxy, 2-carboxy glucuronide, and the 4'N--glucuronide were detected in the urine. Reviewer comment: No quantitation was made in this study.



Quantitation of two metabolites from plasma samples obtained in population study F1D-MC-HGAJ. Reviewer note: The sponsor does not provide solid evidence that these are the two major circulating metabolites. It is possible that other metabolites circulate at significant concentrations.

Correlation Coefficents Relating Immunoquantified Enzyme Levels and Form-Selective Catalytic Activities to Olanzapine Metabolite Formation by a Bank of 14 Human Liver Microsomes Incubated with 20 μM Olanzapine

Cytochrome P450	Olanzapine Metabolites			
	2-OH	N-O	7-OH	NdM
	Correlation Coefficients (r)			
CYP1A2				
Immunoquantified levels	0.20	0.36	0.66**	0.35
Ethoxyresorufin O-deethylase	0.02	0.42	0.74**	0.64*
Caffeine 3-demethylase	0.04	0.22	0.83**	0.66*
CYP2A6				
Immunoquantified levels	0.10	0.23	0.29	0.00
Coumarin 7-hydroxylase	0.19	0.21	0.10	0.13
CYP2C8				
Immunoquantified levels	0.19	0.27	0.23	0.40
CYP2C9				
Tolbutamide 4-hydroxylase	0.63*	0.23	0.04	0.41
CYP2C19				
Immunoquantified levels	0.07	0.23	0.24	0.45
S-Mephenytoin 4'-hydroxylase	0.11	0.28	0.35	0.58*
CYP2D6				
Immunoquantified levels	0.74**	0.24	0.36	0.16
Bufuralol 1"-hydroxylase	0.79**	0.19	0.30	0.14
CYP2E1				
Immunoquantified levels	0.08	0.33	0.20	0.15
N-Nitroso-dimethylamine-N-demethylase	0.06	0.27	0.26	0.16
CYP3A				
Immunoquantified levels	0.25	0.11	0.12	0.36
Erythromycin N-demethylase	0.09	0.04	0.09	0.30
FMO3				
Immunoquantified levels	0.11	0.76**	0.09	0.29
Nicotine N-oxidase	0.04	0.75**	0.22	0.47

** $P < .01$

* $P < .05$

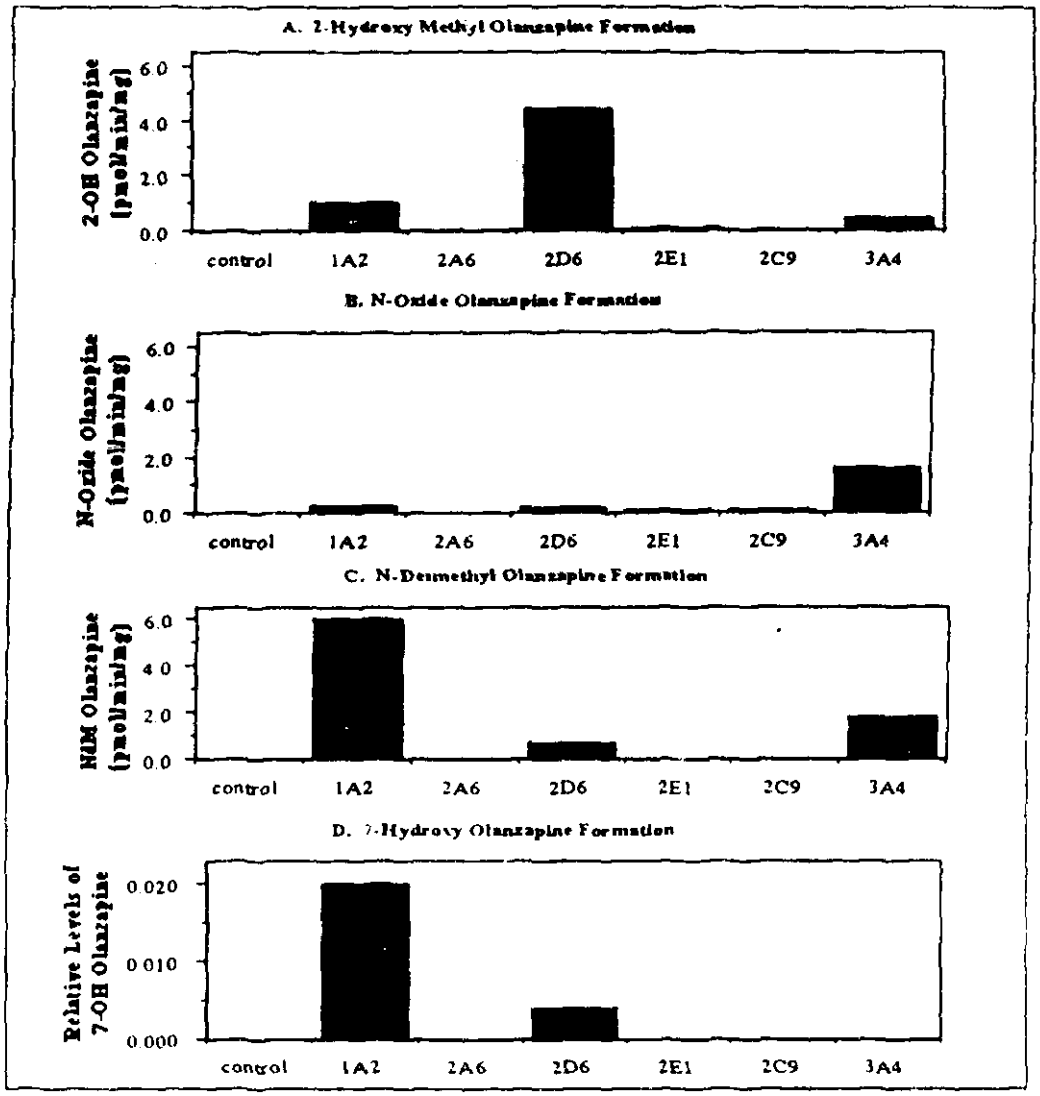


Figure 39.3 Formation of 2-hydroxy methyl olanzapine (A), N-oxide olanzapine (B), N-desmethyl olanzapine (C), and 7-hydroxy olanzapine (D) by cDNA expressed enzymes incubated with 50 µM olanzapine.

Reviewer comment: The results of the 2 studies presented above suggest that CYPs 1A2, 2C19 and 2D6, along with FMO3 participate in the in vitro metabolism of olanzapine.

Inhibition of the CYP3A Catalyzed Formation of 1'-Hydroxy Midazolam *In Vitro* by Ketoconazole, Olanzapine, and Clozapine

Inhibitor	Type of Inhibition	Apparent Ki (µM)
Ketoconazole	Non-competitive	0.11 ± 0.01
Olanzapine	Non-competitive	491 ± 33
Clozapine	Non-competitive	99 ± 7

Midazolam concentrations in the assays containing ketoconazole and olanzapine were 12.5, 25, 50, 75, and 100 µM. Midazolam concentrations in the clozapine assay were 5, 10, 25, 50, and 100 µM. At each substrate concentration, carrier or one of four concentrations of inhibitor were included. The concentrations of ketoconazole were 0.05, 0.1, 0.5, and 1.0 µM, olanzapine were 62.5, 125, 250, and 500 µM, and clozapine were 25, 50, 100, and 200 µM. All incubations were performed in duplicate.

Inhibition of the CYP2D6 Mediated Formation of 1'-Hydroxy Bufuralol *In Vitro* by Quinidine, Olanzapine, And Clozapine

Inhibitor	Type of Inhibition	Apparent Ki (μM)
Quinidine	Competitive	0.03 ± 0
Olanzapine	Competitive	89 ± 5
Clozapine	Competitive	19 ± 2

To duplicate incubations containing bufuralol at concentrations 12.5, 25, 50, 100, and 150 μM, carrier or one of four concentrations of inhibitor were added. The concentrations of quinidine were 0.01, 0.05, 0.10, and 0.20 μM, olanzapine were 50, 100, 200, and 300 μM, and clozapine were 0.5, 1.0, 5.0, and 10 μM.

Inhibition of the CYP2C9 Catalyzed Formation of 4-Hydroxy Tolbutamide *In Vitro* by Phenytoin, Olanzapine, and Clozapine

Inhibitor	Type of Inhibition	Apparent Ki (μM)
Phenytoin	Competitive	17 ± 1
Olanzapine	Non-competitive	715 ± 73
Clozapine	Competitive	31 ± 2

To duplicate incubations containing tolbutamide at concentrations of 25, 50, 100, 200, and 300 μM, carrier or one of four concentrations of inhibitor were added. The concentrations of phenytoin were 5, 10, 25, and 75 μM, olanzapine were 100, 200, 300, and 400 μM, and clozapine were 5, 10, 25, and 50 μM.

Inhibition of the CYP2C19 Catalyzed Formation of 4'-Hydroxy S-Mephenytoin *In Vitro* by Omeprazole, Olanzapine, and Clozapine

Inhibitor	Type of Inhibition	Apparent Ki (μM)
Omeprazole	Competitive	4.1 ± 0.4
Olanzapine	Non-competitive	920 ± 65
Clozapine	Competitive	69 ± 3

S-Mephenytoin concentrations in the assays containing omeprazole and olanzapine were 12.5, 25, 50, 100, and 200 μM. S-mephenytoin concentrations in the clozapine assay were at 6.25, 9.38, 12.5, 25, and 50 μM. At each substrate concentration carrier or one of four concentrations of inhibitor were added. The concentrations of omeprazole were 1.56, 3.13, 6.25, and 12.5 μM, olanzapine were 200, 300, 400, and 500 μM and clozapine were 25, 50, 100, and 200 μM. All incubations were performed in duplicate.

Inhibition of the CYP1A2 Catalyzed Formation of Acetaminophen *In Vitro* by Olanzapine, Clozapine and Theophylline

Inhibitor	Type of Inhibition	Apparent Ki (μM)
Olanzapine	Competitive	36 ± 2
Clozapine	Competitive	22 ± 2
Theophylline	Competitive	362 ± 15

Phenacetin concentrations were 12.5, 25, 50, 75, and 100 μM. At each substrate concentration, carrier or one of four concentrations of inhibitor was added. The concentrations of olanzapine were 10, 25, 50, and 100 uM, clozapine were 10, 25, 50, and 75 uM, and theophylline were 200, 400, 600, and 800 uM

Protein Binding

Table 33.1.
Mean *In Vitro* Binding of ^{14}C-LY170053 to Plasma Proteins of Mouse, Rat, Dog, Monkey and Human as Determined by Radioactivity

	Mean % ^{14}C bound				
Conc.(ng /ml)	Mouse	Rat	Dog	Monkey	Human
100	80.8	83.0	81.2	91.2	92.9

Data represent mean of 5 determinations
Experiment carried out at 37°C

The Percent of [^{14}C]Olanzapine Bound to Proteins in Plasma from Normal Subjects

		BSC Lot #M3509		
Olanzapine conc. (ng/ml)	Percent binding for individual determinations			Mean ± SD
7.4	94.47	93.67	94.23	94.1 ± 0.411
15.6	93.38	93.57	93.72	93.6 ± 0.170
28.2	94.30	94.34	94.10	94.3 ± 0.129
54.6	94.36	94.41	93.80	94.2 ± 0.339
78.7	93.15	92.89	92.76	92.9 ± 0.199
114	94.07	94.01	94.01	94.0 ± 0.035
152	92.79	93.06	92.62	92.8 ± 0.222
218	91.98	91.45	92.51	92.0 ± 0.530
343	91.59	91.24	91.08	91.3 ± 0.261
548	92.94	94.05	93.91	93.6 ± 0.605
852	94.24	93.72	93.93	94.0 ± 0.262
1141	93.47	93.52	93.50	93.5 ± 0.025
		Overall mean ± SD = 93.4 ± 0.940		
		BSC Lot # M3142		
31	97.01	97.62	96.91	97.2 ± 0.384
		BSC Lot #M3139		
31	93.54	94.35	94.16	94.0 ± 0.424

The Percent of [^{14}C]Olanzapine Bound to Purified Plasma Proteins[1]

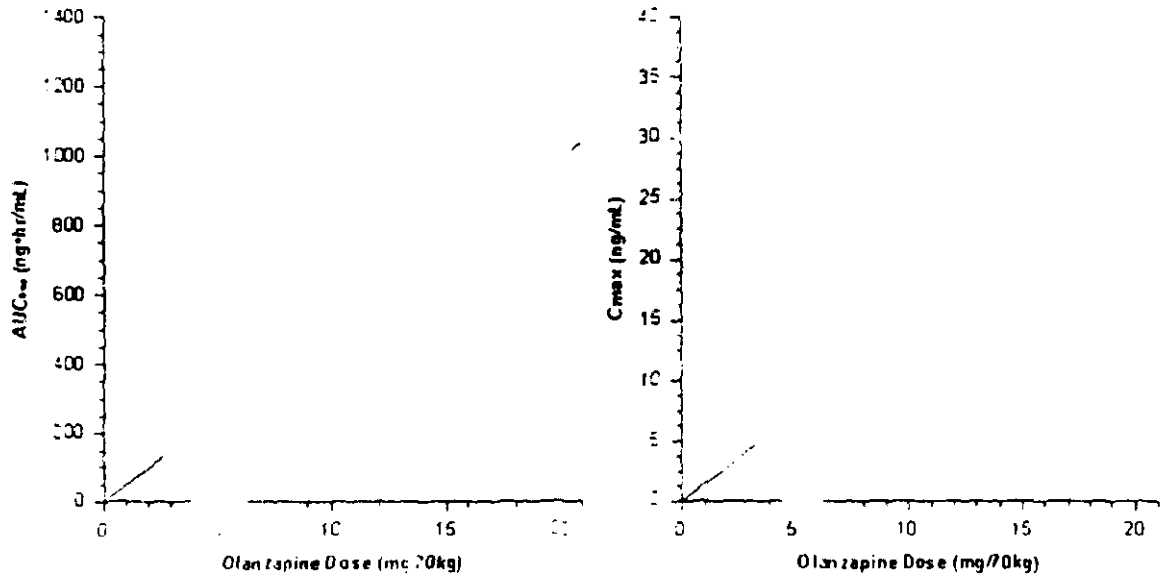
Protein		Percent bound[2]		Mean ± SD
Albumin	85.81	90.09	94.67	90.2 ± 4.431
α_1-acid glycoprotein	75.52	80.37	75.70	77.2 ± 2.750
γ-globulins	24.23	27.53	34.65	28.8 ± 5.325
Mixture of proteins	95.35	95.26	95.42	95.3 ± 0.080

[1] [^{14}C]Olanzapine was added to protein solution in phosphate buffer to give a final concentration of 31 ng/ml.

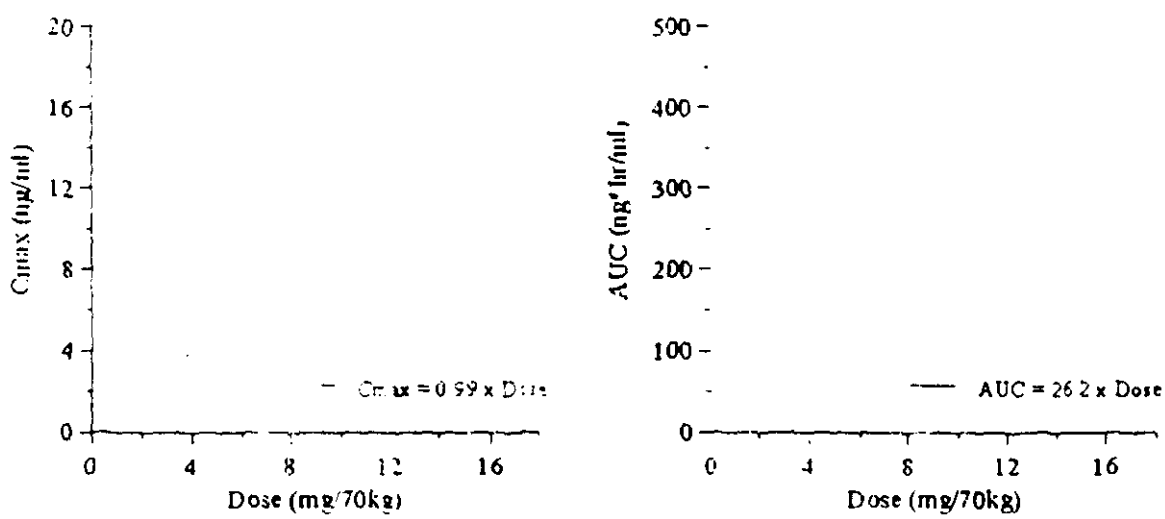
[2] Values are mean of three determinations except for those obtained with mixture of proteins.

DOSE PROPORTIONALITY

Note that small scale pharmacokinetic studies established dose proportionality and linear kinetics for up to 15 mg doses. Population study data was used to establish dose proportionality and linearity for doses up to 20 mg (20 mg is the highest dose indicated in the proposed labeling).

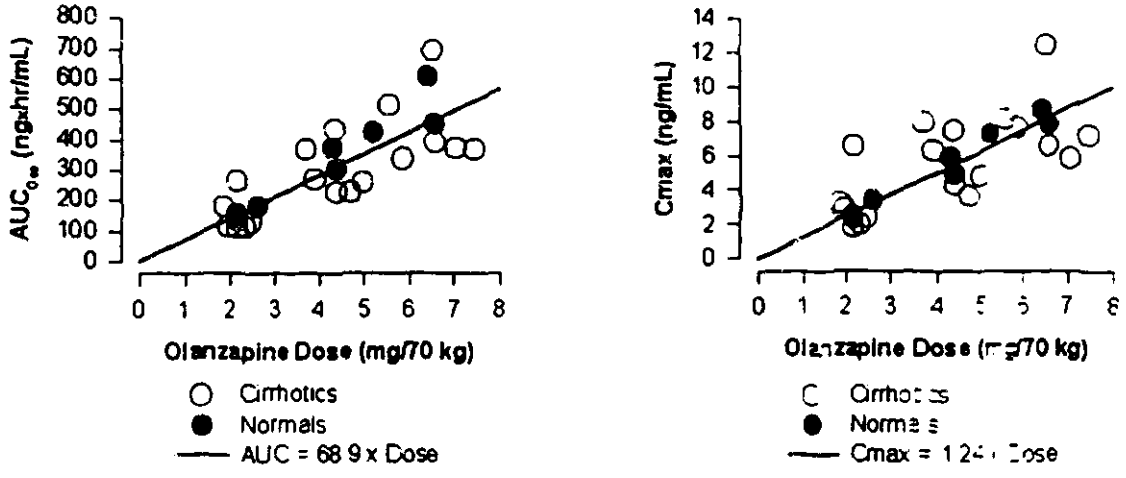


From study HGBY, see Bioequivalence section of the appendix for a description of this study. Note that the dose is normalized to a 70 kg body weight. The highest dose given in this study was 15 mg. (HGBY ... Avoid b ... y.)

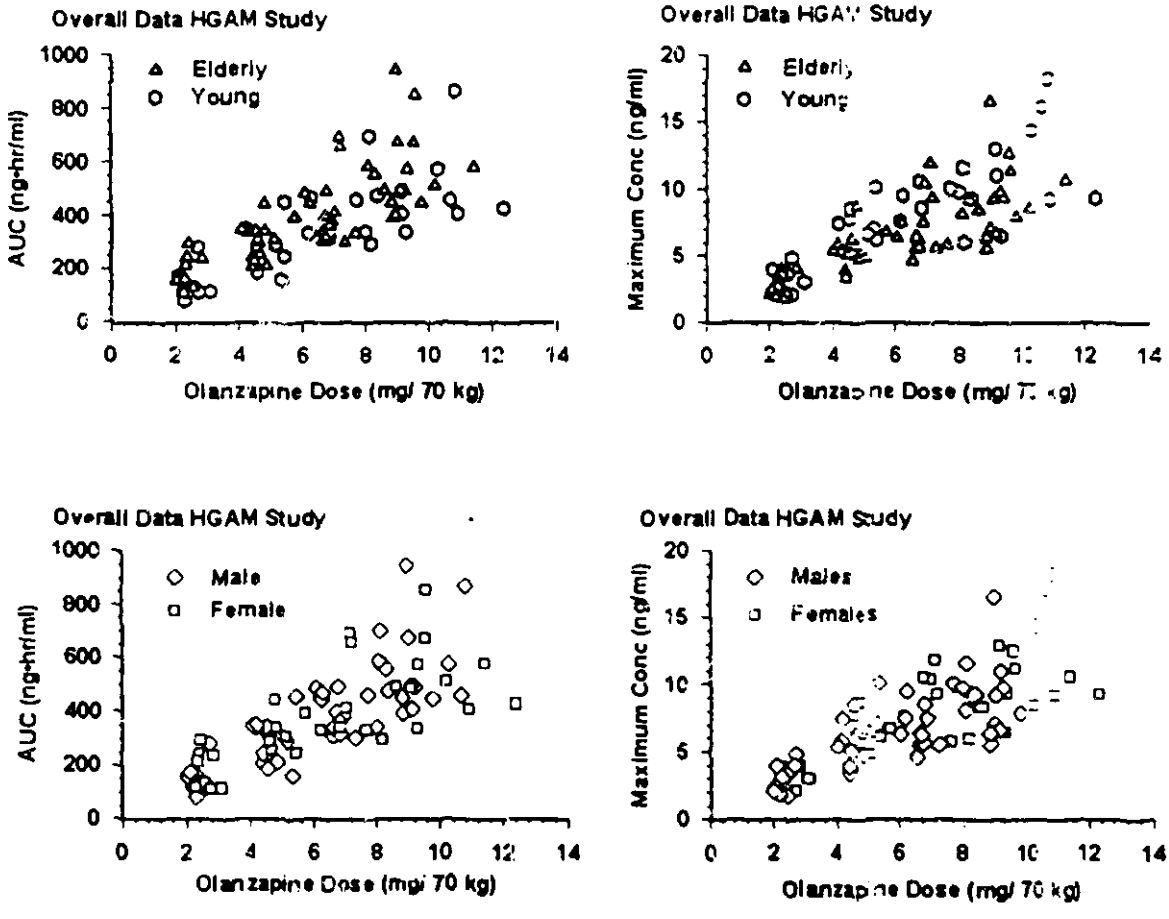


Different symbols represent different individuals.

From study HGAH, see Bioavailability (food effect) section for a description of this study.

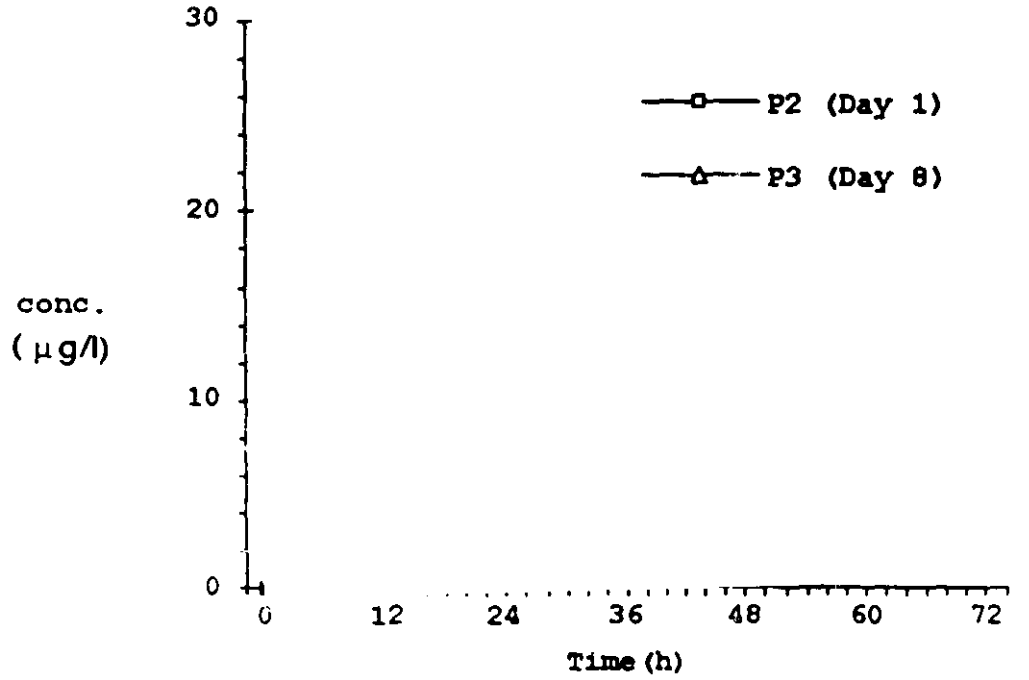


From study HGAU. See Special Population section (liver impairment) for study details.



From study HGAM. See Special Population section (gender and age) for study details.

Figure E001.2. Mean Time Curves of Observed Olanzapine Concentration in Plasma



Note: From study MS-E001, see section on Drug Interactions (lithium) for details of this study. This graph shows that olanzapine concentrations are roughly doubled after multiple dosing (P3) compared to single dosing (P2) of 10 mg olanzapine.

Dose Proportionality Evaluation from Reference Pharmacokinetic Database

	Dose Proportionality Constant				
Variable	Overall	Males	Females	Nonsmoker	Smoker
Cmax	1.18	1.19	1.14	1.29	1.08
AUC	45.1	43.9	52.3	57.8	34.6

From Composite Database. This is pooled data from healthy subjects. See Special Population section of the appendix for a description of this database.

Table 1: Distribution of Doses per Patient

Number of Dose Levels	Number of Patients
2	28
3	153
4	216
5	1
Total	398

Table 2: Dose Frequency Distribution

Olanzapine Dose	Frequency	Number of Patients
5 mg	344	339
10 mg	68	62
15 mg	398	355
20 mg	574	398
Total	1384	398

From Population PK Study
HGAJ

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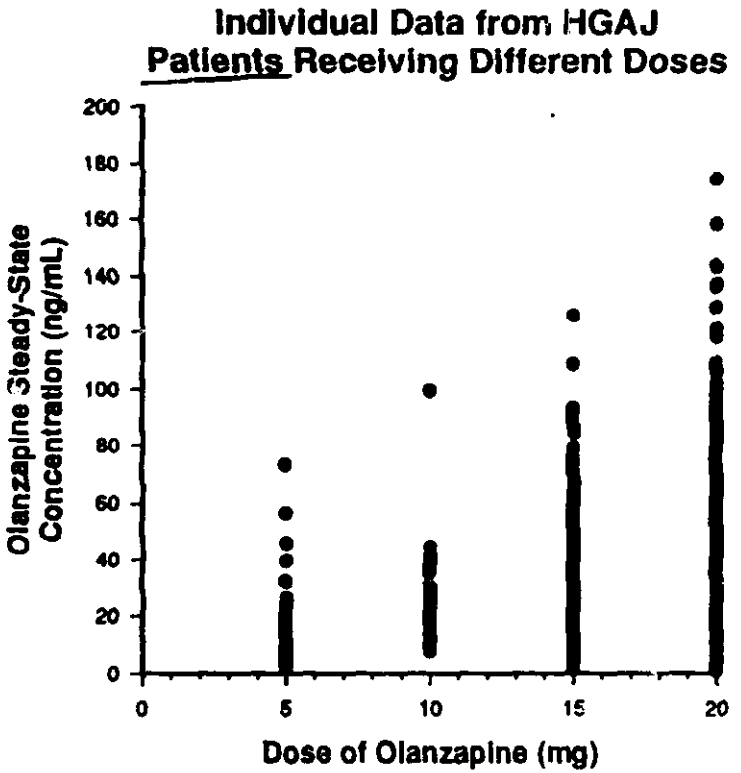
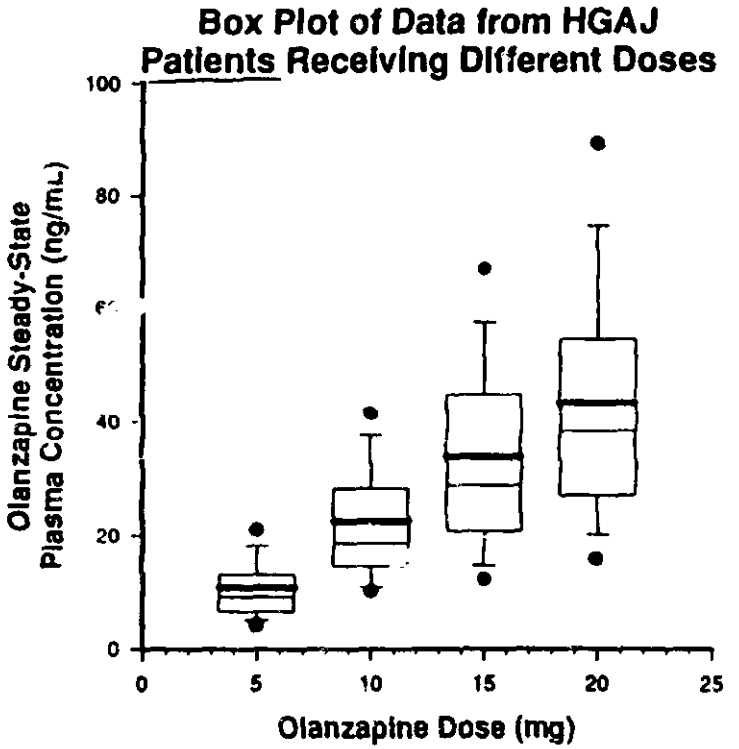
Figure 35
Overall Olanzapine Plasma Concentration vs Dose - Study HGAJ





Heavy solid line is the mean. Box is the 25th, 50th, and 75th percentiles Capped bar is the 10th and 90th percentile, and the solid circle symbols are the 5th and 95th percentile.

A-77

IN VIVO DRUG INTERACTION STUDIES

CLINICAL STUDY SYNOPSIS: Study F1D-LC-HGAN

Title:	Olanzapine: Ethanol Drug Interaction Trial
Investigators:	
Study Centers:	Single-center study
Dates of Study:	July 1993 through December 1993
Clinical Phase:	Phase 1
Objectives:	To determine if an interaction exists between ethanol and olanzapine, and to evaluate the safety, human performance capacity, and immunologic profile of subjects given olanzapine alone and with ethanol.
Methodology:	Open-label, three-arm crossover study.
Number of Subjects:	Fifteen male subjects were enrolled and 11 completed this study. There were 4 discontinuations, 2 due to an "adverse event", 1 due to "sponsor decision", and 1 due to "entry criteria not met".
Diagnosis and Inclusion Criteria:	Healthy male nonalcoholic subjects.
Dosage and Administration:	Test Product CT01832: Olanzapine 2.5-mg capsules CT01833: Olanzapine 5-mg capsules CT01834: Olanzapine 10-mg capsules DSP-KY-41[illegible]. Ethanol, 45 mL/70 kg body weight CT01835: Placebo capsules
Duration of Treatment:	Mutiple doses of olanzapine (2.5 mg x 2 days, 5.0 mg x 2 days and two 7-day 10-mg courses); ethanol 45 mg/kg on two separate occasions; placebo on two separate occasions.
Criteria for Evaluation:	Efficacy-- Not applicable. Safety-- Safety parameters included vital signs, electrocardiograms, chest x-ray, clinical laboratory tests, immunologic profile and noninvasive human performance capacity. Pharmacokinetics-- Pharmacokinetic analysis of olanzapine or ethanol data involved analysis of the concentration time data for each subject. The analysis was compartmental or model-independent as deemed appropriate.
Statistical Methods:	Statistical methods were applied to pharmacokinetic, human performance, questionnaire, and cardiovascular assessments. Methods differed according to the requirements, but all used statistical packet, SAS®.

Table HGAN.3.1. Drug Administration

Treatment	Dose	Schedule
Alcohol	45 mL/70 kg	First and Third Treatments Periods: single doses
Olanzapine	2.5 mg, 5 mg	Second Treatment Period: two daily doses for each dose level
Olanzapine	10 mg	Second and Third Treatments Periods: daily for 7 days
Olanzapine Placebo		Admission and First Treatment Period: single doses

Table HGAN.5.16 Mean Ethanol Pharmacokinetic Variables For a 45 mL/70 kg Single Oral Dose of Ethanol Alone or With Olanzapine

Treatment		Cmax (ng/mL)	Tmax (hr)	AUC0-∞ (ug*hr/mL)	Vβ/FF* (L)	t½ (hr)
A - Alone (n=10)	Mean	456	1.02	1120	19.0	0.409
	CV	10.8	19.6	12.4	28.3	11.6
C - With	Mean	425	1.08	1150	26.3	0.538
Olanzapine (n=8)	CV	17.6	25.9	30.9	26.7	28.4

Cmax=maximum plasma concentration; Tmax=time of maximum plasma concentration; AUC=area under the curve; Clp/FF*=apparent plasma clearance; Vdβ/FF*=apparent volume of distribution; t½=plasma half-life

Figure HGAN.5.3 Ethanol Volume of Distribution Values with and without Concomitant Olanzapine

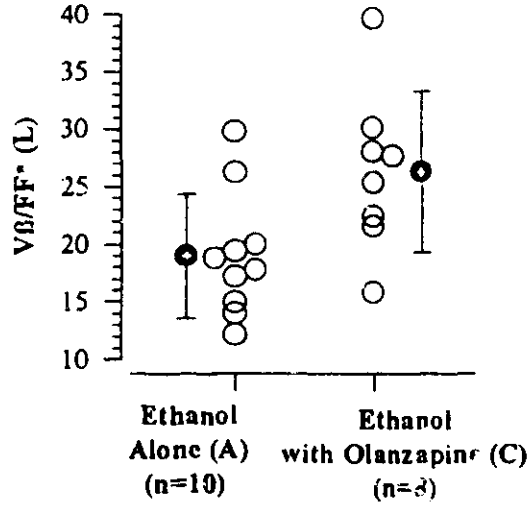


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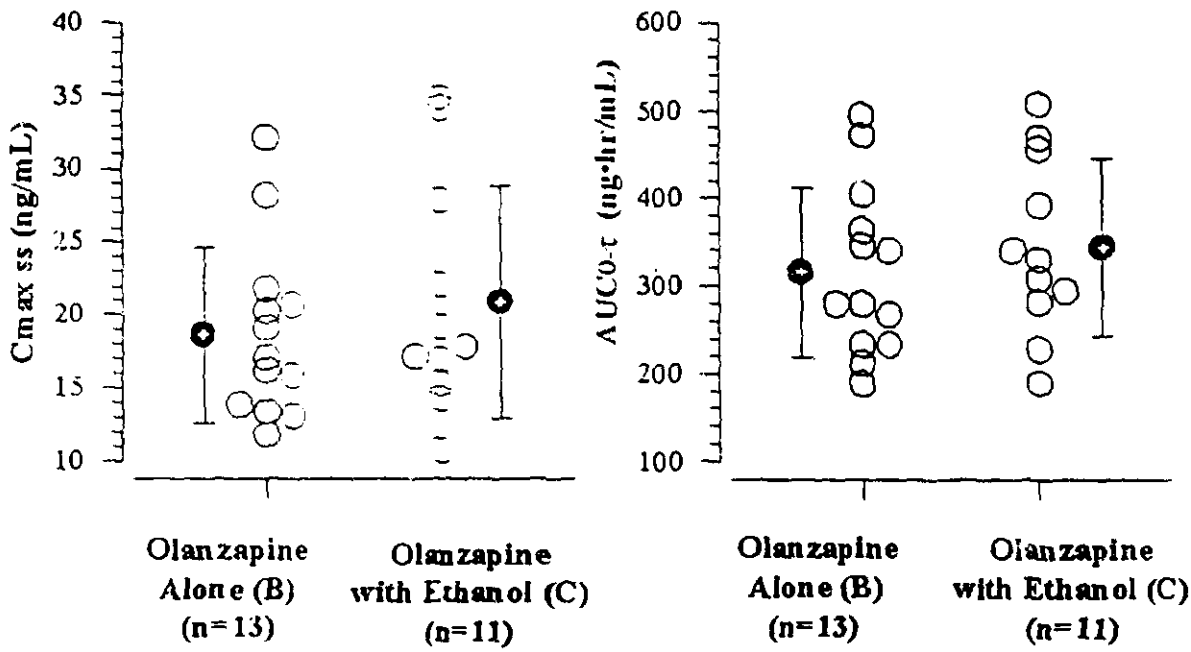
Table HGAN.5.17 Steady-State Mean Olanzapine Pharmacokinetic Variables For 10 mg qd Oral Dosing with and without Ethanol

Treatment		Cmax ss (ng/mL)	Tmax ss (hr)	AUCo-τ (ng*hr/mL)	Cls/FF* (L/hr)	Vβ/FF* (L)	t½ (hr)
B - Alone (n=13)	Mean	18.6	4.46	315.3	34.5	1475	29.8
	CV	32.4	26.9	30.8	29.6	29.2	14.8
C - With Ethanol (n=11)	Mean	20.9	4.27	343.9	31.6	1525	33.1
	CV	38.3	37.9	29.4	31.9	41.8	27.0

Cmax ss=steady-state maximum plasma concentration; Tmax ss=steady-state time of maximum plasma concentration; AUC=area under the curve; Vdβ/FF*=apparent volume of distribution; t½=plasma half-life

Figure HGAN.5.5. Olanzapine Steady-State Cmax and AUC Values with and without Concomitant Ethanol



Note: There did not appear to be a significant interaction between ethanol and olanzapine at the doses administered. Although small changes were observed, they are negligible relative to the variability normally observed.

CLINICAL STUDY SYNOPSIS: Protocol FJD-LC-HGAQ

Title:	Olanzapine: Interaction Study with Imipramine
Investigators:	
Study Centers:	There was one study center.
Dates of Study:	June 18, 1993 through July 28, 1993
Clinical Phase:	Phase 1
Objectives:	To determine the safety, pharmacokinetics, bioavailability and drug interaction of coadministration of olanzapine and imipramine.
Methodology:	Open-label, single-blind, three-way crossover study.
Number of Subjects:	Nine male subjects were entered into and completed the study.
Diagnosis and Inclusion Criteria:	Healthy male subjects.
Dosage and Administration:	Test Product CT01833: Olanzapine, 5-mg 1T154229: Imipramine, 75-mg
Duration of Treatment:	Single doses of olanzapine (5 mg), imipramine (75 mg), and combination of olanzapine (5 mg) and imipramine (75 mg) on three separate occasions.
Criteria for Evaluation:	Efficacy--Not applicable. Safety-- Safety parameters included vital signs, electrocardiograms, chest x-ray, clinical laboratory tests, and a noninvasive measure of psychomotor performance. Pharmacokinetics: Plasma drug concentrations of olanzapine, imipramine, and desipramine (major metabolite of imipramine) were measured and standard pharmacokinetic and bioavailability indices were calculated.
Statistical Methods:	Pharmacokinetic variables, vital signs, subjective tests for sedation, and psychomotor test outcomes were analyzed via a crossover analysis of variance (ANOVA). Single degree-of-freedom contrasts were incorporated to compare the combination versus the separate treatments.

5 days	9 -day "washout"
Assays, Procedures, Safety Tests	

Olanzapine

or Imipramine

or Olanzapine-Imipramine

HGAQ

Statistical Assessment of Change for Imipramine Pharmacokinetic Variables

PK Variable		Treatment †	Mean	Difference	P-Value
Cmax	A	Alone	20.37		
(ng/mL)	C	Combination	20.56	0.9%	0.878
Tmax	A	Alone	5.56		
(hr)	C	Combination	5.89	0.33 ‡	0.397
t½	A	Alone	15.42		
(hr)	C	Combination	16.12	0.70 ‡	0.240
AUC_{0-t}	A	Alone	438.1		
(ng•hr/mL)	C	Combination	468.5	7.0%	0.255
$AUC_{0-\infty}$	A	Alone	451.6		
(ng•hr/mL)	C	Combination	484.4	7.3%	0.226
Cls/FF	A	Alone	223.4		
(L/hr)	C	Combination	207.3	-7.2%	0.200
Vß/FF	A	Alone	4432		
(L)	C	Combination	4231	-4.5%	0.562

† Imipramine was given as a Single 75 mg dose (A) alone or (C) in combination with Olanzapine.
‡ Absolute change between treatment means.

(active metabolite of imipramine)

Statistical Assessment of Change for Desipramine Pharmacokinetic Variables

PK Variable		Treatment †	Mean	Difference	P-Value
Cmax	A	Alone	6.71		
(ng/mL)	C	Combination	6.75	0.6%	0.938
Tmax	A	Alone	8.44		
(hr)	C	Combination	10.33	1.89 ‡	0.394
t½	A	Alone	22.39		
(hr)	C	Combination	22.81	0.42 ‡	0.694
AUC_{0-t}	A	Alone	289.9		
(ng•hr/mL)	C	Combination	298.4	2.9%	0.435
$AUC_{0-\infty}$	A	Alone	309.9		
(ng•hr/mL)	C	Combination	324.9	4.8%	0.201

† Metabolites of Imipramine (Desipramine) were assessed after the administration of Imipramine as a Single 75 mg dose (A) alone or (C) in combination with Olanzapine.
‡ Absolute change between treatment means.

H6AQ

Statistical Assessment of Change for Imipramine Pharmacokinetic Variables

PK Variable		Treatment †	Mean	Difference	P-Value
Cmax	A	Alone	20.37		
(ng/mL)	C	Combination	20.56	0.9%	0.878
Tmax	A	Alone	5.56		
(hr)	C	Combination	5.89	0.33 ‡	0.397
t½	A	Alone	15.42		
(hr)	C	Combination	16.12	0.70 ‡	0.240
AUC0-t	A	Alone	438.1		
(ng•hr/mL)	C	Combination	468.5	7.0%	0.255
AUC0-∞	A	Alone	451.6		
(ng•hr/mL)	C	Combination	484.4	7.3%	0.226
Cls/FF	A	Alone	223.4		
(L/hr)	C	Combination	207.3	-7.2%	0.200
Vß/FF	A	Alone	4432		
(L)	C	Combination	4231	-4.5%	0.562

† Imipramine was given as a Single 75 mg dose (A) alone or (C) in combination with Olanzapine.
‡ Absolute change between treatment means.

(active metabolite of imipramine)

Statistical Assessment of Change for Desipramine Pharmacokinetic Variables

PK Variable		Treatment †	Mean	Difference	P-Value
Cmax	A	Alone	6.71		
(ng/mL)	C	Combination	6.75	0.6%	0.938
Tmax	A	Alone	8.44		
(hr)	C	Combination	10.33	1.89 ‡	0.394
t½	A	Alone	22.39		
(hr)	C	Combination	22.81	0.42 ‡	0.694
AUC0-t	A	Alone	289.9		
(ng•hr/mL)	C	Combination	298.4	2.9%	0.435
AUC0-∞	A	Alone	309.9		
(ng•hr/mL)	C	Combination	324.9	4.8%	0.201

† Metabolites of Imipramine (Desipramine) were assessed after the administration of Imipramine as a Single 75 mg dose (A) alone or (C) in combination with Olanzapine.
‡ Absolute change between treatment means.

HGAQ

Statistical Assessment of Change for Olanzapine Pharmacokinetic Variables

PK Variable		Treatment †	Mean	Difference	P-Value
Cmax	B	Alone	4.06		
(ng/mL)	C	Combination	4.61	13.5%	0.025
Tmax	B	Alone	6.00		
(hr)	C	Combination	5.00	-1.00 ‡	0.148
$t_{1/2}$	B	Alone	28.18		
(hr)	C	Combination	28.82	0.65 ‡	0.694
AUC_{0-t}	B	Alone	132.7		
(ng•hr/mL)	C	Combination	149.1	12.3%	0.246
$AUC_{0-\infty}$	B	Alone	140.9		
(ng•hr/mL)	C	Combination	167.2	18.7%	0.125
Cl/F*	B	Alone	40.10		
(L/hr)	C	Combination	36.29	-9.5%	0.268
Vβ/F*	B	Alone	1526		
(L)	C	Combination	1372	-10.1%	0.060

† Olanzapine was given as a Single 5 mg dose (B) alone or (C) in combination with Imipramine.
‡ Absolute change between treatment means.

Note: A single 5 mg dose of olanzapine did not significantly affect the kinetics of imipramine or its metabolite desipramine. Both drugs are metabolized by CYP2D6, suggesting that this dose of olanzapine does not inhibit this enzyme in vivo (none of the subjects were deficient in CYP2D6 as determined by phenotyping). CYP1A2 is also reported to be involved in imipramine metabolism.

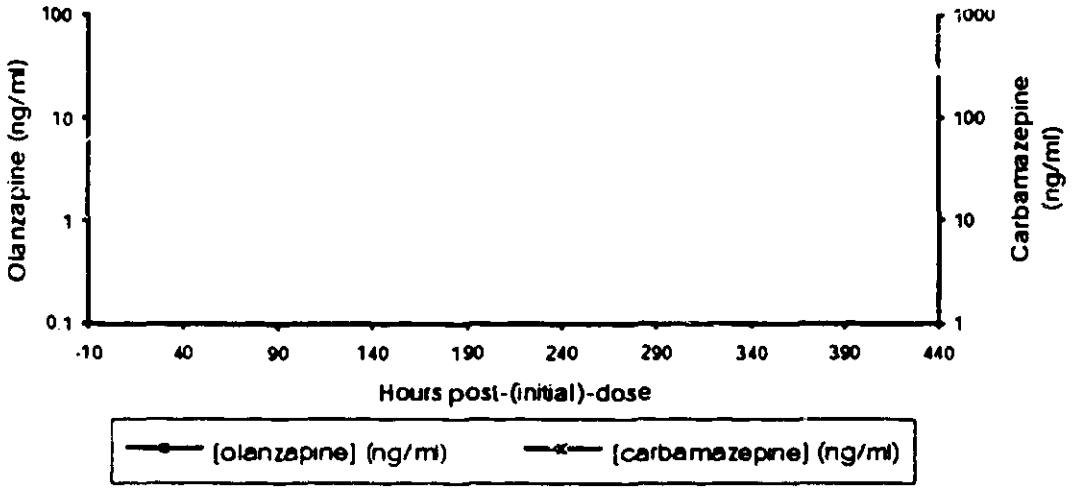
Imipramine caused a 19% increase in olanzapine AUC although this increase was not statistically significant at the $p<0.05$ level. Similarly imipramine caused a 14% increase in olanzapine Cmax. These increases in AUC and Cmax could be due to inhibition of CYP1A2 by imipramine.

It should be noted that olanzapine and imipramine were given as single doses, and that the dose of olanzapine (5 mg) was small. Thus, the plasma concentrations of olanzapine and imipramine achieved in this study were lower than what would normally be achieved in the clinical setting. The low drug concentrations could lead to an underestimation of the extent of a drug interaction.

CLINICAL REPORT SYNOPSIS: Study F1D-EW-HGBC

Title:	An Interaction Study to Determine the Effect of Carbamazepine on the Pharmacokinetic Disposition of Olanzapine in Healthy Subjects
Investigators:	This single-centre study included 1 principal investigator.
Study Centres:	There was 1 study centre.
Dates of Study:	March 1994 through May 1994
Clinical Phase:	Phase 1
Objectives:	To evaluate the potential for pharmacokinetic interaction on olanzapine following multiple doses of carbamazepine
Methodology:	Single centre, open study.
Number of Subjects:	Olanzapine: Male 12, Female 0, Total 12.
Inclusion Criteria:	Normal healthy volunteers, aged between 18 and 45 years
Dosage and Administration:	Test Product Olanzapine: 10 mg, given twice as single doses CT 56346: olanzapine, 10 mg Reference Therapy Carbamazepine: 200 mg, given b.i.d. U01953: Carbamazepine, 200 mg
Duration of Treatment:	Olanzapine: 2 days Carbamazepine: 18 days

HGBC



Olanzapine and carbamazepine concentration vs time profiles for a representative subject. Olanzapine was administered before (Period 1), and 14 days into (Period 2) carbamazepine dosing.

Table HGBC.5.6. Pharmacokinetic parameter ratios (alone / combo) Period1/Period2 For olanzapine

	C_{max}	AUC_{inf}
Upper 90 % C.I.	0.86	0.73
Mean ratio	0.77	0.67
Lower 90 % C.I	0.69	0.63

C.I. = Confidence Interval

Note: These results show that the cytochrome P-450 inducer carbamazepine decreases exposure to olanzapine by approximately 33% (CL is increased by about 50%). Similarly, Cmax for olanzapine is decreased by 23% by carbamazepine. The effect of olanzapine on carbamazepine kinetics was not studied.

CLINICAL REPORT SYNOPSIS: PROTOCOL Protocol No. F1D LC HGAE

Title:	AN ASSESSMENT OF THE POTENTIAL FOR AN INTERACTION OF LY170053 AND DIAZEPAM (VALIUM)
Principal Investigator:	D. P. Henry, M. D.
Study Centers:	Lilly Laboratory for Clinical Research; single site.
Dates of Study:	October 19-November 20, 1990
Clinical Phase:	1
Objectives:	Primary purpose was to evaluate the effect of LY170053 on the pharmacokinetics of diazepam (Valium). Secondary goals include continued evaluations of the safety of LY170053 with emphasis on its effects on subjective central nervous system function, blood pressure and pulse rate.
Methodology:	Single blind, randomized study.
Number of Patients:	Six adult male volunteers signed informed consent and 5 completed the study.
Entry Criteria:	Normal adult male volunteers between the ages of 21 and 55 years, inclusive.
CT MATERIALS /ADMINISTRATION:	LY170053, 10 mg capsules (CT00063) LY170053, 2.5 mg capsules (CT00063) Diazepam, 10 mg tablets (Lot #6648
Duration of Treatment:	Eleven days
Criteria for Evaluation:	Efficacy: N/A
Safety:	Safety was evaluated for LY170053 as well as the interaction of LY170053 with diazepam.
Statistical Methods:	ANOVA

Day 1: The subjects received single 10 mg dose of diazepam at 8 AM. The subjects had bloods drawn for the measurement of diazepam and N-desmethyldiazepam at the times delineated in Section 3.2.3.

Day 8: The subjects were given a single 12.5 mg dose of LY170053 at 8 AM. Subjects had blood drawn for the measurement of LY170053.

Day 15-23: The subjects were given 12.5 mg LY170053 at 7 AM for 9 daily doses.

Day 18: The subjects received 12.5 mg LY170053 at 7 AM. One hour later, 10 mg diazepam was administered to the subjects. Blood samples were obtained for the measurement of diazepam, N-desmethyldiazepam and LY170053.

HGAE

Mean Diazepam Pharmacokinetics After 10 mg Diazepam

Treatment	Cmax (ng/mL)	Half-Life (Hours)	Systemic Clearance (L/hr)
Diazepam Alone	232 ± 67	41.4 ± 13.6	1.98 ± 0.69
Diazepam During Olanzapine	208 ± 35	46.2 ± 18.0	1.94 ± 0.79

Table B

Mean N-Desmethyl Diazepam Pharmacokinetic Values After 10 mg Diazepam

Treatment	Cmax (ng/mL)	AUC_{0-144} (ng*hr/mL)
Diazepam Alone	28.8 ± 3.2	3040 ± 110
Diazepam During Olanzapine	27.9 ± 2.0	2930 + 390

Olanzapine (12.5 mg multiple dose) does not appear to significantly affect the kinetics of diazepam or its major metabolite N-desmethyldiazepam. The effect of diazepam on olanzapine kinetics was not investigated.

CLINICAL STUDY SYNOPSIS. Study FID-LC-HGAT

Title:	Olanzapine: Bioavailability with Cimetidine, Antacid, and Charcoal
Investigators:	J. T. Callaghan, M.D., Ph.D.
Study Centers:	This was a single-center study.
Dates of Study:	*August 1993* through September 1993
Clinical Phase:	Phase 1
Objectives:	To evaluate the safety of olanzapine when administered alone and pairwise with: cimetidine, antacid, and activated charcoal..
Methodology:	Open-label, single-blind, four-way crossover evaluation
Number of Subjects:	Nine subjects entered and 8 (six males and two females) completed the study. One subject discontinued before olanzapine was administered.
Diagnosis and Inclusion Criteria:	Healthy male and female subjects.
Dosage and Administration:	Test Product CT02275: Olanzapine, 7.5 mg LBP124: Antacid(Mylanta 30cc 3D6409: Charcoal, 1 g N7403t26: Cimetidine, 800 mg
Duration of Treatment:	Test drug name: olanzapine (7.5 mg), single dose Antacid (30cc) + olanzapine (7.5 mg), single dose Charcoal (1 g) + olanzapine (7.5 mg), single dose Cimetidine (800 mg) + olanzapine (7.5 mg), single dose
Criteria for Evaluation:	Efficacy-- Not applicable Pharmacokinetics-- Plasma drug concentrations of olanzapine alone and during antacid, charcoal, and cimetidine combination therapies were measured and standard pharmacokinetic and bioavailability indices were calculated. Safety-- Safety parameters included vital signs, electrocardiograms, and clinical laboratory tests

Table HGAT.4.9. Mean Olanzapine Pharmacokinetic Variables For a 7.5-mg Single Oral Dose of Olanzapine

Treatment	Cmax (ng/mL)	Tmax (hr)	AUC$_{0-\infty}$ (ng·hr/mL)	T1/2 (hr)
A - Antacid	**8.41**	**6.0**	**329.6**	**29.0**
CV%	29.7	15.4	43.4	19.7
B - Charcoal	**3.15**	**6.75**	**149.4**	**35.5**
CV%	53.0	37.8	57.7	21.4
C - Cimetidine	**8.36**	**6.88**	**335.4**	**29.5**
CV%	25.0	28.5	34.9	19.6
D - Alone	**8.52**	**6.86**	**315.2**	**28.8**
CV%	33.7	15.6	43.1	21.8

Abbreviations: Cmax = maximum plasma concentration; Tmax = time to Cmax; AUC$_{0-\infty}$ = area under the curve to infinity; T1/2 = half-life; CV % = coefficient of variation

Note: Charcoal had the most significant effect on olanzapine absorption. Olanzapine AUC and Cmax were decreased by 52% and 63% respectively. This result suggests that charcoal may be useful for treating olanzapine overdose.

CLINICAL REPORT SYNOPSIS: Study F1D-MS-E001

Title:	Pharmacokinetic interaction study between olanzapine and lithium, given orally, after single and repeated administration of olanzapine in healthy volunteers
Investigators:	
Study Center:	
Dates of Study:	March 1994 through May 1994
Clinical Phase:	Phase 1 (Interaction Study)
Objectives:	To determine the influence of olanzapine (single and multiple-dose) on the pharmacokinetics (PK) of lithium; to assess the PK of olanzapine (single and multiple-dose) in the presence of lithium; to assess the safety of olanzapine alone and co-administered with lithium.
Methodology:	Open-label study consisting of three periods separated by wash-outs. Subjects received successively : 1) one single dose of lithium; 2) one single dose of lithium co-administered with one single dose of olanzapine; 3) olanzapine once daily for 8 days in order to achieve a steady state, with one single dose of lithium co-administered with the last dose of olanzapine. Sequential serum samples obtained for lithium measurements after each dose up to 72 h post-dose along with urine collections up to 24 h. Sequential plasma samples obtained for olanzapine measurements up to 72 h after the single dose of Period 2 and the last dose of Period 3.
Number of Subjects:	Twelve healthy male volunteers aged between 21 and 40 years.
Dosage at Administration:	Each subject received one oral dose of lithium 32.4 mmol in Periods 1 and 2 and on the last day of Period 3. Each subject received one oral dose of olanzapine 10 mg in Period 2 and 8 oral doses of olanzapine once daily in Period 3. Formulations--Lithium given as Quilonum® tablets each containing 536 mg lithium acetate. Olanzapine given as 10-mg capsules.

Table E001.6. Statistical Comparison of Lithium PK Parameters Between Period 1 (Lithium) and Period 2 (Olanzapine + Lithium)

PK Parameter[1]	Period 1 Least Square Mean	Period 2 Least Square Mean	Ratio Per.2/ Per.1(%)	Limits[2] of Ratio Per.2/Per.1(%) Lower	Upper	P-Value t-test for Equality	P-Value Wilcoxon Signed-Rank Test
C_{max}	1.0122	1.0689	105.6	96.4	115.6	0.31274	0.24023
$AUC_{0-24\ h}$	10.9188	11.6373	106.6	102.5	110.9	0.01138 +	0.01367 +
$AUC_{0-72\ h}$	17.9368	19.0073	106.0	100.7	111.5	0.06214	0.01367 +
$AUC_{0-\infty}$	21.4640	22.5287	105.0	97.9	112.5	0.24478	0.17480
$C_{max}/AUC_{0-24\ h}$	0.0927	0.0919	99.1	90.3	108.7	0.86536	0.96582
$C_{max}/AUC_{0-72\ h}$	0.0564	0.0562	99.7	89.4	111.1	0.95667	0.83105
$C_{max}/AUC_{0-\infty}$	0.0472	0.0474	100.6	88.4	114.5	0.93602	0.76464
$Cl_r(0-12\ h)$	1.5708	1.4684	93.5	83.3	103.7	0.28170	0.08398
Cl_{tot}	1.5344	1.4461	94.2	88.4	100.1	0.10711	0.17480
t_{max}	1.8333	1.8147	99.0	* 71.2	126.8 *	0.95039	0.75781
$t_{1/2}$	29.3667	28.8205	98.1	85.5	110.8	0.80291	0.83105

(1) All parameters except Cl_r, Cl_{tot}, t_{max} and $t_{1/2}$ were log-transformed for the ANOVA analysis
(2) Calculated from the 90 % confidence interval of the mean difference (Per.2/Per.1)
+ p-value < 0.05
* Indicates values out of the 80-120 % confidence range (80-125 % for log transformed data)

Table E001.7. Statistical Comparison of Lithium PK Parameters Between Period 1 (Lithium) and Period 3 (Repeated Olanzapine + Lithium)

PK Parameter[1]	Period 1 Least Square Mean	Period 3 Least Square Mean	Ratio Per.3/ Per.1(%)	Limits[2] of Ratio Per.3/Per.1(%) Lower	Upper	P-Value t-test for Equality	P-Value Wilcoxon Signed-Rank Test
C_{max}	1.0122	1.1298	111.6	101.9	122.2	0.04969 +	0.11816
$AUC_{0-24\ h}$	10.9188	11.3865	104.3	100.2	108.5	0.08160	0.24023
$AUC_{0-72\ h}$	17.9368	19.0000	105.9	100.7	111.4	0.06373	0.08300
$AUC_{0-\infty}$	21.4640	23.1209	107.7	100.5	115.5	0.08057	0.04199 +
$C_{max}/AUC_{0-24\ h}$	0.0927	0.0997	107.0	97.6	117.4	0.22086	0.27832
$C_{max}/AUC_{0-72\ h}$	0.0564	0.0595	105.4	94.5	117.5	0.41698	0.46484
$C_{max}/AUC_{0-\infty}$	0.0472	0.0489	103.6	91.2	117.9	0.63958	0.70019
$Cl_r(0-12\ h)$	1.5708	1.2650	80.5	70.7	90.3	0.00278 +	0.00683 +
Cl_{tot}	1.5344	1.4415	93.9	88.1	99.8	0.09127	0.02441 +
t_{max}	1.8333	1.7433	95.1	67.3	122.9 *	0.76388	1.00000
$t_{1/2}$	29.3667	31.2824	106.5	93.8	119.2	0.38556	0.01367 +

(1) All parameters except Cl_r, Cl_{tot}, t_{max} and $t_{1/2}$ were log-transformed for the ANOVA analysis
(2) Calculated from the 90 % confidence interval of the mean difference (Per.3/Per.1)
+ p-value < 0.05
* Indicates values out of the 80-120 % confidence range (80-125 % for log transformed data)

Note: Although small changes in lithium PK were observed in the presence of olanzapine, lithium alone is bioequivalent to lithium + olanzapine. The effect of lithium on olanzapine kinetics was not studied.

CLINICAL STUDY SYNOPSIS: Study FID-LC-HGBE

Title:	Olanzapine: Interaction Study with Warfarin
Investigators:	
Study Centers:	Single-center study
Dates of Study:	June 1994 through September 1994
Clinical Phase:	Phase 1
Objectives:	To determine the safety and drug interaction of coadministered olanzapine and warfarin.
Methodology:	Single-blind, three-way crossover study.
Number of Subjects:	Nineteen men were enrolled and 15 completed this study. Two discontinued due to "patient decision" and two discontinued due to "physician decision".
Diagnosis and Inclusion Criteria:	Healthy male subjects.
Dosage and Administration:	Test Product CT02276: Olanzapine capsules, 10 mg EFN223A: Warfarin tablets, 10 mg
Duration of Treatment:	Single doses of olanzapine (10 mg) and warfarin (25 mg), each given alone and concomitantly.
Criteria for Evaluation:	Efficacy-- Not applicable. Safety--Safety parameters included vital signs, electrocardiograms and clinical laboratory tests. Pharmacokinetics:--Plasma concentrations of olanzapine and R- and S-warfarin were measured. Standard pharmacokinetic indices were calculated.
Statistical Methods:	Latin square design.

Table HGBE.5.13 Mean Olanzapine Pharmacokinetic Variables For a 10-mg Single Oral Dose with and without Warfarin

	Cmax (ng/mL)	Tmax (hr)	t½ (hr)	MRT (hr)	AUC0-∞ (ng*hr/mL)	Cls/FF* (L/hr)	Vβ/FF* (L)
Alone (n=15)	**10.7**	**5.80**	**27.9**	**38.7**	**377**	**29.8**	**1151**
CV (%)	37.0	20.8	18.6	15.5	44.0	30.7	22.5
With Warfarin (n=15)	**9.5**	**6.33**	**30.0**	**41.7**	**353**	**30.9**	**1303**
CV (%)	29.0	37.6	15.8	14.7	34.9	27.6	22.6

Abbreviations: Cmax = maximum plasma concentration; Tmax = time of maximum plasma concentration; t1/2 = half-life; MRT = mean residence time; AUC = area under the curve; Cls/FF* = apparent systemic clearance; Vβ/ff* = apparent volume of distribution; CV = coefficient of variation

Table HGBE.5.14 Mean S-Warfarin Pharmacokinetic Variables For a 20-mg Single Oral Dose of R/S Warfarin with and without Olanzapine

	Cmax (ng/mL)	Tmax (hr)	t½ (hr)	MRT (hr)	AUC0-∞ (ng*hr/mL)	Cls/FF* (L/hr)	Vβ/FF* (L)
Alone (n=15)	**1333**	**1.20**	**31.3**	**41.4**	**36258**	**0.285**	**12.6**
CV (%)	23.9	66.4	15.9	20.0	17.9	19.7	12.9
With Olanzapine (n=15)	**1249**	**1.33**	**31.3**	**41.4**	**35781**	**0.292**	**12.7**
CV (%)	18.0	70.4	21.6	24.9	23.1	20.1	10.2

Table HGBE.5.15 Mean R-Warfarin Pharmacokinetic Variables For a 20-mg Single Oral Dose of R/S Warfarin with and without Olanzapine

	Cmax (ng/mL)	Tmax (hr)	t½ (hr)	MRT (hr)	AUC0-∞ (ng*hr/mL)	Cls/FF* (L/hr)	Vβ/FF* (L)
Alone (n=15)	**1284**	**1.23**	**37.7**	**52.4**	**48457**	**0.215**	**11.4**
CV (%)	22.3	66.6	16.7	18.7	19.6	23.2	14.2
With Olanzapine (n=15)	**1213**	**1.43**	**39.0**	**54.0**	**47416**	**0.220**	**12.0**
CV (%)	16.2	63.0	21.7	21.3	20.7	22.4	13.3

Note: There does not appear to be a large interaction between olanzapine and warfarin. Warfarin is known to be metabolized by CYP2C9, suggesting that a 10 mg single dose of olanzapine does not inhibit this enzyme in vivo.

Multiple Dose Kinetics and Assessment of
Kinetic and Dynamic Interaction with
Biperiden in Normal Volunteers

Protocol: F1D-EW-E002

Key Dates: Study Period: July - August 1990

Objective: To evaluate the plasma pharmacokinetics of LY170053 in healthy volunteers after multiple doses.

To evaluate the effect of LY170053 on the kinetic disposition of biperiden.

To evaluate the pharmacodynamic effects of LY170053 and biperiden on salivary flow, pupillary diameter after single and multiple doses.

Study Design: The study was conducted in two stages -

Stage 1:

A randomized parallel (observer) single-blind study of a single dose of biperiden (4mg) versus placebo in 8 subjects. Four subjects received biperiden and 4 subjects received placebo.

Stage 2:

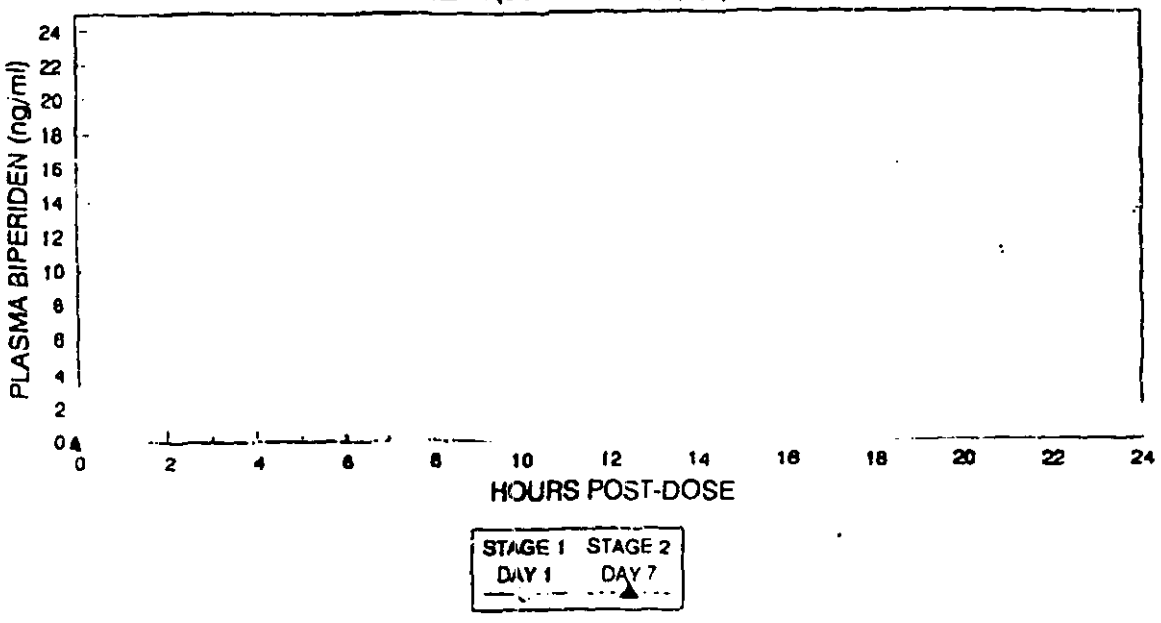
All eight subjects received LY170053 10mg daily for 7 days. Biperiden (4 mg) or placebo was taken with the last dose of LY170053 on day 7.

Study Therapies: 4 mg biperiden or placebo single dose.

10 mg LY170053 daily for 7 days and single dose of biperiden or placebo on day 7.

Volunteers: 8 healthy male volunteers.

F1D-EW-E002 BIPERIDEN PLASMA CONCENTRATIONS
MEAN (SUBJECTS 1,4,6,8)



F1D-EW-E002 Pharmacokinetic Variables for Biperiden

Stage 1 Dose: Biperiden 4 mg

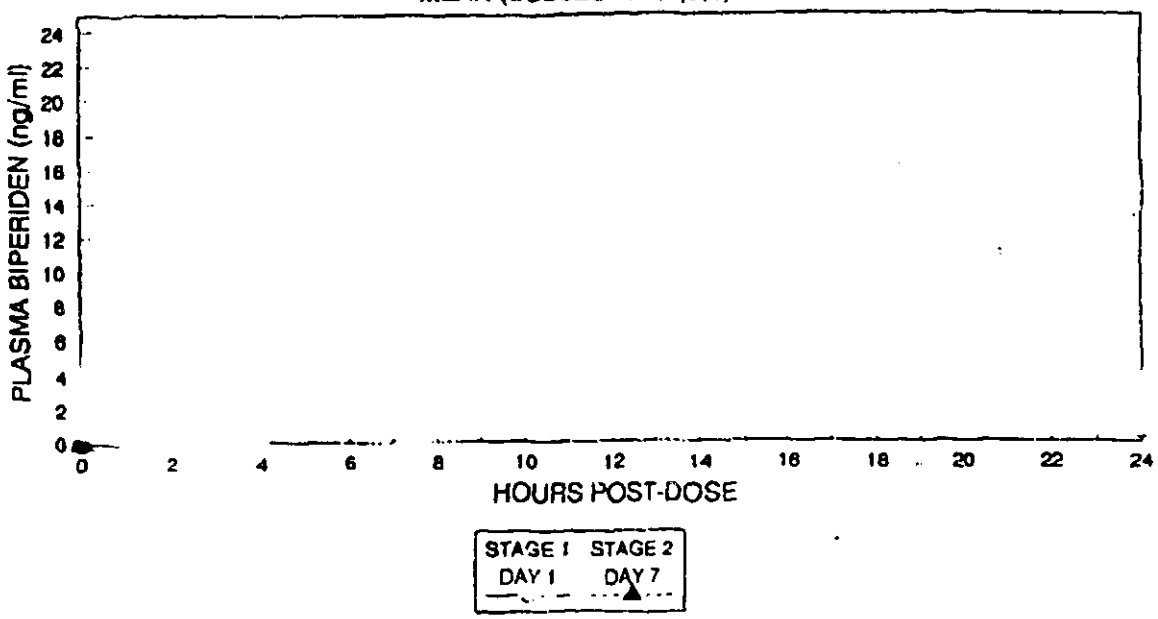
Subject	Dose (mg)	Body Wt (kg)	Dose (mg/kg)	Cmax (ng/ml)	Tmax (hr)	AUC 0-6 hr (ng*hr/ml)	AUC 0-inf (ng*hr/l)	Half Life Elimination (hours)	Rate (l/hr)	Clearance (L/hr)	Clearance (L/kg/hr)	Vol Dist (L)	Vol Dist (L/kg)
MEAN		78.0	0.058	9.6	1.3	34.59							
STD DEV		9.4	0.008	6.4	0.6	29.69							
C.V.%		13.5	14.4	66.7	51.4	85.8							

Stage 2 Dose: Biperiden 4 mg after 7th daily dose LY170053 10 mg

Subject	Dose (mg)	Body Wt (kg)	Dose (mg/kg)	Cmax (ng/ml)	Tmax (hr)	AUC 0-6 hr (ng*hr/ml)	AUC 0-inf (ng*hr/l)	Half Life Elimination (hours)	Rate (l/hr)	Clearance (L/hr)	Clearance (L/kg/hr)	Vol Dist (L)	Vol Dist (L/kg)
MEAN		78.0	0.058	12.3	1.4	34.45	7.0	60.0	0.0115	10.5	0.1	907.8	12.4
STD DEV		9.4	0.008	7.7	0.3	20.12							
C.V.%		13.5	14.4	62.7	18.2	89.4							

Note: Chronic administration of olanzapine caused an approximately 28% increase in the Cmax of biperiden. The cause of this increase is unclear.

F1D-EW-E002 BIPERIDEN PLASMA CONCENTRATIONS
MEAN (SUBJECTS 1,4,6,8)



F1D-EW-E002 Pharmacokinetic Variables for Biperiden

Stage 1 Dose: Biperiden 4 mg

Subject	Dose (mg)	Body Wt (kg)	Dose (mg/kg)	Cmax (ng/ml)	Tmax (hr)	AUC 0-6 hr (ng*hr/ml)	AUC 0-inf (kg*hr/l)	Half Life (hours)	Elimination Rate (1/hr)	Clearance (L/hr)	Clearance (L/kg/hr)	Vol Dist (L)	Vol Dist (L/kg)
MEAN		70.0	0.058	9.6	1.5	34.59							
STD DEV		9.4	0.008	6.4	0.6	29.69							
C.V.%		13.5	14.4	66.7	51.6	85.8							

Stage 2 Dose: Biperiden 4 mg after 7th daily dose LY170053 10 mg

Subject	Dose (mg)	Body Wt (kg)	Dose (mg/kg)	Cmax (ng/ml)	Tmax (hr)	AUC 0-6 hr (ng*hr/ml)	AUC 0-inf (kg*hr/l)	Half Life (hours)	Elimination Rate (1/hr)	Clearance (L/hr)	Clearance (L/kg/hr)	Vol Dist (L)	Vol Dist (L/kg)
MEAN		70.0	0.058	12.3	1.4	38.65	7.0	60.0	0.0115	18.5	0.2	907.8	12.4
STD DEV		9.4	0.008	7.7	0.1	28.12							
C.V.%		13.5	14.4	62.7	10.2	69.4							

Note: Chronic administration of olanzapine caused an approximately 28% increase in the Cmax of biperiden. The cause of this increase is unclear.

SPECIAL POPULATIONS

CLINICAL REPORT SYNOPSIS: Study F1D-LC-HGAM

Title:	Oral Olanzapine: Safety and Pharmacokinetic Study in the Elderly
Investigators:	
Study Centers:	This was a single-center study.
Dates of Study:	March 25, 1993 through May 10, 1993
Clinical Phase:	Phase I
Objectives:	To determine the safety and pharmacokinetic parameters of a single dose of olanzapine administered orally to elderly and young subjects.
Methodology:	Open-label, four-way crossover study
Number of Subjects:	Ten male and 6 female subjects, aged 65 years or older, and 5 male and 3 female subjects, aged between 20 and 45 years. One subject (elderly female) withdrew from the study for personal reasons. She had only received the 2.5-mg dose of olanzapine.
Diagnosis and Inclusion Criteria.	Healthy subjects.
Dosage and Administration:	Test Product Olanzapine: single oral dose. Dose was equal to capsule strength. CT02014: 2.5-mg capsules CT02015: 5.0-mg capsules CT02016: 7.5-mg capsules CT02017: 10.0-mg capsules
Duration of Treatment:	Single dose; washout period of 9 to 14 days between doses.

H6AM

Pharmacokinetic Variable	Gender	Mean Value Young	Elderly	Percentage Difference [a]
Half-Life (hr)	Female	38.5	54.8	42%
	Male	29.0	48.8	68%
	Combined [b]	33.8	51.8	53%
MRT (hr)	Female	52.6	76.4	45%
	Male	41.3	69.0	67%
	Combined [b]	46.9	72.7	55%
Tmax (hr)	Female	5.92	7.10	20%
	Male	6.35	8.10	28%
	Combined [b]	6.13	7.60	24%

a (Elderly - Young) / Young x100

b least-square mean values for males and females by age group

MRT = mean residence time, Tmax = Time of maximum plasma concentration

Pharmacokinetic Variable	Gender	Mean Value Young	Elderly	Percentage Difference [a]
AUC/Dose (kg*hr/L)	Female	3.16	5.15	63%
	Male	4.20	4.28	1.6%
Cmax/Dose (kg/L)	Female	0.078	0.086	10%
	Male	0.104	0.070	-33%
Clp/FF* (L/kg/hr)	Female	0.328	0.210	-38%
	Male	0.266	0.246	-8%
Vdβ/FF* (L/kg)	Female	18.4	16.0	-13%
	Male	10.3	17.2	67%

PK parameters averaged over all doses. (Because olanzapine displays linear kinetics, it is reasonable to average data over all doses). Parameters are normalized to body weight.

Note: This study suggests that olanzapine half-life is increased (by about 50%) by age. This increase in half-life appeared to be primarily due to an increase in Vd (by 67%) in elderly men compared to young men, and a decrease in CL (by 38%) in elderly women compared to young women. In contrast to the results of other studies, young women cleared olanzapine approximately 28% faster than did young men, although an opposite gender difference was observed in the elderly. Because so few subjects were studied (i.e. only 3 young women were examined)

CLINICAL STUDY SYNOPSIS: Study FID EW- HGCC

Title:	**Olanzapine Multidose Pharmacokinetic Dispostion and Safety in Healthy Elderly Subjects.**
Investigator:	
Study Centers:	
Dates of Study:	February 1995 through May 1995
Clinical Phase:	Phase I
Objectives:	To evaluate the pharmacokinetic disposition and safety in healthy elderly after multiple dosing with olanzapine 5 mg.
Methodology:	An open study with no comparator or placebo arm.
Number of Subjects:	Males 4, Females 4, Total 8.
Inclusion Criteria:	Males and females between the ages of 65 and 80 years, in good general health. Subjects with a Body Mass Index not greater than 29 and not less than 20. Subjects with mild chronic bronchitis or emphysema could be included, the expiratory peak flow rate had to be greater than 85% peak of predicted value for age, sex and height. Subjects with mild oedema unrelated to cardiovascular disease. Subjects who gave written informed consent to participate. Subjects taking no concomitant medication.
Dosage and Administration:	Test Product Olanzapine 5 mg/day, given as a single morning dose CT-0246-1D: Olanzapine capsules, 5 mg
Duration of Treatment:	Olanzapine 5 mg daily for 14 days
Criteria for Evaluation:	Pharmacokinetic disposition. Blood sampling for olanzapine content was made at intervals throughout the study to determine standard model independent pharmacokinetic parameters. An estimate of creatinine clearance was made from serum values according to the algorythm of Cockcroft & Gault.

Table 4 Pharmacokinetics of Olanzapine in Healthy Elderly Subjects Given 5 mg Olanzapine Once Daily for 14 Doses

Pharmacokinetic Variable		Mean ± SD			Range		
Half-Life	(hr)	58.5	±	6.7	49.7	to	66.8
Plasma Clearance	(L/hr)	19.5	±	6.6	10.0	to	31.6
Volume of Distribution	(L/kg)	23.1	±	6.6	13.4	to	32.8
Mean Residence Time	(hr)	80.2	±	15.6	63.4	to	102.7

Comparison of Mean Pharmacokinetic Values of Olanzapine from Three Studies

Pharmacokinetic Variable	Study MS E001 Young	Study HGCC Elderly	Study HGAM Elderly	Study HGAM Young
N (subjects)	11	8	15	8
Dosing	Steady-State 10 mg QD x 8	Steady-State 5 mg QD x 14	Single Dose 2.5, 5, 7.5, 10 mg	Single Dose 2.5, 5, 7.5, 10 mg
Clearance (L/hr)	27.5 ± 6.3 (22.9%)	19.4 ± 6.7 (34.4%)	17.8 ± 4.4 (24.9%)	19.9 ± 5.4 (27.4%)
Half-Life (hr)	34.0 ± 8.5 (25.0%)	58.5 ± 6.7 (11.6%)	50.8 ± 9.1 (18.0%)	32.6 ± 8.9 (27.1%)
Mean Residence Time (hr)	nd	78.6 ± 13.5 (17.1%)	71.5 ± 11.9 (16.6%)	45.5 ± 11.7 (25.6%)
Volume of Distribution (L/kg)	18.0 ± 5.4 (29.7%)	22.9 ± 6.7 (29.3%)	16.8 ± 3.7 (21.8%)	13.3 ± 5.1 (38.7%)

nd = not determined

Noncompartmental Pharmacokinetic Analysis of Olanzapine 5 mg Steady State Dose (Dose 14)

Subject		Plasma Clearance (L/hr)	(mL/min)	(L/kg/hr)	Volume Distribution (L)	(L/kg)	AUMC$_{0\text{-}24}$ (ng·hr^2/mL)	Avg. Cmin (ng/mL)	MRT (hr)	Vdss (L)	Vdss (L/kg)
Mean	All	19.4	323	0.276	1598	22.9	3225	9.77	78.6	1482	21.3
S.D.		6.7	111	0.093	439	6.7	1210	4.18	13.5	369	5.8
C.V. %		34.4	34.4	33.6	27.5	29.3	37.5	42.9	17.1	24.9	27.3
Min		10.0	167	0.149	896	13.4	1798	4.70	63.4	875	13.1
Max		31.6	527	0.439	2364	32.8	5581	17.75	94.3	2044	29.9
N		8	8	8	8	8	8	8	8	8	8
Mean	Female	14.6	243	0.243	1282	21.5	4088	12.38	84.1	1215	20.4
S.D.		3.3	55	0.074	297	7.7	1088	4.08	13.9	287	7.5
C.V. %		22.6	22.6	30.4	23.2	35.6	26.6	32.9	16.5	23.6	36.6
Min		10.0	167	0.149	896	13.4	3126	8.43	63.7	875	13.1
Max		17.2	287	0.329	1620	31.8	5581	17.75	94.3	1527	29.9
N		4	4	4	4	4	4	4	4	4	4
Mean	Male	24.1	402	0.310	1915	24.3	2362	7.15	73.1	1749	22.1
S.D.		5.7	95	0.108	309	6.4	499	2.45	12.2	213	4.5
C.V. %		23.6	23.6	35.0	16.1	26.3	21.1	34.2	16.7	12.2	20.6
Min		17.8	297	0.190	1695	18.0	1798	4.70	63.4	1533	18.2
Max		31.6	527	0.439	2364	32.8	3013	10.50	89.9	2044	28.4
N		4	4	4	4	4	4	4	4	4	4

In this study (HGCC), olanzapine clearance in elderly women was about 20% lower than that in elderly men.

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Interim Clinical Study Synopsis: Study FID-LC-HGAL

Title:	Olanzapine: Safety and Pharmacokinetic Study In Patients With Cirrhosis
Investigators:	.
Study Centers:	There ~~were~~ was 1 study center for the interim report.
Dates of Study:	This study started January 25, 1995 and ended May 26, 1995
Clinical Phase:	Phase 1
Objectives:	To determine the safety and pharmacokinetic parameters of single oral doses of olanzapine in subjects with cirrhosis, and to compare PK to normals
Methodology:	*Single dose study administered in three ascending doses*
Number of Subjects:	Nine male patients were enrolled and completed the study. (3 Normals, 6 Cirrhotics)
Diagnosis and Inclusion Criteria:	Cirrhotic and healthy subjects.
Dosage and Administration:	<u>Test Product</u> CT02273: Olanzapine capsules, 2.5 mg CT02274: Olanzapine capsules, 5.0mg CT02275: Olanzapine capsules, 7.5 mg
Duration of Treatment:	Single ascending-doses of olanzapine (2.5 mg, 5.0 mg,and 7.5 mg) were administered
Criteria for Evaluation:	<u>Efficacy</u>-- Not applicable <u>Safety</u>-- Safety parameters included vital signs, electrocardiograms and clinical laboratory tests including hepatitis B surface antigen

- Subjects with cirrhosis had a creatinine clearance >50 mL/min. and at least three of the following characteristics:

1. Two-fold elevations above upper limits of normal (43 U/L for men; 34 U/L for women) of alanine transaminase (ALT)
2. Two-fold elevations above upper limits of normal (36 U/L) of aspartate transaminase (AST)
3. Elevated bilirubin >1.5 mg/dL
4. Increased prothrombin time (PT) (but within 5 seconds of control value)
5. Decreased serum albumin (<3.3 g/dL)
6. Mild to moderate ascites

HGAU

Treatment		Cmax (ng/mL)	Tmax (hr)	Cls/FF* (L/hr)	Vβ/FF* (L)	t½ (hr)
2.5 mg Normal (n=3)	Mean	2.72	6.3	16.6	1075	44.3
	CV	22.4	24.1	14.8	27.4	13.0
2.5 mg Cirrhosis (n=6)	Mean	3.15	6.8	18.7	981	38.0
	CV	56.2	45.6	30.1	26.7	24.1
5 mg Normal (n=3)	Mean	6.01	7.3	14.1	995	48.8
	CV	19.9	55.1	17.1	24.6	17.0
5 mg Cirrhosis (n=6)	Mean	5.75	7.7	18.8	1010	39.3
	CV	30.8	25.6	24.6	21.5	10.1
7.5 mg Normal (n=2)	Mean	8.23	10	14.6	1130	54.7
	CV	6.8	0	21.0	0.7	20.3
7.5 mg Cirrhosis (n=6)	Mean	7.99	7.2	18.1	1111	43.0
	CV	29.5	35.8	24.2	23.5	14.1

Abbreviations: Cmax = maximum concentration; Tmax = time of maximum concentration; Cls/FF* = apparent systemic clearance; Vβ/FF* = apparent volume of distribution; t1/2 = half-life; CV = coefficient of variation.

Note: The clearance of olanzapine appeared to be slightly (about 20%) increased in the hepatically impaired subjects. However, these results are confounded by the fact that 4 of 6 hepatically impaired subjects were smokers and only 1 of 3 normals were smokers. Because of the low number of subjects studied, the only conclusion that can be made is that olanzapine clearance is not greatly affected in patients with liver impairment.

Interim Clinical Study Synopsis: Study F1D-LC-HGAW

Title:	**Olanzapine In Subjects With and Without Chronic Renal Failure**
Investigators:	
Study Centers:	
Dates of Study:	**Started December 1994 and is ongoing**
Clinical Phase:	**Phase 1**
Objectives:	**To determine the safety and disposition of olanzapine in subjects with renal failure.**
Methodology:	**This is an open-label, fixed-dose study.**
Number of Subjects:	**Olanzapine: Male 8, Female 8, Total 16;**
Diagnosis and Inclusion Criteria:	**Normal subjects and subjects with moderate or severe renal failure.**
Dosage and Administration:	**Test Product** **CT02274: Olanzapine capsules, 5 mg**
Duration of Treatment:	**Single doses of olanzapine (5 mg) were administered.**
Criteria for Evaluation:	**Efficacy-- Not applicable** **Safety-- Safety parameters measured includes vital sign measurements, electrocardiograms, clinical laboratory tests, blood chemistry tests, urinalysis tests and hematology tests.**

Group 1: **Subjects with creatinine clearance >90 mL/min/1.73 M^2**
Number of subjects enrolled to date: 6

Group 2: **Subjects with creatinine clearance between 10 and 49 mL/min/1.73 M^2**
Number of subjects enrolled to date: 3

Group 3: **Subjects with creatinine clearance <10 mL/min/1.73 M^2 (dosed 24 hours after hemodialysis)**
Number of subjects enrolled to date: 6

Group 4: **Subjects requiring chronic hemodialysis with creatinine clearance <10 mL/min/1.73 M^2 (dosed 1 hour prior to hemodialysis). Number of subjects enrolled to date: 6**

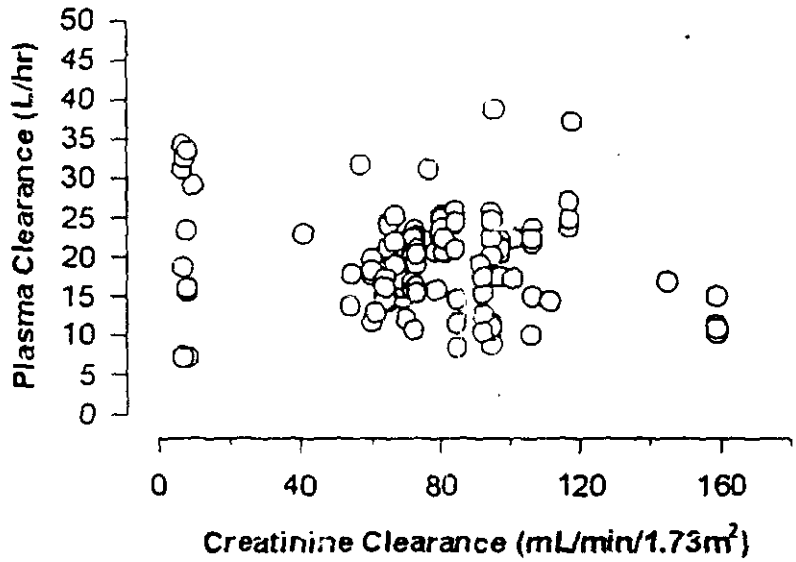
Note: 5 subjects crossed over between groups 3 and 4.

HGAW

Treatment		Cmax (ng/ml)	Tmax (hr)	Cls/FF* (L/hr)	Vβ/FF* (L)	t½ (hr)
Group 1 (n=6)	Mean	5.93	6.2	25.0	1119	32.3
	CV%	32.3	26.0	40.7	30.5	17.6
Group 2 (n=3)	Mean	7.21	6.0	15.5	1180	53.4
	CV%	39.5	57.7	29.7	26.8	18.5
Group 3 (n=6)	Mean	8.18	5.2	21.2	1057	37.7
	CV%	55.0	19.0	59.5	47.7	20.5
Group 4 (n=6)	Mean	9.53	4.2	21.3	1019	35.8
	CV%	32.3	23.6	45.5	33.7	22.4

C_{max} = maximum plasma concentration; T_{max} = time of maximum plasma concentration; Cls/FF* = apparent plasma clearance; Vβ/FF* = apparent volume of distribution; t½ = half-life

Olanzapine Plasma Clearance versus Creatinine Clearance



Note: Renal status does not appear to have a large affect on olanzapine pharmacokinetics as evidenced by the fact that there is no correlation between olanzapine clearance and creatinine clearance. This result is expected because only a small fraction of an olanzapine dose is excreted unchanged in the urine. Although Group 2 (moderate impairment) subjects had, on average, a 38% lower clearance than Group 1 (control) subjects, Group 3 and 4 subjects (severe impairment) had a clearance that was only about 15% lower than the control group. Thus, the differences between the groups, may be primarily due to the intersubject variability observed with olanzapine. Olanzapine was not released into the dialysate fluid, which is consistent with the finding that there is no difference as to wether the drug is given before or after dialysis. Renal status did not affect protein binding (see protein binding section of appendix for details.)

The sponsor states that a subpopulation analysis of the data from this study showed that olanzapine clearance was 40% higher in smokers compared to nonsmokers and 33% lower in women compared to men, although they do not present a formal analysis. These results are consistent with the results of many other studies presented in this section and do not affect our conclusions.

HGBY

Mean Pharmacokinetic Data (± SD) Overall and for Smoker and Gender Subgroups

Group	Number of Subjects (n)	Apparent Plasma Clearance CLp/FF* (L/hr)	Elimination Half-life t½ (hr)	Apparent Volume of Distribution (L/kg)
Overall	49	24.3 ± 8.2	31.2 ± 6.3	14.0 ± 4.3
Smokers	19	27.5 ± 7.7	29.3 ± 4.0	16.1 ± 5.4
Nonsmokers	30	22.3 ± 7.9	32.5 ± 7.2	12.7 ± 2.8
Males	44	24.7 ± 8.4	31.2 ± 6.2	13.8 ± 4.3
Females	5	20.6 ± 5.0	32.2 ± 7.1	15.9 ± 4.6

Study HGBY

These results from study HGBY are consistent with other results presented in this section. Clearance is about 25% higher in smokers compared to nonsmokers and about 20% higher in men than in women. See Bioequivalence section of the for details of study HGBY.

Japanese DATA

study JE-205E

All Data in These Tables are from Japanese Subjects.

Step 3: Mean Bioavailability and Pharmacokinetic Variables for 2.5- and 5-mg Tablet Formulations of Olanzapine

Bioavailability and Pharmacokinetic Variable		2.5-mg Tablet Subj. 41-46	5-mg Tablet Subj. 41-46	2.5-mg Tablet Subj. 47-52	5-mg Tablet Subj. 47-52	2.5-mg Tablet n=11	5-mg Tablet n=11
C_{max}	(ng/mL)	14.4	12.9	13.8	13.3	14.1	13.1
T_{max}	(hr)	4.6	5.0	4.5	4.3	4.5	4.6
AUC_{0-t}	(ng×hr/mL)	355.5	323.6	343.6	336.1	349.0	330.4
$AUC_{0-\infty}$	(ng×hr/mL)	358.8	355.4	373.9	366.8	379.8	361.6
Half-life	(hr)	25.2	26.9	27.7	28.2	27.0	27.6
MRT	(hr)	34.7	36.0	36.2	36.8	35.5	36.4
Clp/FF*	(L/hr)	14.3	15.4	13.9	14.3	14.1	14.6
Vβ/FF*	(L)	521.2	567.7	554.5	584.1	538.9	576.7

Step 4: Mean Bioavailability and Pharmacokinetic Variables for 2.5- and 5-mg Capsule Formulations of Olanzapine

Bioavailability and Pharmacokinetic Variable		2.5-mg Capsule Subj. 61-66	5-mg Capsule Subj. 61-66	2.5-mg Capsule Subj. 67-72	5-mg Capsule Subj. 67-72	2.5-mg Capsule n=12	5-mg Capsule n=12
C_{max}	(ng/mL)	14.1	15.4	14.2	13.3	14.5	14.4
T_{max}	(hr)	4.3	4.3	5.3	5.3	4.8	4.8
AUC_{0-t}	(ng×hr/mL)	421.4	415.4	353.0	343.5	387.4	379.5
$AUC_{0-\infty}$	(ng×hr/mL)	484.7	454.0	386.1	373.6	435.4	418.8
Half-life	(hr)	33.4	30.4	26.9	26.5	30.1	28.5
MRT	(hr)	44.4	40.5	36.3	35.8	40.3	38.2
Clp/FF*	(L/hr)	10.7	11.0	14.2	14.5	12.5	12.8
Vβ/FF*	(L)	507.3	482.5	523.0	533.3	515.5	507.9

A cross-study comparison of the results of Japanese study JE-205E (see bioequivalence section of appendix for details of this study) to the data acquired in the American studies (from reference data base) suggests that the apparent clearance and volume of olanzapine may be lower in the Japanese men (CL/FF = 14 L/hr, V/FF = 330 L/hr) compared to American men (CL/FF = 25 L/hr, V/FF = 1200 L) whereas half life does not appear to be as greatly affected (28 hr Japanese vs 30 hr American). These results are consistent with the Cmax and Tmax comparisons shown below. It is possible that these differences are due to differences in body composition and hepatic enzyme levels or due to differences in the extent of absorption. Interpretation of cross-study comparisons are difficult because of different study designs, different assays, and different variables (e.g. smoking status was not recorded in the Japanese study). The sponsor states that they are currently performing a study (HGAX) that is designed to examine racial differences in olanzapine pharmacokinetics.

Comparisons of C_{max} Values Normalized for Dose from US and Japan Studies

US (N=24)		Japan (N=22)	
C_{max}* ($L^{-1} \cdot 10^{-3}$)	T_{max} (hr)	C_{max}* ($L^{-1} \cdot 10^{-3}$)	T_{max} (hr)
1.0 ± 0.2	3.1 ± 1.2	2.1 ± 0.5	5.7 ± 1.8

* Normalized C_{max} ($L^{-1} \times 10^{-3}$) × dose (mg) = C_{max} (ng/mL). N = number of subjects
Studies US: HGAV, HGAE, and HGAH; Japan: JE-P100, JE-P200, and JE-P201

n = 7

Covariate Partitions in Reference Pharmacokinetic Database

Covariate	Category	Number of Observations	Number of Subjects
		(N=505)	(N=193)
Gender	Females	68	28
	Males	437	165
Smoker	No	258	88
	Yes	235	93
Origin	Asians	3	1
	Black	32	16
	Caucasian	437	158
	Hispanic	24	9
	Native American	1	1
CYP2D6 Phenotype	EM	250	86
	PM	12	4
NAT2 Phenotype	FA	27	10
	SA	81	32

Age Distribution in Reference Pharmacokinetic Database

Age Decade (yr)	Number of Subjects
	(N=193)
19	7
20-29	61
30-39	65
40-49	25
50-59	9
60-69	10
70-79	16

Ref. Data Base

Table 5
Summary Characteristics of Key Pharmacokinetic Variables

Statistic	Clearance CLp/FF* (L/hr)	Volume of Distribution Vβ/FF* (L)	Half-Life $t_{1/2}$ (hr)	Elimination Rate Constant β (hr^{-1})	Mean Residence Time MRT (hr)
Number of Observations	491	479	491	479	408
Mean	26.1	1148	33.1	0.0226	48.2
Median	23.6	1091	30.5	0.0225	44.2
Standard Deviation	12.1	360	10.3	0.0063	14.5
Coefficient of Variation	46%	31%	31%	28%	30%
5th Percentile	12.0	660	20.7	0.0127	31.5
95th Percentile	46.9	1792	54.1	0.0333	77.2
Minimum	7.1	400	14.5	0.0087	20.9
Maximum	142.0	2438	79.5	0.0478	109.8

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Ref. Data Base

Table 12
Effects of Study Covariates on Key Pharmacokinetic Variables

Variable	Age Slope	Smoker	Least-Square Mean	Difference	Gender	Least-Square Mean	Difference
CLp/FF*	0.064	No	18.6	~~-39%*~~	Female	18.9	-31%*
		Yes	27.7	(+49%)	Male	27.3	
Vβ/FF*	8.22*	No	967	-16%*	Female	944	-20%*
		Yes	1158		Male	1181	
t½	0.317*	No	38.0	8.2 hr*	Female	36.7	4.4 hr*
		Yes	30.4		Male	32.3	
β	-1.58×10^{-4}*	No	0.020	-20%*	Female	0.021	-9%
		Yes	0.025		Male	0.023	
MRT	0.489*	No	53.0	10.4 hr*	Female	49.5	3.4 hr
		Yes	42.6		Male	46.1	

* $P < 0.01$
Reference pharmacokinetic database

Table 13
Regression Assessment of Covariate Contribution

Parameter	Covariate	Sign of Slope†	Nullity p-Value	Coefficient of Determination
CLp/FF* (L/hr)	Smoker	+	<0.001	24.3%
	Gender	-	<0.001	30.3%
Vβ/FF* (L)	Age	+	<0.001	7.8%
	Smoker	+	<0.001	18.3%
	Gender	-	0.005	22.9%
t½ (hr)	Age	+	<0.001	44.1%
	Smoker	-	<0.001	54.2%
	Gender	+	0.007	56.6%
β (hr^{-1})	Age	-	<0.001	31.8%
	Smoker	+	<0.001	42.1%
	Gender	-	0.028	44.2%
MRT (hr)	Age	+	<0.001	47.1%
	Smoker	-	<0.001	58.2%
	Gender	+	0.057	59.3%

Smoker: (0 = No, 1 = Yes); (+)=a larger value for smokers; (-)=a larger value for nonsmokers
Gender: (0 = Male, 1 = Female); (+)=a larger value for females; (-)=a larger value for males
Age entered as regressor variable

Olanzapine Pharmacokinetic Variables for Poor Metabolizers of Dextromethorphan and All Healthy Subjects in the Clinical Pharmacology Database

	Half-life (hr)	CLp/FF* (L/hr)	Vβ/FF* (L)
Poor metabolizers	32.7 ± 2.7	24.6 ± 6.4	1171 ± 376
All subjects	33.1 ± 10.3	26.1 ± 12.1	1148 ± 360

POPULATION ANALYSIS

CONCLUSIONS (Written by sponsor)

Population pharmacokinetic modeling was performed on data from healthy subject studies (HGAV, HGAM) and data from large-scale clinical trials of olanzapine in patients with schizophrenia (HGAD, E003, HGAP, HGAJ) using NONMEM. The modeling of the healthy volunteer data (intensive sampling but few subjects) shows that the one-compartment model adequately characterizes the pharmacokinetics of olanzapine. The pharmacokinetic parameter estimates from the population modeling are consistent with those derived by traditional methods. The modeling of the schizophrenic patient population data (sparse sampling but many patients) identify important covariates that are influential on the pharmacokinetics of olanzapine.

Olanzapine pharmacokinetics were most notably influenced by smoking and gender differences. The results suggest that smokers have a higher olanzapine clearance and shorter half-life than nonsmokers. Men have a higher olanzapine clearance and shorter half-life than women. Analysis of the combined factors of smoking and gender suggests that olanzapine clearance for a nonsmoking female is about 2.5 fold lower than that for a smoking male. These differences in the olanzapine clearance may be attributable to CYP1A2 metabolic enzyme activity or other enzymes that metabolize olanzapine. Age was also an important covariate but was less influential on the model than either smoking or gender.

Table A
Summary Of The Effect Of Covariates On Olanzapine Pharmacokinetics

Olanzapine Clearance Estimates for Men and Women in HGAD, E003, HGAJ, and Combined Analyses

Parameter	HGAD	E003	HGAJ	Combined
Cl/FF* - Men (L/hr)	23.6	28.4	20.0	21.2
Cl/FF* - Women (L/hr)	17.5	16.9	16.1	16.7

Olanzapine Clearance Estimates for Smokers and Nonsmokers in HGAJ

Parameter	HGAJ
Cl/FF* - Smoker (L/hr)	21.8
Cl/FF* - Nonsmoker (L/hr)	15.1

The final structural model for the combined analysis of studies HGAD, E003, HGAP and HGAJ was the one-compartment model with first-order absorption and elimination from the central compartment. A constant coefficient of variation (CCV) model was used for interindividual variability in the apparent clearance and volume of distribution, and for random residual variability. The structural model included two distributions for clearance (a mixture model). Population 1 was a "low" clearance group where the typical value of the clearance was 13.4 L/hr. Population 2 was a "high" clearance group where the typical value of clearance was 26.4 L/hr.

The structural model also included the influence of gender on clearance. This model was consistent with that developed for the individual analysis of studies HGAD and E003 (Table B). According to this model, 655 patients were in a low-clearance group (38%) and 1056 patients in a high-clearance group. In both populations, olanzapine clearance was lower in women than in men (≈20% and 27%, respectively). Both men and women in the high clearance group had an approximately two-fold higher clearance than those in the low clearance group.

Table B
Summary Of Population Pharmacokinetic Parameters Obtained Using The Influence Of Gender On Mixture Model For Clearance

Study	ka (hr^{-1})	Men Cl_1/FF^a (L/hr)[b]	Women Cl_1/FF^a (L/hr)[c]	Men Cl_2/FF^a (L/hr)[d]	Women Cl_2/FF^a (L/hr)[e]	V_{ss}/FF^a (L)	Pf
HGAD	0.543	16.9	14.0	33.7	24.8	994	0.473
E003	0.358	20.1	11.2	38.7	28.0	2310	0.405
Combined	0.543[a]	14.5	11.5	29.1	21.2	1060	0.383

a = Value of ka fixed from the final model in study HGAD
b = Clearance Estimate in Men in Population 1
c = Clearance Estimate in Women in Population 1
d = Clearance Estimate in Men in Population 2
e = Clearance Estimate in Women in Population 2
f = Fraction of Patients in Population 1

HGAJ was the only Phase 2/3 study where smoking information was available and modeled. The final model (a mixture model) indicated that the population consisted of two subpopulations based on clearance (high and low). Smoking and gender were important factors on clearance only in the high-clearance group. Smoking and gender were also important factors for the volume of distribution across the entire population. According to the mixture model, 27% of the population (245 patients) belonged to the low-clearance group and 73% were in the high-clearance group. In the higher clearance group, male and female nonsmokers had a lower clearance (≈37% and 48%) than smokers, while women had a lower clearance than men (≈19% in smokers and 33% in nonsmokers). The histogram of the post hoc estimates of individual clearances (Figure A) from this model indicated that distribution of clearances was skewed. CYP1A2, one of the major enzymes responsible for olanzapine metabolism, can be induced by several factors such as smoking Guengrich and Shimada 1991; Kalow and Tang, 1991), and dietary factors (Conney et al. 1976). Also CYP1A2 activity in men is higher than in women (Relling et al. 1992). Therefore, the skewed platykurtic distribution of olanzapine clearances could be explained by the underlying multimodality in the CYP1A2 activities for the four different groups (male and female smokers, male and female nonsmokers).

Influence Of Smoking and Gender On Population Pharmacokinetic Parameters In Study HGAJ

		Smoker	Nonsmoker	% Difference[a]
Cl/FF* (L/hr)	Male	22.8	16.5	38.18
	Female	20.3	13.4	51.49
	% Difference[b]	-10.96	-18.79	
V_{SS}/FF* (L/hr)	Male	1360	944	44.10
	Female	1120	780	43.59
	% Difference[b]	-17.65	-17.37	

[a] = (Smoker - NonSmoker) / NonSmoker x 100

[b] = (Male - Female) / Male x100

Population Parameter Estimates For The Final Model Using Influence Of Gender And Smoking On Mixture Model For Clearance (Study HGAJ)

POPULATION PARAMETER ESTIMATES							
				Interindividual Variability		Intraindividual Variability	
	Pharmacokinetic Parameter	Parameter Value	Precision (%CV)	Omega (%CV)	Precision (%CV)	Sigma	Precision (%CV)
	ka (hr^{-1})[a]	.543	-	-	-	17.66	6.22
Population 1	Clearance (L/hr)						
	Cl_1/FF*	13.50	5.53	35.36[b]	16.16[b]		
Population 2	Clearance (L/hr)						
	Cl_2/FF*						
	Male Smoker	28.40	2.91				
	Female Smoker	23.06	3.82				
	Male Nonsmoker	18.01	4.84				
	Female Nonsmoker	12.01	7.02				
				25.92[c]	11.56[c]		
	V_{SS}/FF* (L)						
	Male Smoker	1360.0	8.46				
	Female Smoker	961.52	17.11				
	Male Nonsmoker	918.0	13.19				
	Female Nonsmoker	788.80	12.12				
				97.62	31.58		
	p[d]	0.731	6.43				

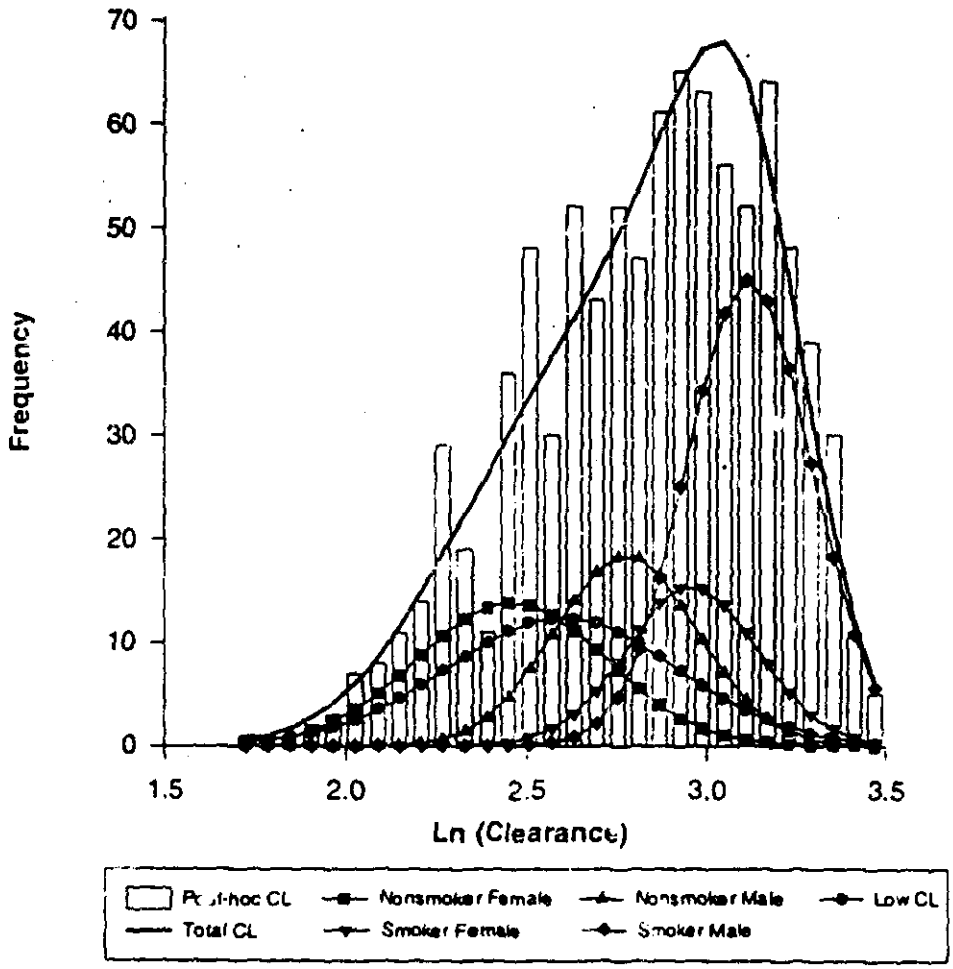
[a] = Value fixed from the final model in study HGAD

[b] = % Interindividual variability in clearance for Population 1

[c] = % Interindividual variability in clearance for Population 2

[d] = Fraction of patients in Population 2

Figure 27
Histogram Of The Clearance Estimates From The Final Population Pharmacokinetic Model for Study HGAJ



Description of Patient Populations

Study HGAV, a bioequivalence study in healthy Caucasian subjects, included 10 healthy male subjects. These subjects ranged in age from 22 to 51 years. Seven subjects were cigarette smokers.

Study HGAM included 15 male subjects (10 elderly, 5 young) and 9 female subjects (6 elderly, 3 young). Twenty-one participants were Caucasian and 3 subjects were Hispanic (2 elderly and 1 young). All subjects were nonsmokers.

The combined NONMEM analyses of HGAV and HGAM included 1605 observations from 133 doses. Plasma concentration-time data combined from these studies included 16 elderly (≥65 years) and 19 young (20 to 51 years) subjects. The 25 men and 9 women ranged in age from 20 to 79 years.

For study HGAD, olanzapine plasma concentrations from 188 patients (162 men and 26 women) in the acute (6 weeks) and/or extension (up to 1 year) phases were included in the population

DRUG FORMULATIONS &
DISSOLUTION SPECIFICATIONS

Unit Formula for Olanzapine Tablet Formulations

Ingredient	2.5 mg	5 mg	7.5 mg	10 mg
→ CORE				
Olanzapine				
(% Tablet Core)				

Unit Formula for Olanzapine Capsule Formulations

Capsule Strength	Olanzapine (% of Capsule)	Starch (% of Capsule)	Dimethicone (% of Capsule)	Capsule Fill Weight (mg)
2.5 mg				
5 mg				
7.5 mg				
10 mg				

PIVOTAL BIOSTUDY FORMULATIONS

Olanzapine Capsule, Tablet, and Granule Formulation Bioequivalence

Protocol F1D-LC-HGBY

The following CT materials were used in the pivotal bioequivalence study F1D-LC-HGBY which compared the oral bioavailability of 1, 5, 10, and 15 mg Olanzapine Capsule Formulations and 1, 5, 7.5, and 10 mg Olanzapine Tablet Formulations. The study was conducted in three parts.

Formulations Tested in PART 1

	Treatments	CT Materials Used		Expiration Date
A	Olanzapine 1 mg Capsules (five given)	P02418	CT03781	1 May 95
B	Olanzapine 5 mg Capsules (one given)	P02419	CT03782	1 May 95
C	Olanzapine 1 mg Tablets (five given)	P02422	CT03785	1 May 95
D	Olanzapine 5 mg Tablets (one given)	P02423	CT03786	1 May 95

Formulations Tested in PART 2

	Treatments	CT Materials Used		Expiration Date
A	Olanzapine 10 mg Capsules (one given)	P02420	CT03783	1 May 95
B	Olanzapine 5 mg Tablets (two given)	P02423	CT03786	1 May 95
C	Olanzapine 10 mg Tablets (one given)	P02425	CT03788	1 May 95

Formulations Tested in PART 3

	Treatments	CT Materials Used		Expiration Date
A	Olanzapine 15 mg Capsules (one given)	P02421	CT03784	1 May 95
B	Olanzapine 7.5 mg Tablets (two given)	P02424	CT03787	1 May 95
C	Olanzapine 5 mg Tablets (three given)	P02423	CT03786	1 May 95

The following manufacturing and control information for these formulations is provided to assist the reviewers of the report in ready access to the information. Complete details about the olanzapine manufacturing process and controls are provided in the chemical and pharmaceutical documentation.

Site of Manufacture and Batch Size – Batches used in Pivotal BE Study (HGBY)

Dose	Dosage Form	CT Number (final package)	Manufacture Lot Number	Site of Manufacture	Batch Size
1 mg	Capsule	CT03781	56344		
5 mg	Capsule	CT03782	56356		
10 mg	Capsule	CT03783	56346		
15 mg	Capsule	CT03784	CT-0250-1B		
1 mg	Tablet	CT03785	CT03751 (D20418)		
5 mg	Tablet	CT03786	CT03641 (D20423)		
7.5 mg	Tablet	CT03787	CT03750 (D20424)		
10 mg	Tablet	CT03788	CT03749 (D20426)		

Unit Formula for Olanzapine Capsule Formulations - Percentage of Content

Ingredient (% of total fill weight)	1 mg Capsule	5 mg Capsule	10 mg Capsule	15 mg Capsule

Unit Formula for Olanzapine Capsule Formulations - Actual Fill Weight

Ingredient	1 mg Capsule	5 mg Capsule	10 mg Capsule	15 mg Capsule

Unit Formula for Olanzapine Tablet Formulations - Percentage of Content

Ingredient (% of total tablet weight)	1 mg Tablet	5 mg Tablet	7.5 mg Tablet	10 mg Tablet

Unit Formula for Olanzapine Tablet Formulations - Actual Weight

Ingredient	1 mg Tablet	5 mg Tablet	7.5 mg Tablet	10 mg Tablet

Quality Control Data for the Formulations

Clinical Trial Materials Lot Numbers, Analytical Control Information, Assay Potency, Content Uniformity, and Dissolution Data

Biobatches From pivotal BE study - HGBY

Formulation Lot Number	Assay Potency (mg/capsule) (mg/tablet) or (mg/sachette)	Content Uniformity (mg/capsule) (mg/tablet) or (mg/sachette)	Dissolution Time (minutes)	Percent Dissolved (% of label amount) (Data Source: UK) avg. range (n=6)
1 mg Capsule Package Lot # CT03781 Manufacture Lot # 56344				
5mg Capsule Package Lot # CT03782 Manufacture Lot # 56356				
10 mg Capsule Package Lot # CT03783 Manufacture Lot # 56346				
15 mg Capsule Package Lot # CT03784 Manufacture Lot # CT-0250-1B				

Biobatches from Pivotal BE Study HGBY

Formulation Lot Number	Assay Potency (mg/capsule) (mg/tablet) or (mg/sachet)	Content Uniformity (mg/capsule) (mg/tablet) or (mg/sachette)	Dissolution Time (minutes)	Percent Dissolved (% of label amount) Source: Puerto Rico x-z-range (n=6)
1 mg Tablet Package Lot # CT03785 Manufacture Lot # CT03751 (D20418)				
5mg Tablet Package Lot # CT03786 Manufacture Lot # CT03641 (D20423)				
7.5 mg Tablet Package Lot # CT03787 Manufacture Lot CT03750 (D20424)				
Formulation Lot Number				
10 mg Tablet Package Lot # CT03788 Manufacture Lot # CT03749 (D20426)				

OLANZAPINE DRUG PRODUCT DISSOLUTION PROFILES- 2.5 MG TABLETS

Date of test	Dosage Form and Strength	Lot Number	Dissolution Apparatus	Media/ Temperature	Speed of Rotation/ Flow	Collection Times	Units Mean % (n=6)	Units Range %	RSD %
20 April 94									
20 April 94									
12 April 94									
12 April 94									
22 April 94									
26 April 94									

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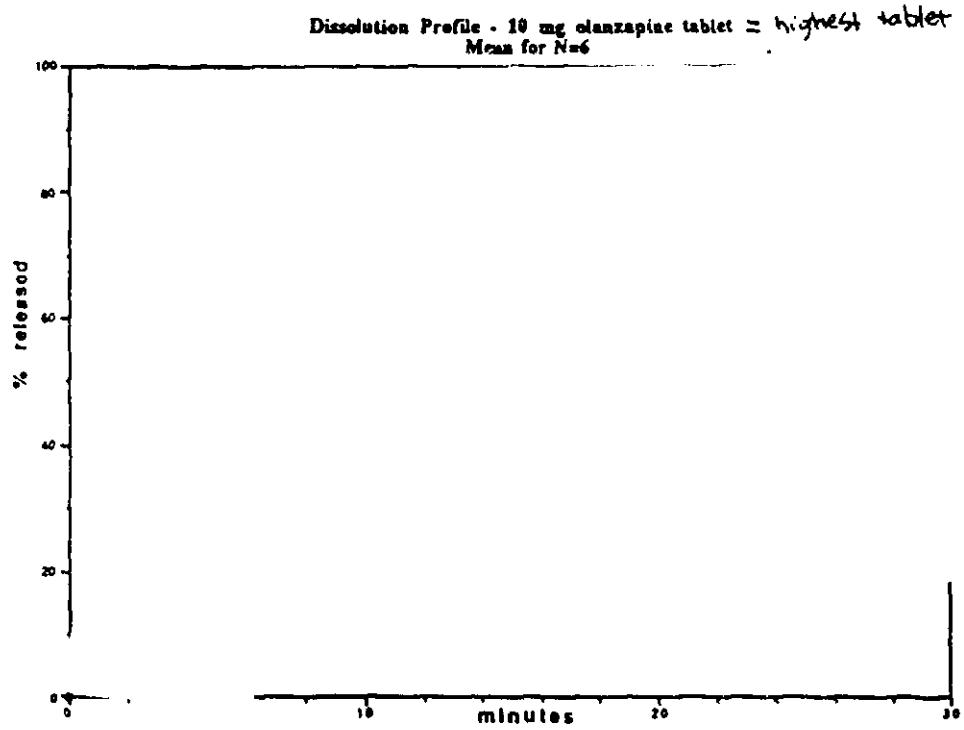
DISSOLUTION PROFILES FOR 10 MG OLANZAPINE TABLETS IN VARIOUS MEDIA

The dissolution medium is 0.1N HCl. This medium closely approximates the physiological environment to which the dosage form is first exposed and is a preferred medium.

The following data are the means (N=6) in % of label claim for a 10-mg dose.

Sampling times	purified water	0.1 N HCl	pH 4.5 buffer	pH 6.8 buffer
10 minutes				
20 minutes				
30 minutes				

The plots of this data illustrate the decreasing rate of release of olanzapine due to the more limited solubility at neutral pH.



PROPOSED TABLET DISSOLUTION METHOD AND SPECIFICATION

1. Dosage Form:	Tablet
2. Strength(s):	2.5 mg, 5 mg, 7.5 mg, and 10 mg
3. Apparatus Type:	
4. Media:	
5. Volume:	
6. Speed of Rotation:	
7. Sampling Time(s):	
8. Brief Description of Dissolution Analytical Method:	
9. Recommended Dissolution Specification:	

Acceptance Criteria (USP <711>)

Stage	Number tested	Acceptance Criteria
S1	6	
S2	6	
S3	12	

DISSOLUTION METHOD DESCRIPTION

performance.

Solubility Profile:

Medium	Solubilities at Room Temperature pH of Medium at Saturation	Solubility (mg/mL)	Solubility Classification
Acetonitrile	–	11.5	sparingly soluble
Buffer pH 2	5.87	2.5	slightly soluble
Buffer pH 4	5.97	11.0	sparingly soluble
Buffer pH 6	6.04	4.3	slightly soluble
Buffer pH 7	7.08	0.4	very slightly soluble
Buffer pH 10	9.92	0.1	very slightly soluble
Ethanol, anhydrous	–	7.0	slightly soluble
Ether	–	7.6	slightly soluble
0.1N HCl	5.38	20.6	sparingly soluble
Methanol	–	4.5	slightly soluble
0.1N NaOH	12.83	0.3	very slightly soluble
n-Propanol	–	43.9	soluble
Propylene Glycol: H_2O (1:5)	–	0.1	very slightly soluble
Water	–	<0.1	practically insoluble

BIOEQUIVALENCE

Clinical Study Synopsis: Study F1D-LC-HGBY

Title:	Olanzapine: Bioequivalency of Capsules and Tablets.
Investigators	
Study Centers	Single center study.
Dates of Study	November 1994 through March 1995
Clinical Phase:	Phase 1
Objectives:	Primary: to measure the pharmacokinetics and assess relative bioavailability of olanzapine when administered in various single oral doses in capsules and tablet formulations. Secondary: to evaluate the safety of olanzapine when administered in capsule and tablet dosage forms at various doses.
Methodology:	Open-label crossover single dose
Number of Subjects:	Forty-nine subjects were enrolled (44 males and 5 females). Forty-six subjects completed the study according to the protocol; 2 subjects discontinued due to adverse events, and 1 subject discontinued due to personal decision.
Diagnosis and Inclusion Criteria:	Healthy subjects.
Dosage and Administration:	CT03781 1-mg capsule CT03782 5-mg capsule CT03783 10-mg capsule CT03784 15-mg capsule CT03785 1-mg tablet CT03786 5-mg tablet CT03787 7.5-mg tablet CT03788 10-mg tablet
Duration of Treatment:	To span the different tablet and capsule formulations, this study compared 1-, 5-, 7.5-, and 10-mg tablets to 1-, 5-, 10-, and 15-mg capsule formulations. The study was conducted in three parts I:(1-mg tablet and capsule versus 5-mg tablet and capsule formulations); II: (5- and 10-mg tablet versus 10-mg capsule formulations); and III (5- and 7.5-mg tablet versus 15-mg capsule formulations).

Notes: The 5 mg tablet provides a common link between the three study parts. The sponsor plans on marketing 2.5, 5, 7.5 and 10 mg tablet strengths. The 2.5 mg strength was not utilized in this study but can be linked to other strengths via dissolution/formulation data. In addition, in a Japanese study JE-205E, description follows results of this study) it was demonstrated that 2 x 2.5 mg tablets are bioequivalent to 1 x 5 mg tablet. Although study HGBY adequately links the 1 mg tablet to other tablet and capsule strengths, the sponsor will not market this tablet strength. The highest capsule strength used in the clinical studies was 17.5 mg, the highest capsule strength used in this study was 15 mg.

5-mg Dose (n=16 Subjects)				
Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng×hr/mL)	$AUC_{0-\infty}$ (ng×hr mL)
A: Capsule (1 mg x 5)	5.5	7.8	200	222
CV%	33.3	42.4	36.8	39.9
B: Capsule (5 mg x 1)	5.6	7.2	200	223
CV%	35.5	22.3	39.5	41.5
C: Tablet (1 mg x 5)	5.5	6.8	201	224
CV%	36.5	37.6	34.7	35.7
D: Tablet (5 mg x 1)	5.7	6.1	200	226
CV%	36.3	37.4	36.8	38.2
Overall Mean	5.6	7.0	201	224
Inter-subject CV%	35.2	---	38.3	40.3
Intra-subject CV%	9.7	---	8.2	8.4
Inter-subject Variance	3.87	---	5893	8134
Intra-subject Variance	0.29	---	272	352
Composite Means				
Capsule (1 & 5 mg)	5.55	7.50	200	222
Tablet (1 & 5 mg)	5.63	6.44	201	225
1-mg Dose (tab & cap)	5.52	7.31	201	223
5-mg Dose(tab & cap)	5.66	6.63	200	224

Abbreviations: Cmax = maximum plasma concentration; Tmax = time of maximum concentration; AUC = area under the curve; CV = coefficient of variation.

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5-mg Dose (n=16 Subjects)

Bioavailability Variable	Comparison	p value	Dosage Form Contrast†	Mean Separation	Ratio of Means	90% Confidence Interval §	
C_{max}*	sequence group	0.503	A vs B	-1.6%	0.993	0.94 - 1.05	P
(ng/mL)	interaction ¶	0.528	C vs B	-1.0%	0.987	0.94 - 1.04	P
	tablet vs capsule	0.733	D vs B	2.4%	1.022	0.97 - 1.08	P
	1 mg vs 5 mg	0.356					
			T vs C	1.5%	1.01	0.97 - 1.05	P
			1 vs 5	-2.5%	0.98	0.94 - 1.02	P
Tmax	sequence group	0.127	A vs B	0.63 ‡	na	na	
(hr)	interaction ¶	0.911	C vs B	-0.38 ‡	na	na	
	tablet vs capsule	0.065	D vs B	-1.13 ‡	na	na	
	1 mg vs 5 mg	0.225					
			T vs C	-1.06 ‡	na	na	
			1 vs 5	0.69 ‡	na	na	
AUC_{0-t}*	sequence group	0.833	A vs B	-0.1%	1.004	0.96 - 1.05	P
(ng×hr/mL)	interaction ¶	0.951	C vs B	0.5%	1.010	0.96 - 1.06	P
	tablet vs capsule	0.798	D vs B	0.1%	1.004	0.96 - 1.05	P
	1 mg vs 5 mg	0.796					
			T vs C	0.3%	1.01	0.97 - 1.04	P
			1 vs 5	0.1%	1.01	0.97 - 1.04	P
$AUC_{0-\infty}$*	sequence group	0.838	A vs B	-0.6%	0.998	0.95 - 1.05	P
(ng×hr/mL)	interaction ¶	0.944	C vs B	0.6%	1.015	0.97 - 1.06	P
	tablet vs capsule	0.329	D vs B	1.4%	1.021	0.97 - 1.07	P
	1 mg vs 5 mg	0.846					
			T vs C	1.3%	1.02	0.99 - 1.05	P
			1 vs 5	-0.7%	1.00	0.99 - 1.03	P

* Analysis performed on the log-transformed variables.

† Treatments: A = 1-mg Capsule, B = 5-mg Capsule, C = 1-mg Tablet, D = 5-mg Tablet.
T v C = composite tablet versus composite capsule comparison
1 vs 5 = composite 1-mg tablet and capsule versus composite 5-mg tablet and capsule comparison

‡ Absolute difference. na = not applicable.

§ Lower and Upper bound. P=pass F=fail Bioequivalence Criterion 0.8 - 1.25.

¶ Interaction between solid dosage form and strength.

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Part II Olanzapine Bioavailability and Variability Assessment

10-mg Dose (n= 15 Subjects)

Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng×hr/mL)	$AUC_{0-\infty}$ (ng×hr/mL)
A: Capsule (10 mg x 1)	12.1	5.8	401	429
CV%	27.6	41.3	36.5	37.4
B: Tablet (5 mg x 2)	12.7	5.7	402	431
CV%	34.7	33.8	30.6	31.6
C: Tablet (10 mg x 1)	12.3	5.3	397	429
CV%	29.7	30.0	34.8	36.1
Overall Mean	12.4	5.6	400	430
Inter-subject CV%	29.1	---	33.5	34.4
Intra-subject CV%	13.0	---	8.5	8.6
Inter-subject Variance	12.94	---	17917	21813
Intra-subject Variance	2.58	---	1156	1369

Table E
Statistical Outcome Tests and Separation of Formulation Means for Specific Comparisons Between Formulations for Part II

10-mg Dose (n=15 Subjects)

Bioavailability Variable	Comparison	p value	Dosage Form Contrast†	Mean Separation	Ratio of Means	90% Confidence Interval §	
C_{max}*	sequence group	0.647					
(ng/mL)	5-mg Tab vs Cap	0.468	B vs A	4.7%	1.01	0.95 - 1.08	P
	10-mg Tab vs Cap	0.785	C vs A	1.3%	1.03	0.96 - 1.10	P
Tmax	sequence group	0.476					
(hr)	5-mg Tab vs Cap	0.810	B vs A	-0.13 ‡	na	na	
	10-mg Tab vs Cap	0.339	C vs A	-0.53 ‡	na	na	
AUC_{0-t}*	sequence group	0.525					
(ng×hr/mL)	5-mg Tab vs Cap	0.467	B vs A	0.3%	1.03	0.97 - 1.09	P
	10-mg Tab vs Cap	0.999	C vs A	-0.9%	1.00	0.94 - 1.06	P
$AUC_{0-\infty}$*	sequence group	0.499					
(ng×hr/mL)	5-mg Tab vs Cap	0.481	B vs A	0.4%	1.02	0.97 - 1.08	P
	10-mg Tab vs Cap	0.860	C vs A	-0.0%	1.01	0.95 - 1.06	P

* Analysis performed on the log-transformed variables.

† Treatments: A = 10-mg Capsule, B = 5-mg Tablet, C = 10-mg Tablet

‡ Absolute difference. na = not applicable

§ Lower and Upper bound. P=pass F=fail Bioequivalence Criterion 0.8 - 1.25

H6B4

15-mg Dose (n=15 Subjects)

Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng×hr/mL)	$AUC_{0-\infty}$ (ng×hr/mL)
A: Capsule (15mg x 1)	20.7	5.4	680	734
CV%	26.8	41.3	28.1	30.0
B: Tablet (7.5 mg x 2)	23.4	4.5	719	782
CV%	25.7	41.6	28.8	31.5
C: Tablet (5 mg x 3)	20.7	5.0	685	740
CV%	21.9	28.3	28.0	30.6
Overall Mean	21.6	5.0	695	752
Inter-subject CV%	15.5	---	28.1	31.0
Intra-subject CV%	15.8	---	8.7	9.4
Inter-subject Variance	11.18	---	37980	54495
Intra-subject Variance	11.70	---	3686	4949

Abbreviations: Cmax = maximum plasma concentration; Tmax = time of maximum concentration; AUC = area under the curve; CV = coefficient of variation.

15-mg Dose (n=15 Subjects)

Bioavailability Variable	Comparison	p value	Dosage Form Contrast†	Mean Separation	Ratio of Means	90% Confidence Interval §	
C_{max}*	sequence group	0.052					
(ng/mL)	7.5-mg Tab vs Cap	0.035	B vs A	12.9%	1.13	1.03 - 1.24	P
	5-mg Tab vs Cap	0.885	C vs A	0.1%	1.01	0.92 - 1.10	P
Tmax	sequence group	0.616					
(hr)	7.5-mg Tab vs Cap	0.054	B vs A	-0.87 ‡	na	na	
	5-mg Tab vs Cap	0.358	C vs A	-0.40 ‡	na	na	
AUC_{0-t}*	sequence group	0.598					
(ng×hr/mL)	7.5-mg Tab vs Cap	0.113	B vs A	5.8%	1.05	1.00 - 1.11	P
	5-mg Tab vs Cap	0.860	C vs A	0.7%	1.01	0.95 - 1.06	P
$AUC_{0-\infty}$*	sequence group	0.740					
(ng×hr/mL)	7.5-mg Tab vs Cap	0.103	B vs A	6.5%	1.06	1.00 - 1.11	P
	5-mg Tab vs Cap	0.896	C vs A	0.8%	1.00	0.95 - 1.06	P

* Analysis performed on the log-transformed variables.

† Treatments: A = 15-mg Capsule, B = 7.5-mg Tablet, C = 5-mg Tablet.

‡ Absolute difference. na = not applicable

§ Lower and Upper bound. P=pass F=fail Bioequivalence Criterion 0.8 - 1.25

INTERIM CLINICAL STUDY SYNOPSIS: Study F1D-JE-205E

Title:	Clinical Pharmacology Study of Olanzapine (LY170053), Bioequivalence of Capsule and Tablet Formulations of Olanzapine (LY170053) and the Effects of a Meal
Investigators:	This single center study included 1 principal investigator.
Study Centers:	There was 1 study center.
Dates of Study:	August 1994 to March 1995, analysis ongoing
Clinical Phase:	Phase 1 Clinical Pharmacology (Bioequivalence Study)
Objectives:	To investigate the bioequivalence between capsule and tablet formulations of olanzapine and the effects of a meal on the bioavailability of olanzapine tablets in healthy male adults by crossover method.
Methodology:	Open-label, randomized, 2-way cross-over design
Number of Subjects:	Olanzapine: Male 52, Total 52
Diagnosis and Inclusion Criteria:	Male subjects, 20 to 35 years of age, were selected if they were Japanese, healthy, members of the Volunteer Association and had received a screening health check within one month before the study
Dosage and Administration:	The dosage and administration of four separate, open-label, randomized, 2-way crossover studies (steps) were as follows: STEP 1: The subjects received a 5 mg olanzapine tablet after fasting 12 hours and a 5 mg olanzapine tablet thirty minutes after breakfast on separate occasions. There was at least a 10-day washout between treatments (n=16). STEP 2: After fasting for 12 hours, the subjects received a 5 mg olanzapine tablet and a 5 mg olanzapine capsule on separate occasions. There was at least a 16-day washout between treatments (n=12). STEP 3: After fasting for 12 hours, the subjects received two 2.5 mg olanzapine tablets and one 5 mg olanzapine tablet on separate occasions. There was at least a 16-day washout between treatments (n=12 enrolled, 11 completed). STEP 4: After fasting for 12 hours, the subjects received two 2.5 mg olanzapine capsules and one 5 mg olanzapine capsule on separate occasions. There was at least a 16-day washout between treatments (n=12). Test Products CT-0245-1A: olanzapine capsules, 2.5 mg CT-0246-1D: olanzapine capsules, 5.0 mg 56663: olanzapine tablets, 2.5 mg 56664: olanzapine tablets, 5.0 mg
Duration of Treatment	Olanzapine: Single oral 5 mg doses of olanzapine were given on two occasions separated by a period of at least 10 days (step 1) or at least 16 days (steps 2, 3, and 4).
Criteria for Evaluation	Safety--Subjective symptoms were assessed. These included: a physician administered questionnaire, vital signs, laboratory tests, electrocardiogram (ECG), plasma concentrations of olanzapine, and adverse event and side effects.
Statistical Methods:	Evaluation included all data available from all subjects entering the study. Descriptive statistical analyses were performed. Physiological and laboratory test values were compared before and after dosages using a paired T-test. The level of significance was set at 5% (two-tailed). Bioequivalence between formulations and the effect of the meal were evaluated by calculating the 90% confidence interval of difference for the mean of both formulations regarding the AUC and Cmax. The assessment tested whether the differences of mean AUC and Cmax values were within 20% between the 5 mg tablet given fed or fasted; between the 5 mg capsule and 5 mg tablet, between 2.5 mg tablet and 5 mg tablet, and between the 2.5 mg capsule and 5 mg capsule. The analysis also tested the significance of any subject/drug/sequence/time period effects using ANOVA

JE-205E

Step 3: 90% Confidence Intervals on Bioequivalence Variables
2X 2.5-mg Tablet vs 5-mg Tablet

Pharmacokinetic Variable		Ratio of Means	90% CI Lower Limit	90% CI Upper Limit	Bioequivalence Criteria† Pass/Fail
C_{max}	(ng/mL)	1.07	1.02	1.12	Pass
AUC_{0-t}	(ngxhr/mL)	1.06	1.00	1.13	Pass
$AUC_{0-\infty}$	(ngxhr/mL)	1.05	0.99	1.12	Pass

† Bioequivalence Range: 0.80 to 1.25
Based upon log transformation of the values.

Note: This study was reviewed ~~solely~~ to provide additional evidence that 2 x 2.5 mg tablets is bioequivalent to the 5 mg tablet. See study HGBY for the pivotal biostudy.

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OLANZAPINE ASSAY

3 Pages Purged

RELEVANT PORTIONS OF LABELING WRITTEN BY SPONSOR

8Pages
Purged

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 6, 1996

FROM: Glenna G. Fitzgerald, Ph.D GGF
Pharmacology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA 20-592
Olanzapine; Zyprexa
Eli Lilly & Co.

SUBJECT: Addendum to July 24, 1996 Overview

My original overview was completed prior to the drafting of the CAC-EC minutes for olanzapine. These minutes are still in draft form because they have not been officially signed by the CAC-EC Chair, but they are complete, having addressed all issues raised at the meeting of the committee on June 11, 1996. A copy of that report is attached to this memo.

This memo is intended to explain how the decision about which tumors to include in labeling was reached.

Mammary gland adenomas and adenocarcinomas: There was a significant increase in females in both mouse studies. Although the increase in female rats was not statistically significant, it fell outside the sponsor's historical control data. Because of this, as well as the fact that it is an expected tumor in female rodents receiving drugs which elevate prolactin, we have included the rat tumors as well as the mouse tumors in labeling. The sponsor had also included rat malignant mammary tumors in labeling.

Lung adenocarcinomas: The sponsor found this tumor to be significant in female mice in one study only; the FDA statistician found significance in the trend test but not in the pairwise analysis in female mice in the other study only. The incidences were within historical control ranges from the sponsor, and we did not include this tumor in the labeling.

Lymphosarcomas: The sponsor found this tumor to be significantly increased , but the effect was not dose-dependent, in one mouse study in females only. The FDA statistician did not find significance and the incidence was within historical control data. It is not included in labeling.

Liver hemangiomas & hemangiosarcomas: The sponsor found the occurrence of hemangiosarcomas to be significantly increased at high dose in female mice in one of the studies only. The FDA analysis did not show significance. The CAC recommended combining hemangiomas with hemangiosarcomas for analysis. Our statistician found the combination to be significant by both trend and pairwise analyses. Sponsor's historical data are not available, but the incidence was higher than published data available, and the finding is included in labeling.

Recommendation:

The mouse and rat mammary tumors are already included in recommended labeling. The following sentence should be inserted following sentence number 3 of the carcinogenesis section of the label: **The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in female mice dosed at 8 mg/kg/day (2 times the recommended human dose on a mg/m2 basis).**

NDA 20-592
(attachment)
HFD-120:

Leber
Laughren
Andreason
Atrakchi
Fitzgerald
Hardeman
Mille

DRAFT

Executive CAC
June 11, 1996

Committee members: James Farrelly, Ph.D., Acting Chair, HFD-530
Alex Jordan, Ph.D., Rotating member, HFD-580
Charles Resnick, Ph.D., HFD-110
Glenna Fitzgerald, Ph.D., Team Leader, HFD-120
Sharon Olmstead, Executive Secretary, HFD-006

NDA 20-592 (Atrakchi; HFD-120)
Zyprex (olanzapine)
Eli Lilly and Co.

The sponsor submitted carcinogenicity study results from a single rat study and two mice studies. The rat carcinogenicity study used doses of 0.25, 1.0, 2.5 and 4.0 mg/kg. Doses for the female rats in the 2 HD groups were increased at day 211 to 4.0 and 8.0 mg/kg, respectively, due to a limited effect on body weight. Decreases in percent of body weight gain were 11% for HD males and 18% and 33% in the two HD female groups. The sponsor reported statistically significant increases in female mammary gland adenocarcinomas; however, the FDA statistician did not agree with the sponsor's analysis. The FDA statistican found no significant increases in tumor types for either sex by any of the statistical tests conducted (trend and pairwise).

The sponsor conducted two separate mice carcinogenicity studies (the second study was conducted at the sponsor initiation). The original study using doses of 3, 10 and 30 mg/kg (lowered to 20 mg/kg due to excessive mortality in males)reported no significant increases of tumors in males. However, for the female mice, significant increases were reported for lung adenomas and carcinomas in the LD group, mammary gland adenomas and carcinomas in MD&HD group, and a significant but non-dose dependent increase in combined incidence of lymphosarcomas. The validity of this study was questioned by the FDA statistician due to the extreme mortality rate observed within this study.

The second mouse study used doses of 0.5, 2, and 8 mg/kg. The sponsor reported significant increases in the female mice for both mammary gland adenocarcinomas at the MD&HD and the combined ~~onset~~ **rates (fatal & incidental)** of liver hemangiosarcomas in the HD group. No significant increases in tumor types were reported in the male mice. The FDA statistician reported a significant increase in lung adenocarcinomas in females not reported by the sponsor. **The FDA statistician showed a significant increase in combined incidence of liver hemangioma and hemangiosarcoma in HDf mice. The incidence for each othese liver tumors is higher than the reported historical incidence for this strain.**

Recommendations:
The committee found the study design and dose selection acceptable for both the rat and mouse carcinogenicity studies.

The committee recommended that historical control data for mouse lung adenocarcinomas, and mouse and rat mammary gland adenocarcinomas and adenomas be obtained from the sponsor, and that our statistician conduct a pairwise comparison for those tumors. **The committee also recommended that the combined incidence for liver hemangioma and hemangiosarcoma be analyzed by our statistician.**

Post-meeting addendum:
Pairwise comparisons did not show the lung tumors to be significantly increased and were found to be within the historical control range. The mammary gland tumors were found not to be significantly increased in the rats; however, the mammary gland tumors were siginificantly increased in both the mouse studies. The mammary gland tumors were higher than historical control data in mice and rats. **It should be noted that the 2 tumors noted in the female mice namley lymphosarcoma and lung adenomas and carcinomas, are not included in labelling for the following reasons:**

1. **Lymphosarcoma:** **Finding non-dose dependent,**
Only in female mice in 1 of the 2 carcinogenicity studies,
Not found in male or female rats,
Incidence within historical background data for this strain,
Not statistically significant by FDA statistical analysis.

2. **Lung tumors:** **Finding only in HD female mice but observed in both mouse studies*,**
Not found in male or female rats,
Within historical background data for this strain,
Statistically significant by FDA analysis only in 1 of the 2 carcinogenicity studies.

Although liver hemangiomas and hemangiosarcomas were:
Found only in HD female mice in 1 of the 2 carcinogenicity studies and,
Not found in male or female rats,

It is included in labelling because:
The combined incidence for hemangiomas and hemangiosarcomas was statistically significant by FDA analysis,
The sponsor found the incidence for hemangiosarcoma to be statistically significant in HDf and,

The incidence for each tumor or the incidence combined, was higher than the published historical background data for this strain.

*** statistically significant by the sponsor only in 1 of the 2 studies; FDA analysis also significant only in 1 of the 2 studies as indicated above.**

James Farrelly, Ph.D., HFD-530
Acting Chair, CAC

cc: NDA file
Division file
HFD-120/GFitzgerald/AAtrakchi
CAC files

Statistical Review and Evaluation

DATE:

NDA#: 20-592 MAY 14 1996

APPLICANT: Lilly Research Laboratories

NAME OF DRUG: Zyprex(olanzapine)

DOCUMENTS REVIEWED: Undated Deskcopies of "Books 1/10 - 10/10" and a Submission dated Nov. 27, 1995 containing the diskette.

I. Background

Dr. A. Atrakchi (HFD-120) has requested the Division of Biometrics I for a statistical review of the mouse and the rat studies data as well as an evaluation of the sponsor's findings.

II. The Rat Study * RC/740/report#42

II.a. Design

The product was studied for 104 weeks in male and female Fisher 344 rats. The animals were randomly assigned to groups of 60 each. The male rats received the compound as 0 (controls), .25 mg/kg/day (low 1), 1.0 mg/kg/day (low 2), 2.5 mg/kg/day (medium) and 4.0 mg/kg/day via gavage. The female medium and high doses were raised to 4.0 and 8.0 mg/kg/day respectively after six months. Water was available ad libitum. Terminal sacrifice on surviving animals was performed after 725 days of drug exposure.

II.b. Sponsor's Analyses of the Rat Study

Survival Analysis:

The sponsor presented survival curves for each sex and noted that by Tarone's method there was no evidence of treatment related increase in mortality ($p=.96$ for males, $p=.98$ for females). In fact, he observed a two-tailed p-value of .036 for females suggesting a significant decrease in mortality with dose. The 24-month survival rates for males were 40, 43, 42, 47, and 55% for the control, low1, low2, medium, and high doses. The corresponding survival rates for the females were 65, 57, 58, 62, and 83%.

Tumor Data Analysis:

Peto's survival adjusted trend test was used as a screen to identify individual site/neoplasms of potential concern with a one-tailed p-value of $\leq .05$. The sponsor scaled the doses by 0, 1, 2,

3, and 4. The only significant positive finding was incidental adenocarcinoma of the mammary gland in females where a statistically significant difference between high dose and control and medium dose and control was observed. The associated one-sided p-value was .03. The sponsor also discussed some statistically significant results of negative trends.

II.c. Reviewer's Analyses

This reviewer independently performed analyses on the survival and the tumor data. For survival analysis the methods described in papers of Cox (Regression models and life tables, Journal of the Royal Statistical Society B 34, 187-220, 1972), and of Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika 52, 203-223, 1965) were used. The corresponding computer program was written by Thomas, Breslow, and Gart (Trend and homogeneity analyses of proportions and life table data, Computers and Biomedical Research 10, 373-381, 1977, Version 2.1). The tumor data were analyzed using the methods described in the paper of Peto et al. (Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International Agency for Research against Cancer Monographs, Annex to Supplement, WHO, Geneva, 311-426, 1980) and the method of the exact permutation trend test developed by the Division of Biometrics. The following criteria for the levels of significance ensure a false positive rate of about ten percent for the trend tests of the usual two-species two-sexes studies: Tumors with less than 1.00% occurrence in the control group are considered rare and a positive trend test is statistically significant when it reaches a p-value of $\leq .025$ (one-sided). Higher tumor occurrences in the control group are considered common for these animals and a positive trend is statistically significant when its p-value is less than .005 (one-sided). An approximate permutation trend test is used when fatal and incidental tumors of the kind are combined and have overlapping time intervals. All tests are survival adjusted and ient groups are weighted by the actual dose levels.

There are minor numeric differences between the sponsor's final number of animals surviving and this reviewer's. These seem to be due to animals dying a natural death during the time of Terminal Sacrifice which this reviewer treated the same as if sacrificed. The data on diskette have a code for Terminal Sacrifice. The earliest time associated with this code was day 726. Therefore, all animals dying on or after day 726 were treated as terminally sacrificed.

Survival Analysis

Survival at Terminal Sacrifice ranged from 42 to 58 percent (controls - high dose) among the male rats and from 67 to 85 percent (low1 dose - high dose) among the female rats as can be seen in the Table 1 and Figures 1 and 2. Though the high dose experienced the best survival this trend did not reach significance at the $p = .05$ level in the male rats. The pairwise comparison between control and high dose reached statistical significance ($p = .05$) using Fisher's Exact test, but not when using the more conservative Cox's or Generalized Kruskal/Wallis tests. Among the female rats there was a statistically significant increase in

survival with dose ($.003 \leq p \leq .007$, depending on type of test) The high dose animals experienced significantly better survival than any of the other dose groups ($.001 \leq p \leq .035$). There were no other pairwise comparisons that reached statistical significance (Table2).

Tumor Data Analysis

In either sex there were tumors classified as 'metastatic', rather than fatal or incidental. In consultation with Drs. Atrakchi and Fitzgerald, it was decided that metastatic tumors should be treated as incidental.

Applying the above described methodology, the data did not contain a single positive linear trend among the tumor rates of the male nor of the female rats (Table 3). Therefore, it needs to be determined whether the high dose animals were fully necropsied and whether the study was valid. On page 13 of the Toxicology Report No. 42 the sponsor states that all animals were necropsied. Therefore, the general validity of the study needs to be examined.

II.d. Validity of the Rat Study

Before concluding that the rat study showed no tumorigenic effect of olanzapine, the validity of the study needs to be determined. For this, two questions need to be answered (Haseman, Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol 58, pp 385-392, 1984):

(i) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?

(ii) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

The following are some rules of thumb as suggested by experts in the field: Haseman (Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol 5, pp 66-78, 1985) had found that on the average, approximately 50 % of the animals in the high dose group survived the two-year study. In a personal communication with Dr. Karl Lin of HFD-715, he suggested that 50 % survival of the usual 50 initial animals in the high dose group between weeks 80-90 would be considered as a sufficient number and adequate exposure. Chu, Cueto, and Ward (Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981) proposed that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greather than 50 % survival at one year". From these sources, it appears that the proportions of survival at weeks 52, 80-90, and at two years are of interest in determining the adequacy of exposure and number of animals at risk.

In determining the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD. Chu, Cueto, and Ward (1981) suggest:

(i) "A dose is considered adequate if there is a detectable weight loss of up to 10 % in a dosed group relative to the controls."

(ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

In another paper, Bart, Chu, and Tarone (Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute 62, 957-974, 1979), stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, "Usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is a indication that the treatment has been tested on levels at or approaching the MTD."

The survival of male and female rats at 1, 1 1/2, and 2 years is given below. It is apparent that there remained a sufficient number of animals, especially in the high dose, to believe that late developing tumors had a chance to manifest themselves:

Percent Survival (n = 60/group)

Dose:		Controls	Low 1	Low 2	Medium	High
MALE	52 weeks	98	97	98	100	100
	78 weeks	92	90	87	93	88
	104 weeks	42	52	43	50	58
FEMALE	52 weeks	100	100	98	100	100
	78 weeks	93	95	95	90	98
	104 weeks	67	57	62	62	85

As can be seen from Figures 3 and 4, (sponsor's figures E-1.1 and E-1.2). the compound seems to affect weight gain at the medium and high dose levels. The sponsor reports that weight gain

was up to 13 and 27 percent less than controls among the male rats. For the female rats the medium and high doses were actually raised to observe a more dramatic reduction in weight gain than the approximately 10 percent observed during the first 7 months when these animals had been dosed at 2.5 and 4.0 mg/kg/day respectively. It therefore appears that the sponsor tailored the doses to achieve this criterion for assessing the MTD. The recommendation by Chu, Cueto, and Ward actually looks for a decreased body weight gain of less than or equal to 10 percent. These animals exceded that measure by far and it is no longer clear whether these data are supportive. Clearly, if leaner animals have less tumors, then the lack of any significant positive trends in tumor incidence rates (and in this case, the observed and sometimes significant negative trends in tumor incidence rates) does not necessarily lead to a conclusion that this substance is non-carcinogenic.

The high dose animals did not experience an increase in mortality but an increase in survival. Therefore, this evaluation does not suggest that the high dose may have been close to the MTD. The pharmacologist may want to evaluate possible dose relationships in clinical signs and histopathological effects in her conclusion whether the study was conducted in such a way that tumors could have been detected if the compound causes them.

III.The Mouse Study #HC2627/report #49

III.a. Design

In this study, 240 mice were treated for 82 weeks (females) and 91 weeks (males) with doses of 0, 3, 10, and 30 mg/kg/day of the compound. Terminal sacrifice was performed on all surviving animals.

III.b. Sponsor's Analyses of the Mouse Study

The documents reviewed by this reviewer did not contain the sponsor's results and evaluation of the mouse study, only the data on diskette. In the interest of time, this reviewer did not request the corresponding documentation of the sponsor but only performed her own analyses based on the data on diskette.

III.c. Reviewer's Analyses

The same statistical methods and approaches as discussed for the rat study were applied here.

Survial Analysis

For the male mice there was an extraordinary effect on survival for the medium and the high dose groups (Table 4, Figure 5). The probablity associated with the trend test was .0000 regardless of the statistical test method. Only the control and low dose groups did not differ from each other in the pairwise comparisons. The female mice experienced a similar, though

not as pronounced fate (Table 4, Figure 6). The trend tests were significant at p=.006 or less, depending on the type of adjustment used (Table 5). The high dose animals died significantly earlier than the controls ($p \leq .003$); other pairwise comparisons reflected the general observed trend in mortality with increasing dose but did not sustain statisical significance with Cox's or Kruskall/Wallis exact inverse or conservative tests.

Tumor Data Analysis

The male mice showed no statistically increasing tumor trends with dose. Among the females, adenocarcinoma of the lung showed a posi ive linear trend which was significant at p=.0259, just above the criterion for significance for rare tumors ($p \leq .025$). One could therefore conclude that the female mouse study was valid. However, for the male mice, the lack of any significant tumor findings necessitated the evaluation of its validity. I assumed that all animals were completely necropsied.

III.d. Validity of the Male Mouse Study

Using the same criteria as outlined for the rat study, we observe that at the end of the mouse study the controls still had adequate survival (70 %) whereas the medium and high doses had already dropped under 50 % (high dose: 23 %). This study was terminated at the time (weeks 80-90) when the second interim survival would have been assessed. Survival at one year was greater than 50 %, but it seems clear that there were not enough animals living long enough for late developing tumors to manifest themselves.

The weight gain data was not analyzed by this reviewer. It is still recommended that clinical signs or severe histopathologic toxic effects are evaluated, but with the extreme effect on mortality, the validity of this study seems to be highly questionable.

IV. Summary and Conclusions

This submission has been difficult to analyze because of inconsistencies in the data. This Division is working on developing programs which check the data for internal consistencies as well as on providing more detailed instructions for Industry to follow when using the Studies data format.

The Rat Study

As noted above there were small numeric differences in survival rates due to differences in classification of animals as terminally sacrificed or as dying naturally. These differences do not affect interpretation of results. Also, the sponsor noted a significant difference in incidental adenocarcinomas of the mammary gland between the controls and the medium dose, and

between the controls and the high dose female rats. The observed p-value of .03 does not come close to the level of statistical significance for common tumors ($p \leq .005$) used if one controls for the overall false positive rate.

As there were no statistically significant increases with dose in tumor incidence rates, this reviewer evaluated the validity of the study. Survival was better among the high dose animals than among the controls, to a significant degree among the female rats. Therefore, a sufficient number of animals was available for late developing tumors to occur. The assessment as to whether the high dose was close to the MTD proved more difficult. It is not clear to this reviewer whether mean body weight gain was reduced to such an extent as to affect potential tumor development. The presence of significant negative trends in some tumors may support this concern, especially as the compound did not have a negative effect on survival. It remains for the pharmacologist to decide whether changes in clinical signs and histopathological effects support the notion that the high dose level was close to the MTD.

The Mouse Study

In the interest of time, this reviewer did not review any documentation by the sponsor, but analyzed only the data provided on diskette.

The data showed a very strong and highly significant trend in mortality with increasing dose, especially for the male mice. Only the female data showed a, although borderline, statistically significant trend in adenocarcinomas of the lung. For the male data, on the other hand, no statistically significant trends in tumor incidence rates (mortality adjusted) were observed. When the validity of the male study was investigated, it appeared that the early and strong mortality experience, especially in the high dose group, did not allow the animals to live long enough to manifest late developing tumors. The body weight data were not analyzed by this reviewer. Another measure of assessing the high dose as being close to the MTD failed, inasmuch as the increase in mortality with dose was not just numeric but highly significant. The evaluation of clinical signs or severe histoplathologic toxic effects is left to the expertise of the pharmocologist.

Roswitha E. Kelly
Mathematical Statistician

Concur:

Todd Sahlroot, Ph. D.
Acting Team Leader

5/14/96
George Chi, Ph.D.
Director, DB I

cc:Archival NDA 20-592, Zyprex (olanzapine), Lilly

HFD-120/Division File
HFD-120/Dr. Atrakchi
✓ HFD-120/Dr. Fitzgerald
HFD-344/Dr. Lisook
HFD-710/Chron.
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/Ms. Kelly

HFD-710/RKELLY/04/30/96/wp-zyprex.rev

Table 1
INTERCURRENT MORTALITY RATES

MALE RATS

Days	0	.25	mg/kg/day 1.0	2.5	4.0
0 -365	1/60 (2%)	2/60 (3%)	1/60 (2%)	0/60 (0%)	0/60 (0%)
366-548	4/59 (8%)	4/58 (10%)	7/59 (13%)	4/60 (7%)	7/60 (12%)
549-654	13/55 (30%)	11/54 (28%)	9/52 (28%)	10/56 (23%)	8/53 (25%)
655-725	17/42 (58%)	12/43 (48%)	17/43 (57%)	16/46 (50%)	10/45 (42%)
Term. Sac.	25/60 (42%)	31/60 (52%)	26/60 (43%)	30/60 (50%)	35/60 (58%)

FEMALE RATS

Days	0	.25	mg/kg/day 1.0	4.0	8.0
0 -365	0/60 (0%)	0/60 (0%)	1/60 (2%)	0/60 (0%)	0/60 (0%)
366-548	4/60 (7%)	3/60 (5%)	2/59 (5%)	6/60 (10%)	1/60 (2%)
549-654	9/56 (22%)	12/57 (25%)	5/57 (13%)	7/54 (22%)	6/59 (12%)
655-725	7/47 (33%)	11/45 (43%)	15/52 (38%)	10/47 (38%)	2/53 (23%)
Term. Sac.	40/60 (67%)	34/60 (57%)	37/60 (62%)	37/60 (62%)	51/60 (85%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

Table 2

Results of Intercurrent Mortality Analyes

Male Rats

Groups Compared	Direction	Two-tailed P-Value of Test	
		Cox	Kruskal/Wallis
C,L1,L2,M,H	neg	.113	.139
C,L1	neg	.418	.434
C,L2	neg	.859	.761
C,M	neg	.349	.261
C,H	neg	.114	.130
L1,L2	pos	.588	.624
L1,M	pos	.966	.834
L1,H	neg	.550	.493
L2,M	neg	.554	.474
L2,H	neg	.186	.213
M,H	neg	.544	.582

Female Rats

Groups Compared	Direction	Two-tailed P-Value of Test	
		Cox	Kruskal/Wallis
C,L1,L2,M,H	neg	.005**	.007**
C,L1	pos	.366	.331
C,L2	pos	.821	.848
C,M	pos	.712	.637
C,H	neg	.035*	.025*
L1,L2	neg	.582	.410
L1,M	neg	.725	.673
L1,H	neg	.002**	.001**
L2,M	pos	.993	.756
L2,H	neg	.010**	.010**
M,H	neg	.008**	.005**

Interpretation of Direction of Trend: Trend is labeled positive when survival is poorer (i.e. mortality is greater) in the comparison (right-hand) group than in the reference (left-hand) group; the trend is labeled negative when survival is better in the comparison group than in the reference grcup.

Table 3: MALE Rats, p-values for positive trend

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L1	L2	M	H
[illegible]NAL	ADRENOCORTICAL ADENOMA	S	0.6240	0.62215	1	1	1	0	1
[illegible]AL	PHEOCHROMOCYTOMA	S	0.9995	0.99905	6	10	6	5	0
[illegible]AL	PHEOCHROMOCYTOMA, MALIGNANT	S	0.4743	0.44875	1	0	1	0	1
[illegible]	OSTEOSARCOMA	S	0.2384	0.06885	0	0	0	0	1
CEREBRUM	GLIOMA, MALIGNANT	S	0.8299	0.82345	0	1	0	0	0
JEJUNUM	ADENOCARCINOMA	M	0.8465	0.84935	1	0	1	0	0
JEJUNUM	ADENOMA	S	0.3529	0.21375	0	0	0	1	0
JEJUNUM	LEIOMYOSARCOMA	S	0.5972	0.63930	0	0	1	0	0
KIDNEY	LIPOMA	S	0.1389	0.03005	0	0	0	0	1
KIDNEY	RENAL CELL CARCINOMA	M	0.9878	0.94595	2	1	0	0	0
KIDNEY	TRANSITIONAL CELL CARCINOMA	S	0.6191	0.67210	0	0	1	0	0
LIVER	ACINAR CELL CARCINOMA	S	1.0000	0.84135	1	0	0	0	0
LIVER	HEPATOCELLULAR ADENOMA	S	0.6605	0.65680	1	1	0	2	0
LIVER	HEPATOCELLULAR CARCINOMA	S	0.4208	0.42705	0	1	1	0	1
LIVER	SARCOMA, UNDIFFERENTIATED	S	0.3611	0.21185	0	0	0	1	0
LUNG	ALVEOLAR/BRONCHIOLAR ADENOM	S	0.2381	0.06865	0	0	0	0	1
LUNG	C-CELL CARCINOMA	S	1.0000	0.82340	1	0	0	0	0
LUNG	OSTEOMA	S	0.2381	0.06865	0	0	0	0	1
LUNG	RENAL CELL CARCINOMA	S	1.0000	0.87240	1	0	0	0	0
LUNG	SARCOMA, UNDIFFERENTIATED	S	0.3611	0.21185	0	0	0	1	0
LUNG	SQUAMOUS CELL CARCINOMA	S	0.4402	0.29540	0	0	0	1	0
LYMPH NODE	RENAL CELL CARCINOMA	S	1.0000	0.87240	1	0	0	0	0
LYMPH NODE	SERTOLI CELL TUMOR, MALIGNA	S	0.6923	0.68960	0	0	1	0	0
MAMMARY GLAND	ADENOCARCINOMA	S	0.3611	0.21185	0	0	0	1	0
MAMMARY GLAND	FIBROADENOMA	M	0.6825	0.65065	1	0	0	1	0
PANCREAS	ACINAR CELL CARCINOMA	S	1.0000	0.85660	1	0	0	0	0
PANCREAS	ISLET CELL ADENOMA	S	0.5597	0.55790	4	7	2	6	5
PANCREAS	RENAL CELL CARCINOMA	S	1.0000	0.87240	1	0	0	0	0
PARATHYROID	ADENOMA	S	0.6191	0.67210	0	0	1	0	0
PERITONEUM	HEMANGIOSARCOMA	S	0.7807	0.82200	0	1	1	0	0
PERITONEUM	MESOTHELIOMA, BENIGN	S	0.5340	0.47895	0	0	1	1	0
PERITONEUM	MESOTHELIOMA, MALIGNANT	S	0.4444	0.29980	0	0	0	1	0
PERITONEUM	RENAL CELL CARCINOMA	S	1.0000	0.87240	1	0	0	0	0
PITUITARY	ADENOCARCINOMA	M	0.9684	0.94625	1	2	0	0	0
PITUITARY	ADENOMA	M	0.9308	0.92915	32	26	38	32	26
[illegible]	SQUAMOUS CELL CARCINOMA	S	0.3611	0.21185	0	0	0	1	0
[illegible]IAL GLAND	ADENOMA	S	0.9070	0.89990	1	1	3	0	0
PROSTATE	ADENOCARCINOMA	S	1.0000	0.86205	1	0	0	0	0
PROSTATE	MESOTHELIOMA, MALIGNANT	S	0.3611	0.21185	0	0	0	1	0
SEMINAL VESICLE	RENAL CELL CARCINOMA	S	1.0000	0.87240	1	0	0	0	0
SKELETAL MUSCLE	SARCOMA, UNDIFFERENTIATED	S	0.3611	0.21185	0	0	0	1	0
SKIN	BASAL CELL EPITHELIOMA	S	0.3175	0.26480	1	0	0	0	1
SKIN	FIBROMA	S	0.8392	0.83500	2	1	2	0	1
SKIN	FIBROSARCOMA	S	1.0000	0.86205	1	0	0	0	0
SKIN	KERATOACANTHOMA	S	0.2381	0.06865	0	0	0	0	1
SKIN	LIPOMA	S	0.7119	0.71655	0	2	2	0	1
SKIN	PAPILLOMA	S	0.8799	0.87515	1	2	0	1	0
SKIN	SQUAMOUS CELL CARCINOMA	S	0.1389	0.03005	0	0	0	0	1
SPINAL CORD	ASTROCYTOMA, MALIGNANT	S	0.2381	0.06865	0	0	0	0	1
SPLEEN	RENAL CELL CARCINOMA	S	1.0000	0.87240	1	0	0	0	0
STOMACH	ADENOCARCINOMA	S	0.8299	0.82345	0	1	0	0	0
TESTIS	INTERSTITIAL CELL TUMOR	S	1.0000	1.00000	26	37	27	12	12
TESTIS	MESOTHELIOMA, MALIGNANT	S	0.3611	0.21185	0	0	0	1	0
TESTIS	SERTOLI CELL TUMOR, MALIGNA	S	0.5972	0.64020	0	0	1	0	0
THYROID	C-CELL ADENOMA	S	0.9251	0.92105	8	6	4	2	5
THYROID	C-CELL CARCINOMA	M	1.0000	0.93355	2	0	0	0	0
THYROID	FOLLICULAR CELL ADENOMA	S	0.8299	0.82345	0	1	0	0	0
WHOLE ANIMAL	HISTIOCYTIC SARCOMA	S	.	.	2	0	0	0	0
WHOLE ANIMAL	KERATOACANTHOMA	S	0.6398	0.67505	0	0	1	0	0
WHOLE ANIMAL	LYMPHOSARCOMA	M	0.4194	0.41870	0	2	1	5	0
WHOLE ANIMAL	MONONUCLEAR CELL LEUKEMIA	M	.	.	23	24	25	23	25
WHOLE ANIMAL	SARCOMA, UNDIFFERENTIATED	S	.	.	0	0	0	1	0
ZYMBAL'S GLAND	SQUAMOUS CELL CARCINOMA	S	.	.	2	0	0	0	0

Table 3: FEMALE Rats, p-values for positive trend
cont'd

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L1	L2	M	H
ADRENAL	ADRENOCORTICAL ADENOMA	S	0.2563	0.06170	0	0	0	0	1
ADRENAL	HEMANGIOSARCOMA	S	0.2563	0.06170	0	0	0	0	1
ADRENAL	PHEOCHROMOCYTOMA	S	0.6699	0.67315	2	4	1	1	2
ADRENAL	PHEOCHROMOCYTOMA, MALIGNANT	S	0.1605	0.09565	0	0	0	1	1
BONE	OSTEOSARCOMA	S	0.6268	0.73000	0	0	1	0	0
BRAIN STEM	ADENOCARCINOMA	S	1.0000	0.82525	1	0	0	0	0
BRAIN STEM	ASTROCYTOMA, MALIGNANT	S	0.8007	0.78745	0	1	0	0	0
CEREBRUM	GRANULAR CELL TUMOR, BENIGN	S	0.7692	0.74660	0	1	0	0	0
CERVIX	SARCOMA, UNDIFFERENTIATED	S	0.7987	0.78660	0	1	0	0	0
CLITORAL GLAND	ADENOMA	M	0.9498	0.93620	3	4	0	0	1
DIAPHRAGM	ALVEOLAR/BRONCHIOLAR CARCIN	S	0.8444	0.75460	0	1	0	0	0
EAR	NEUROFIBROMA	S	1.0000	0.77365	1	0	0	0	0
EAR	NEUROFIBROSARCOMA	S	1.0000	0.90765	2	0	0	0	0
HEART	NEURILEMMOMA, BENIGN	S	1.0000	0.82525	1	0	0	0	0
JEJUNUM	SARCOMA, UNDIFFERENTIATED	S	0.6179	0.71430	0	0	1	0	0
KIDNEY	LEIOMYOSARCOMA	S	0.1538	0.02075	0	0	0	0	1
KIDNEY	LIPOMA	S	0.2667	0.12070	0	0	0	1	0
LIVER	ADENOCARCINOMA	S	0.2667	0.12070	0	0	0	1	0
LIVER	HEMANGIOSARCOMA	S	0.2563	0.06170	0	0	0	0	1
LIVER	HEPATOCELLULAR ADENOMA	S	0.8629	0.86585	1	0	1	0	0
LUNG	ADENOCARCINOMA	S	0.4422	0.38110	0	0	0	1	0
LUNG	ALVEOLAR/BRONCHIOLAR ADENOM	S	0.7806	0.78635	0	0	3	1	0
LUNG	ALVEOLAR/BRONCHIOLAR CARCIN	M	0.7801	0.84610	0	1	1	0	0
LUNG	NEUROFIBROSARCOMA	S	1.0000	0.82525	1	0	0	0	0
LUNG	PHEOCHROMOCYTOMA, MALIGNANT	S	0.1605	0.09565	0	0	0	1	1
MAMMARY GLAND	ADENOCARCINOMA	M	0.0349	0.03065	2	3	2	9	7
MAMMARY GLAND	ADENOMA	S	0.0685	0.05635	2	0	1	5	3
MAMMARY GLAND	CARCINOSARCOMA	S	0.6281	0.73435	0	0	1	0	0
MAMMARY GLAND	FIBROADENOMA	M	0.9573	0.95475	13	15	16	7	11
OVARY	ALVEOLAR/BRONCHIOLAR CARCIN	S	0.8444	0.75460	0	1	0	0	0
PANCREAS	ISLET CELL ADENOMA	S	0.6143	0.61740	2	2	1	1	2
PERITONEUM	MESOTHELIOMA, MALIGNANT	S	0.6000	0.70690	0	0	1	0	0
PITUITARY	ADENOCARCINOMA	M	0.9038	0.90410	1	2	1	1	0
PITUITARY	ADENOMA	M	1.0000	1.00000	39	36	37	38	19
[illegible]ELETAL MUSCLE	HEMANGIOSARCOMA	S	0.2563	0.06170	0	0	0	0	1
[illegible]ELETAL MUSCLE	OSTEOSARCOMA	S	0.6000	0.62435	0	0	1	0	0
[illegible]ELETAL MUSCLE	RHABDOMYOSARCOMA	S	0.4170	0.35320	0	0	0	1	0
SKIN	BASAL CELL EPITHELIOMA	S	0.7990	0.80460	0	1	0	0	0
SKIN	FIBROMA	S	0.6150	0.65320	0	1	0	1	0
SKIN	FIBROSARCOMA	S	0.2563	0.06170	0	0	0	0	1
SKIN	KERATOACANTHOMA	M	0.7785	0.84360	0	1	1	0	0
SKIN	LIPOMA	S	0.9440	0.94220	2	0	2	0	0
SKIN	PAPILLOMA	S	0.9604	0.89825	1	1	0	0	0
SKIN	SQUAMOUS CELL CARCINOMA	S	0.4167	0.34965	0	0	0	1	0
THYMUS	THYMOMA, BENIGN	S	0.2563	0.06170	0	0	0	0	1
THYROID	C-CELL ADENOMA	S	0.9710	0.96690	10	6	5	6	3
TONGUE	PAPILLOMA	S	0.2563	0.06170	0	0	0	0	1
UTERUS	ADENOCARCINOMA	S	1.0000	0.81350	1	0	0	0	0
UTERUS	ENDOMETRIAL STROMAL SARCOMA	S	0.9197	0.90650	1	1	1	0	0
UTERUS	ENDOMETRIAL STROMAL TUMOR,	S	0.9984	0.99685	7	11	4	5	1
UTERUS	LEIOMYOSARCOMA	M	0.4835	0.49245	0	2	0	0	1
VAGINA	LEIOMYOMA	S	1.0000	0.81635	1	0	0	0	0
VESSEL	ALVEOLAR/BRONCHIOLAR CARCIN	S	0.6281	0.73435	0	0	1	0	0
WHOLE ANIMAL	HISTIOCYTIC SARCOMA	S	0.8023	0.79020	0	1	0	0	0
WHOLE ANIMAL	LYMPHOSARCOMA	S	0.9104	0.91030	1	2	2	1	0
WHOLE ANIMAL	MONONUCLEAR CELL LEUKEMIA	M	1.0000	0.99990	19	16	15	7	5
WHOLE ANIMAL	SQUAMOUS CELL CARCINOMA	S	1.0000	0.81245	1	0	0	0	0
ZYMBAL'S GLAND	ADENOMA	S	0.4422	0.38110	0	0	0	1	0
ZYMBAL'S GLAND	SQUAMOUS CELL CARCINOMA	M	0.5903	0.62875	0	1	0	1	0

Figure 1 : Survival - Male Rats

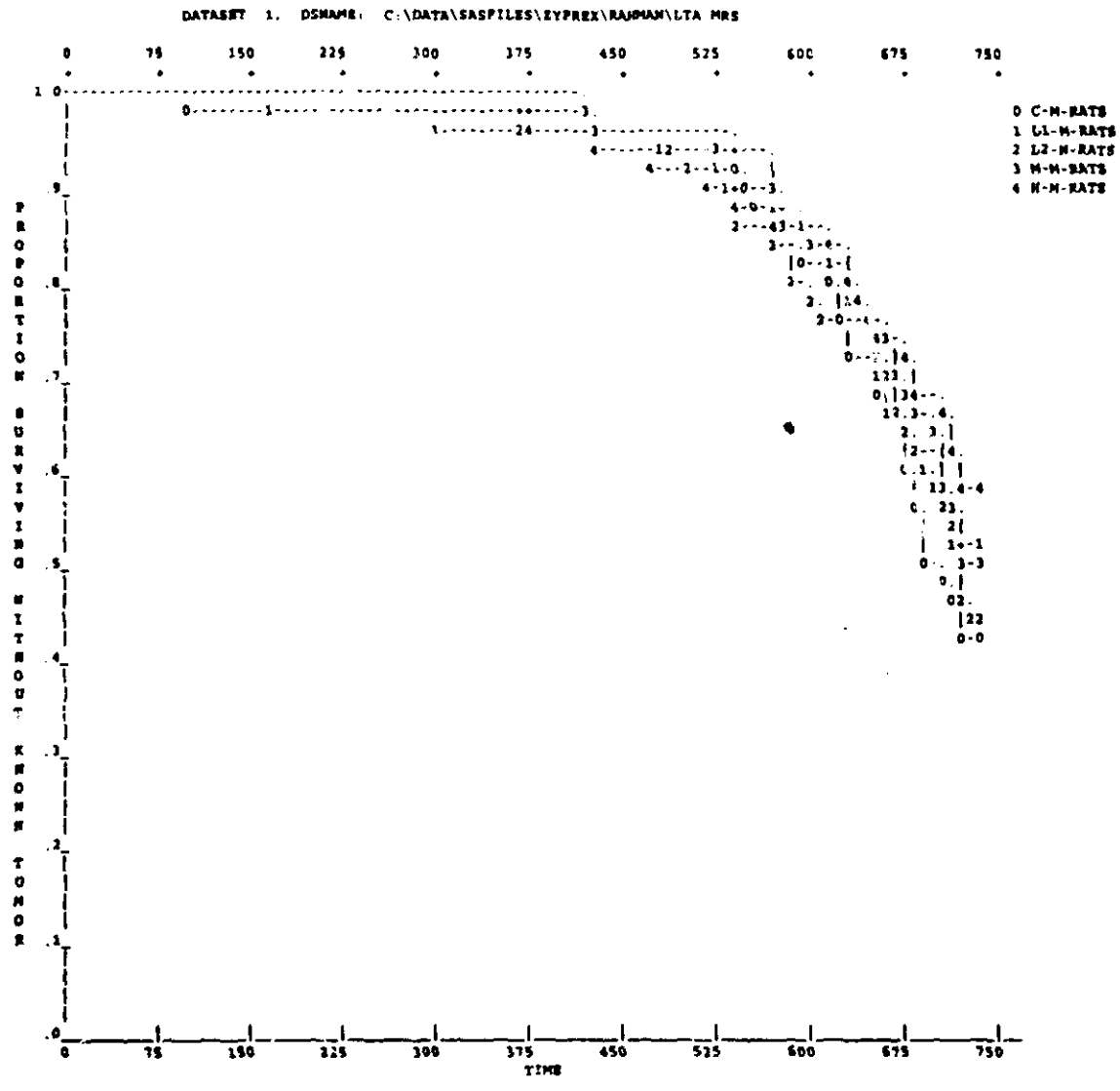


Figure 2: Survival female rats

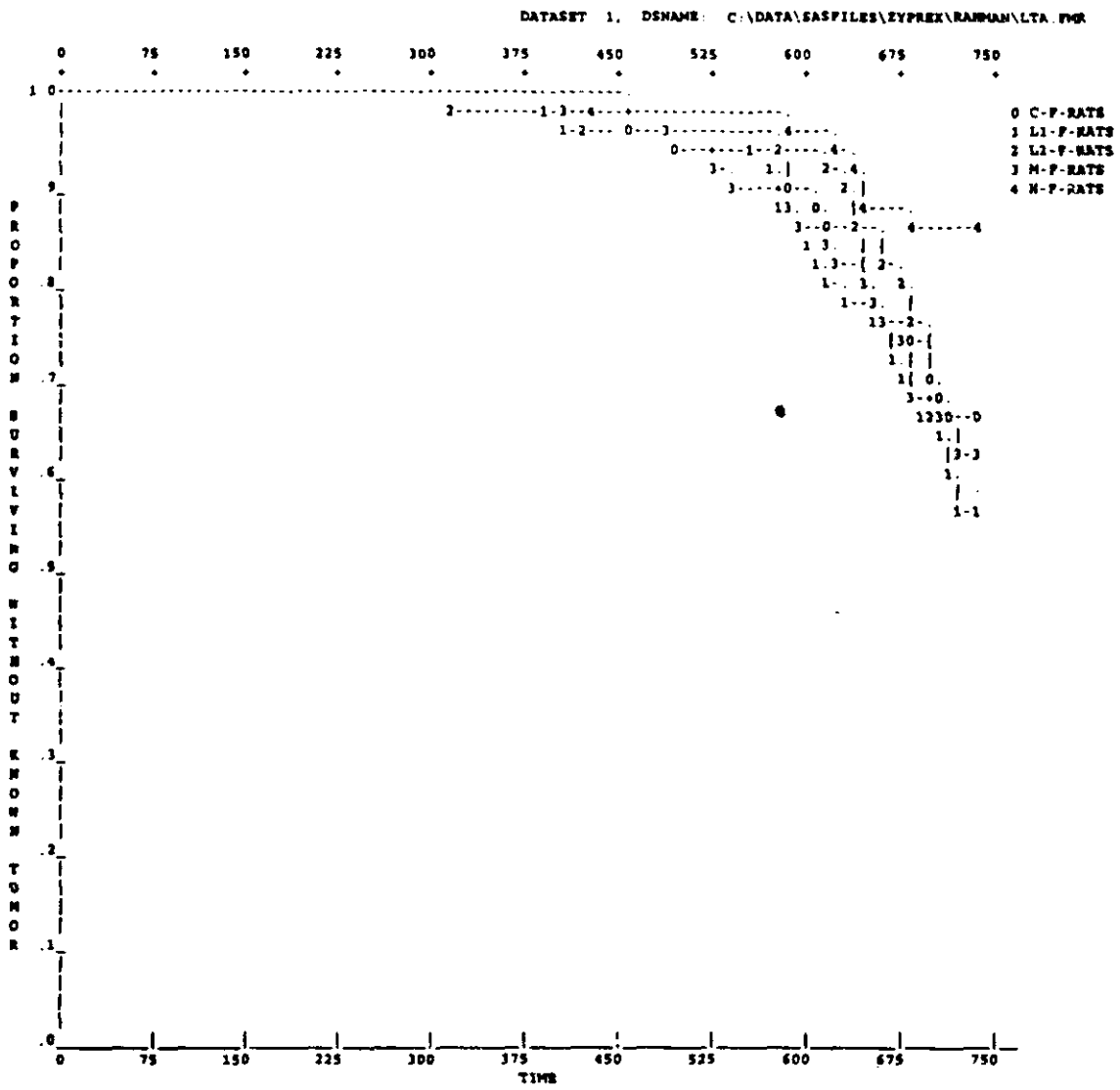


Figure 3 :
(Figure E-1.1) Mean Body Weight.

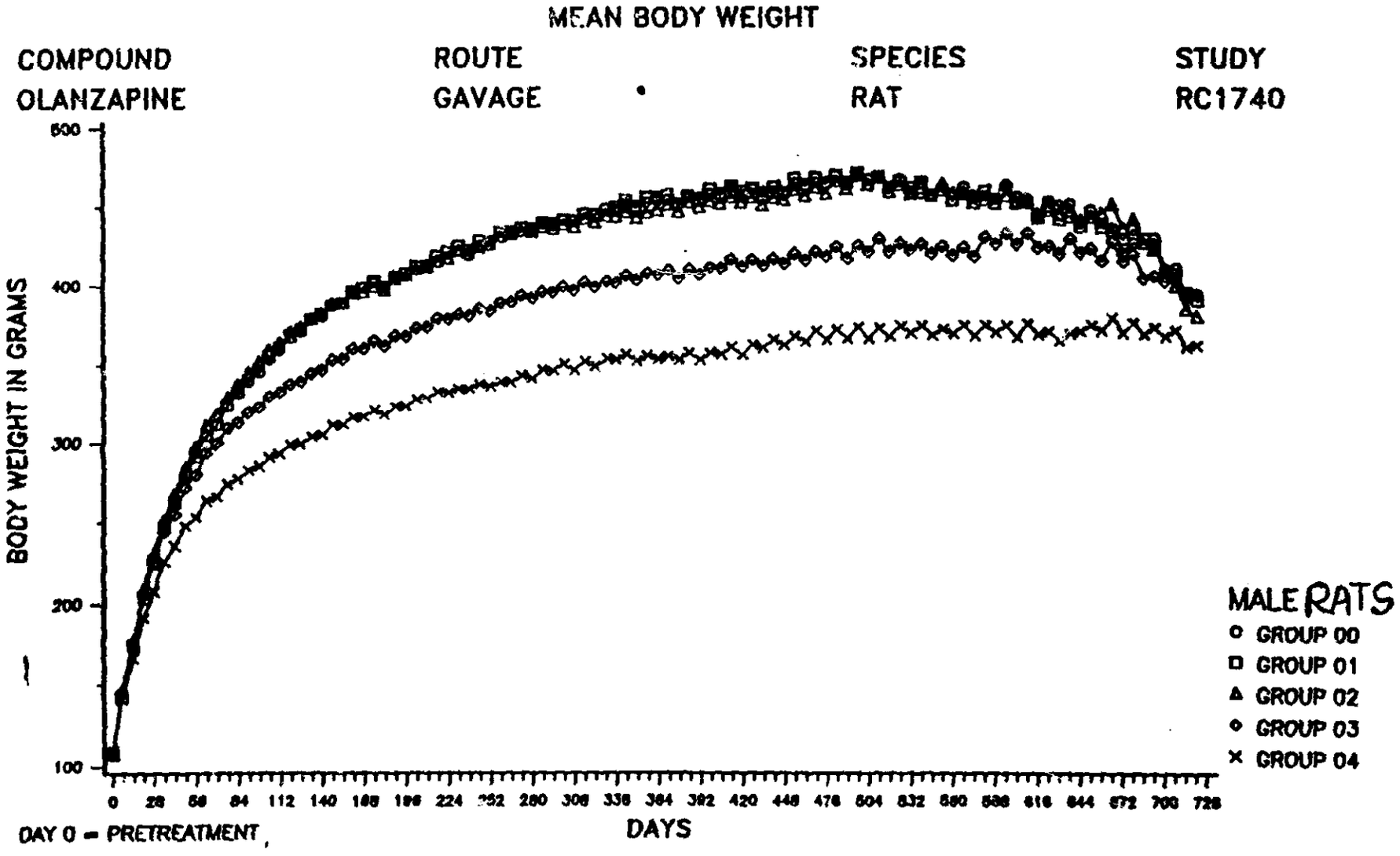


Figure 4:
(Figure E-1.2) Mean Body Weight.

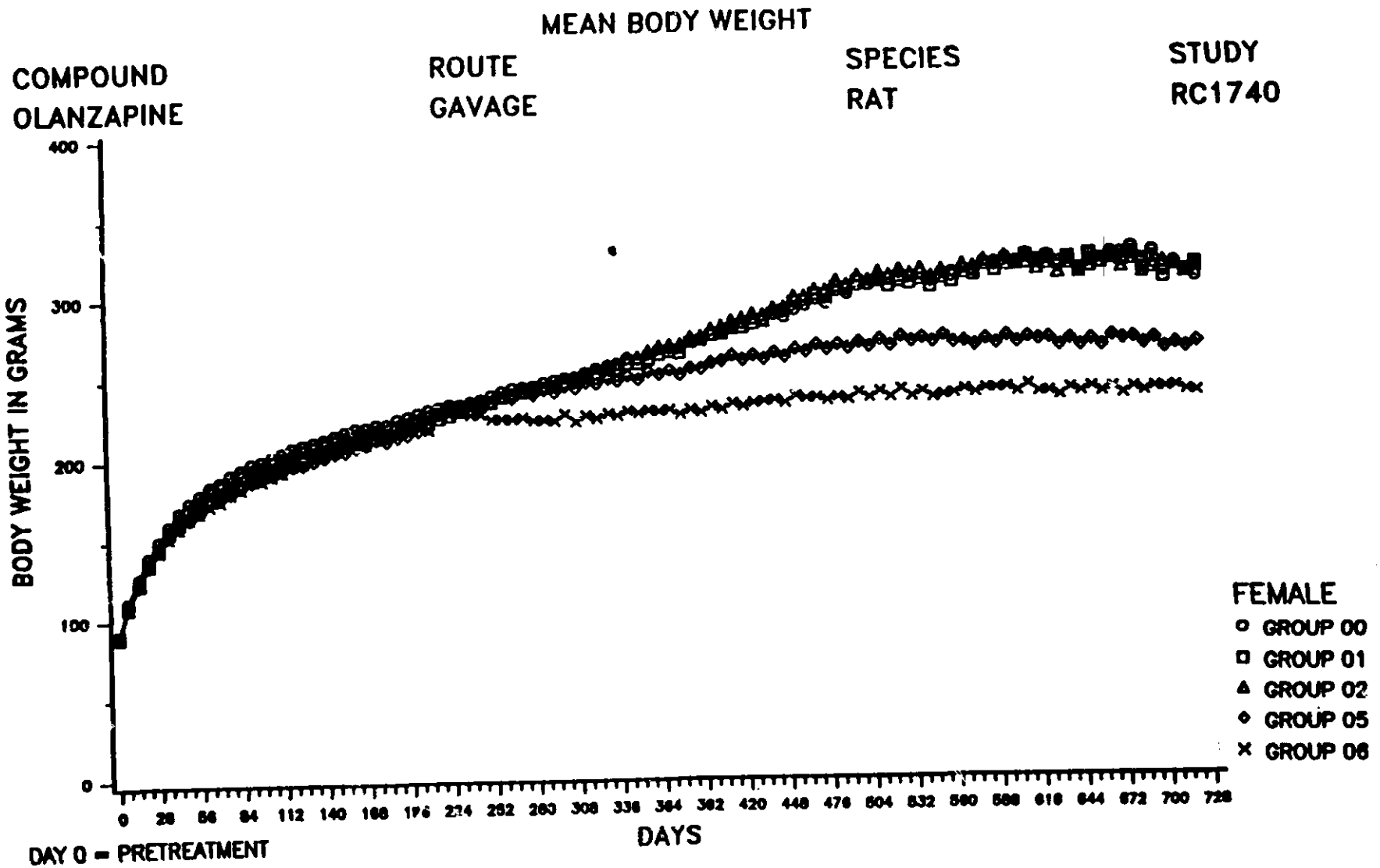


Table 4
INTERCURRENT MORTALITY RATES

MALE MICE

Days	0 mg/kg/day	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
0 -365	5/60 (8%)	3/60 (5%)	14/60 (23%)	26/60 (43%)
366-548	10/55 (25%)	15/57 (30%)	17/46 (52%)	18/34 (73%)
549-574	3/45 (30%)	2/42 (33%)	4/29 (58%)	2/16 (77%)
Term. Sac.	42/60 (70%)	40/60 (67%)	25/60 (42%)	14/60 (23%)

FEMALE MICE

Days	0 mg/kg/day	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
0 -365	4/60 (7%)	5/60 (8%)	7/60 (12%)	6/60 (10%)
366-548	8/56 (20%)	17/55 (37%)	13/53 (33%)	21/54 (45%)
549-637	13/48 (42%)	8/38 (50%)	15/40 (58%)	14/33 (68%)
Term. Sac.	35/60 (58%)	30/60 (50%)	25/60 (42%)	19/60 (32%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

Table 5

Results of Intercurrent Mortality Analyes

Male Mice

Groups Compared	Direction	Two-tailed P-Value of Test	
		Cox	Kruskal/Wallis
C,L,M,H	pos	.000**	.000**
C,L	pos	.819	.704
C,M	pos	.002**	.001**
C,H	pos	.000**	.000**
L,M	pos	.005**	.002**
L,H	pos	.000**	.000**
M,H	pos	.010**	.004**

Female Mice

Groups Compared	Direction	Two-tailed P-Value of Test	
		Cox	Kruskal/Wallis
C,L,M,H	pos	.003**	.006**
C,L	pos	.327	.219
C,M	pos	.083	.068
C,H	pos	.003**	.003**
L,M	pos	.594	.662
L,H	pos	.096	.139
M,H	pos	.267	.242

Interpretation of Direction of Trend: Trend is labeled positive when survival is poorer (i.e. mortality is greater) in the comparison (right-hand) group than in the reference (left-hand) group; the trend is labeled negative when survival is better in the comparison group than in the reference group.

Table 6: MALE MICE, p-values for Positive Trend

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
ADRENAL	ADRENOCORTICAL ADENOMA	S	0.2221	0.22020	4	1	2	2
ADRENAL	PHEOCHROMOCYTOMA	S	0.5143	0.55950	0	1	2	0
DIAPHRAGM	HEMANGIOSARCOMA	S	0.8333	0.78915	0	1	0	0
DIAPHRAGM	HEPATOCELLULAR CARCINOMA	S	0.6529	0.64895	0	1	0	0
HARDERIAN GLAND	ADENOCARCINOMA	S	1.0000	0.76040	1	0	0	0
HARDERIAN GLAND	ADENOMA	S	0.9496	0.92445	4	5	1	0
LIVER	HEMANGIOSARCOMA	S	0.6945	0.68565	0	1	0	0
LIVER	HEPATOCELLULAR ADENOMA	S	0.4768	0.49105	2	4	3	1
LIVER	HEPATOCELLULAR CARCINOMA	M	0.6123	0.62555	1	3	3	0
LUNG	ALVEOLAR/BRONCHIOLAR ADENOM	S	0.9734	0.96280	8	6	6	0
LUNG	ALVEOLAR/BRONCHIOLAR CARCIN	S	0.6177	0.66115	1	1	1	0
LUNG	HEMANGIOSARCOMA	S	0.8333	0.78915	0	1	0	0
SEMINAL VESICLE	SARCOMA, UNDIFFERENTIATED	S	0.1157	0.00550	0	0	0	1
SKIN	LIPOMA	S	1.0000	0.76040	1	0	0	0
SKIN	OSTEOGENIC SARCOMA	S	0.7264	0.71835	0	1	0	0
SKIN	SARCOMA, UNDIFFERENTIATED	S	1.0000	0.77070	1	0	0	0
STOMACH	ADENOMA	S	0.1157	0.00550	0	0	0	1
TESTIS	INTERSTITIAL CELL TUMOR	S	0.6529	0.64895	0	1	0	0
THYROID	FOLLICULAR CELL ADENOMA	S	0.3223	0.35340	0	0	1	0
TONGUE	SQUAMOUS CELL CARCINOMA	S	0.8333	0.78915	0	1	0	0
WHOLE ANIMAL	LYMPHOSARCOMA	M	0.7613	0.76575	4	5	0	1
WHOLE ANIMAL	PLASMA CELL MYELOMA	S	1.0000	0.77715	1	0	0	0
ZYMBAL'S GLAND	SQUAMOUS CELL CARCINOMA	S	1.0000	0.76040	1	0	0	0

Table 6 con'd: FEMALE MICE, p-values for Positive Trend

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
ADRENAL	ADRENOCORTICAL ADENOMA	S	0.9008	0.83140	1	1	0	0
ADRENAL	PHEOCHROMOCYTOMA	S	0.4345	0.45635	0	0	1	0
DIAPHRAGM	FIBROSARCOMA	S	0.5762	0.61785	0	0	1	0
HARDERIAN GLAND	ADENOMA	S	0.6320	0.64360	2	2	2	1
KIDNEY	FIBROSARCOMA	S	0.5762	0.61785	0	0	1	0
KIDNEY	GRANULOSA-THECA TUMOR, MALI	S	0.3559	0.09660	0	0	0	1
LIVER	GRANULOSA-THECA TUMOR, MALI	S	0.3559	0.09660	0	0	0	1
LIVER	HEMANGIOSARCOMA	S	0.3559	0.09660	0	0	0	1
LIVER	HEPATOCELLULAR ADENOMA	S	1.0000	0.79245	1	0	0	0
LUNG	ADENOCARCINOMA	S	0.0259	0.01705	0	1	3	4
LUNG	ALVEOLAR/BRONCHIOLAR ADENOM	S	0.9036	0.89910	5	10	7	3
LUNG	ALVEOLAR/BRONCHIOLAR CARCIN	S	0.9121	0.90490	1	5	1	0
LUNG	BASAL CELL CARCINOMA	S	0.7143	0.68915	0	0	1	0
LUNG	SARCOMA, UNDIFFERENTIATED	S	0.7143	0.68915	0	0	1	0
LUNG	SQUAMOUS CELL CARCINOMA	S	0.8644	0.80520	0	1	0	0
LYMPH NODE	FIBROSARCOMA	S	0.3559	0.09660	0	0	0	1
LYMPH NODE	SARCOMA, UNDIFFERENTIATED	S	1.0000	0.79245	1	0	0	0
MAMMARY GLAND	ADENOCARCINOMA	M	0.0282	0.01850	0	2	4	4
MAMMARY GLAND	ADENOMA	S	0.0336	0.00270	0	0	0	2
OVARY	GRANULOSA-THECA TUMOR, MALI	S	0.2197	0.03755	0	0	0	1
OVARY	PAPILLARY CYSTADENOMA	S	0.2475	0.24545	1	0	2	1
PANCREAS	LEIOMYOSARCOMA	S	0.4345	0.45635	0	0	1	0
PERITONEUM	FIBROSARCOMA	S	0.5762	0.61785	0	0	1	0

Table 6 con'd

FEMALE MICE

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
PERITONEUM	LEIOMYOSARCOMA	S	0.4345	0.45635	0	0	1	0
PERITONEUM	SARCOMA, UNDIFFERENTIATED	S	1.0000	0.79245	1	0	0	0
PITUITARY	ADENOMA	S	0.2000	0.02980	0	0	0	1
SKELETAL MUSCLE	SARCOMA, UNDIFFERENTIATED	S	1.0000	0.79245	1	0	0	0
SKIN	BASAL CELL CARCINOMA	S	0.1266	0.07200	0	0	1	1
SKIN	FIBROMA	S	0.6828	0.70455	0	1	0	0
SKIN	FIBROSARCOMA	S	0.1704	0.11555	0	0	1	1
SKIN	HEMANGIOSARCOMA	S	0.4123	0.44185	0	0	1	0
SKIN	KERATOACANTHOMA	S	0.4345	0.45635	0	0	1	0
SKIN	MIXED TUMOR, MALIGNANT	S	1.0000	0.81740	1	0	0	0
SKIN	SARCOMA, UNDIFFERENTIATED	S	0.8452	0.83495	2	0	1	0
SKIN	SQUAMOUS CELL CARCINOMA	M	0.3554	0.34450	0	2	0	1
SPLEEN	HEMANGIOSARCOMA	M	0.3538	0.23340	1	0	0	1
URINARY BLADDER	TRANSITIONAL CELL CARCINOMA	S	0.5232	0.61530	0	1	1	0
UTERUS	CHORIOCARCINOMA	S	1.0000	0.79245	1	0	0	0
UTERUS	ENDOMETRIAL STROMAL TUMOR,	S	0.2766	0.28370	0	1	2	1
UTERUS	FIBROMA	S	0.6828	0.70455	0	1	0	0
UTERUS	HEMANGIOMA	S	0.2199	0.15660	0	1	0	1
UTERUS	LEIOMYOMA	S	0.9570	0.88175	1	1	0	0
UTER	LEIOMYOSARCOMA	S	0.6819	0.69160	1	0	1	0
WHO IMAL	FIBROUS HISTIOCYTOMA, MALIG	S	1.0000	0.78665	1	0	0	0
WHO IMAL	LYMPHOSARCOMA	M	0.0492	0.04335	4	10	9	10

Figure 5: Survival - Male Mice

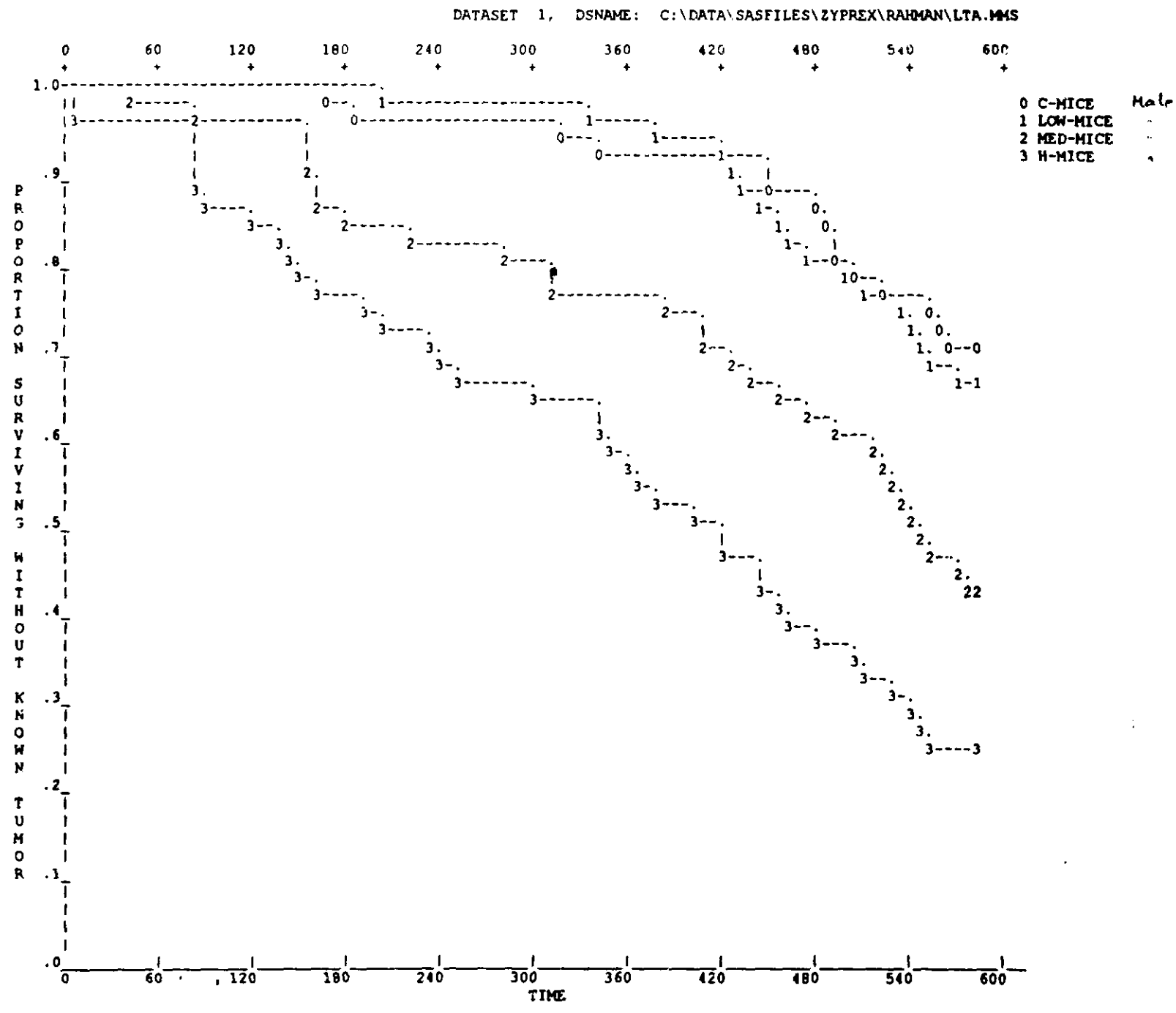
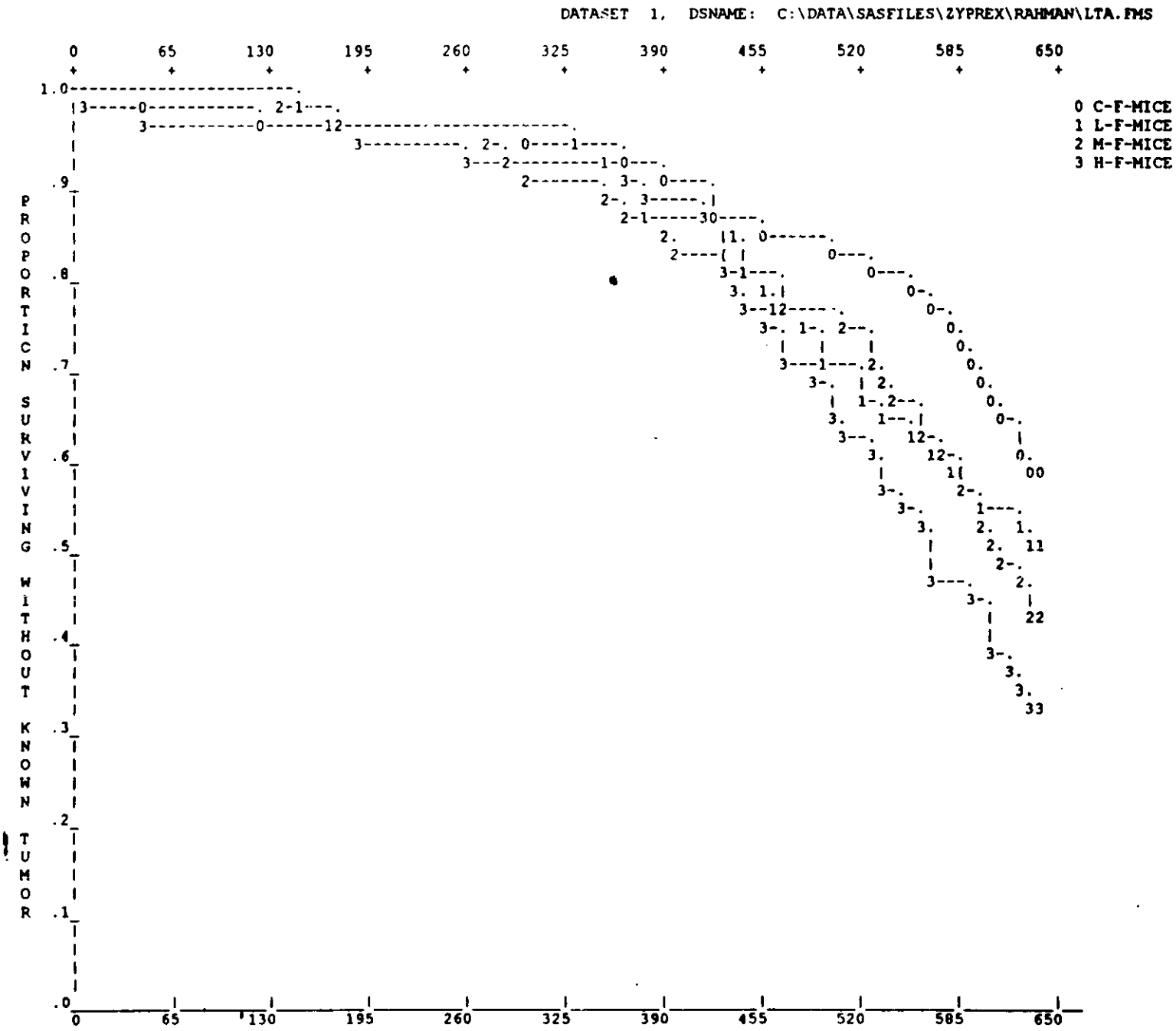


Figure 6: Survival - Female Mice



Statistical Review and Evaluation
Second Mouse Study

DATE: MAY 20 1996
RETURN
MAY 2 1

NDA#: 20-592

APPLICANT: Lilly Research Laboratories

NAME OF DRUG: Zyprex(olanzapine)

DOCUMENTS REVIEWED: Volumes 7.1 - 7.6 of 11/24/95 Submission and Data Diskette Sent 01/15/96.

I. Background

Due to high mortality the original mouse study had been considered a failed study. This submission contained a new 21 months study with lower doses. Dr. A. Atrakchi (HFD-120) has requested the Division of Biometrics I for a statistical review of the second mouse study data as well as an evaluation of the sponsor's findings.

There were an additional 36 mice per sex studied for up to one year for changes in plasma concentrations. These data were not statistically analyzed.

II. The Mouse Study

II.a. Design

The study was actually two parallel studies of 30 Crl:CDR-1 (ICR) male and female mice per dose group which were conducted one week apart. The compound was administered via gavage in strengths of 0 (vehicle control), 0.5 (low), 2.0 (medium), and 8.0 (high) mg/kg/day for 639 days. Water was available ad libitum. All animals surviving until the end of the study were killed starting on day 640.

II.b. Sponsor's Analyses

Survival Analysis:

The sponsor compared mortality curves with Tarone's test using SAS's PROC CHRONIC. Doses were replaced by the ordinal scale of 0 - 3. No significant increase in mortality occurred in either the male or female mice. With respect to the two parallel studies the sponsor observed similar survival for the males but differential overall survival (63 % vs. 44%) for the females. However, the trends in survival rates across the treatment groups were similar for the two replicate studies in the females.

Tumor Data Analysis:

Peto's survival adjusted trend test was used as a screen to identify individual site/neoplasms of potential concern with a one-tailed p-value of $\leq$ .05 using again the ordinal scale of 0 - 3 for the dose levels. Low tumor incidence rates were analyzed by randomization trend tests using StatXact software. No significant treatment-related effects were observed in tumor incidence rates among the male mice. Adenocarcinoma of the mammary gland and hemangiosarcoma of the liver showed asymptotically significant trends with dose among the female mice. The exact tests for the onset of adenocarcinoma and for the combined (fatal and incidental) tumor rates of hemangiosarcoma resulted in p-values greater than .05 (.055 and .066, respectively).

II.c. Reviewer's Analyses

This reviewer independently performed analyses on the survival and the tumor data. For survival analysis the methods described in papers of Cox (Regression models and life tables, Journal of the Royal Statistical Society B 34, 187-220, 1972), and of Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika 52, 203-223, 1965) were used. The corresponding computer program was written by Thomas, Breslow, and Gart (Trend and homogeneity analyses of proportions and life table data, Computers and Biomedical Research 10, 373-381, 1977, Version 2.1). The tumor data were analyzed using the methods described in the paper of Peto et al. (Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International Agency for Research against Cancer Monographs, Annex to Supplement, WHO, Geneva, 311-426, 1980) and the method of the exact permutation trend test developed by the Division of Biometrics. The following criteria for the levels of significance ensure a false positive rate of about ten percent for the trend tests of the usual two-species two-sexes studies: Tumors with less than 1.00% occurrence in the control group are considered rare and a positive trend test is statistically significant when it reaches a p-value of $\leq$ .025 (one-sided). Higher tumor occurrences in the control group are considered common for these animals and a positive trend is statistically significant when its p-value is less than or equal to .005 (one-sided). An approximate permutation trend test is used when fatal and incidental tumors of the same kind are combined and have overlapping time intervals. All tests are survival adjusted and treatment groups are weighted by the actual dose levels.

There are minor numeric differences between the sponsor's final number of animals surviving and this reviewer's. These are due to animals dying a natural death during the time of Terminal Sacrifice which this reviewer treated the same as if sacrificed. The data on diskette have a code for Terminal Sacrifice. The earliest time associated with this code was day 640. Therefore, all animals dying on or after day 640 were treated as terminally sacrificed.

Survival Analysis:

Survival at Terminal Sacrifice ranged from 53 to 67 percent (high dose - controls) among the male mice and from 47 to 60 percent (low dose - high dose) among the female mice as can be seen in the Table 1. The survival experience of either sex showed no signs of statistical linear trends or significant heterogeneity (Table 2, Figures 1, 2). None of the pairwise comparisons of the treated groups reached statistical significance.

Tumor Data Analysis

In either sex there were tumors classified as 'metastatic', rather than fatal or incidental. In consultation with Drs. Atrakchi and Fitzgerald, it was decided that metastatic tumors should be treated as incidental.

Among the male mice the exact permutation test for the incidence rates of interstitial cell tumor of the testes reached a p-value of .043 (Table 3). However, this level is not significant when one adjusts for the multiplicity of tests performed. Among the female mice adenocarcinomas of the lung and of the mammary glands reached p-values which are considered significant by this reviewer, namely .012 and .002 respectively. Neither tumor appeared among controls, so that a p-value of less than or equal to .025 is considered a statistically significant finding. The sponsor treated adenocarcinoma and multifocal adenocarcinoma of the lung as two separate tumor types, neither of which reached statistical significance. However, when they are combined, as done by this reviewer, the trend test was statistically significant.

As the male mice exhibited no statistically significant tumor trends, an evaluation of this study's validity is warranted.

II.d. Validity of the Male Mouse Study

Before concluding that the male mouse study showed no tumorigenic effect of olanzapine, the validity of the study needs to be determined. For this, two questions need to be answered (Haseman, Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol 58, pp 385-392, 1984):

(i) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?

(ii) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

The following are some rules of thumb as suggested by experts in the field: Haseman (Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol 5, pp 66-78, 1985) had found that on the average, approximately 50 % of the animals in the high dose

group survived the two-year study. In a personal communication with Dr. Karl Lin of HFD-715, he suggested that 50 % survival of the usual 50 initial animals in the high dose group between weeks 80-90 would be considered as a sufficient number and adequate exposure. Chu, Cueto, and Ward (Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981) proposed that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greather than 50 % survival at one year". From these sources, it appears that the proportions of survival at weeks 52, 80-90, and at two years are of interest in determining the adequacy of exposure and number of animals at risk.

In determining the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD. Chu, Cueto, and Ward (1981) suggest:

(i) "A dose is considered adequate if there is a detectable weight loss of up to 10 % in a dosed group relative to the controls."

(ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

In another paper, Bart, Chu, and Tarone (Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute 62, 957-974, 1979), stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, "Usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is a indication that the treatment has been tested on levels at or approaching the MTD."

The survival of male mice at 1, 1 1/2, and 91 weeks is given below:

Percent Survival (n=60/group)

Dose:		Controls	Low	Medium	High
MALE	52 weeks	95	93	90	87
	78 weeks	85	77	80	72
	91 weeks	67	60	62	53

It is apparent that there remained a sufficient number of animals at all times of the study for any manifestation of late developing tumors. One needs to ask, however, whether the length of a study in this species should have been a full two years and whether the added exposure could have resulted in significant tumor trends.

The sponsor reported that male mice experienced decreased body weight and body weight gain when compared to their controls. At 11 months this body weight difference was the largest at 7 percent. This figure would indicate that the high dose was close to the MTD according to one of Chu, Cueto and Ward criteria. Also, the high dose males experienced somewhat higher mortality than their controls, which is another indicator that the high dose was close to the MTD. The evaluation of possible associations of clinical signs and severe histopathologic toxic effects with dose is left to the expertise of the pharmacologist. However, based on the statistical criteria used by this Division, the study in male mice appears to be valid inasmuch as there were enough animals exposed for 639 days to a sufficiently high dose to develop late occurring tumors if the compound causes them. It needs to be decided whether an additional three months of exposure would have been appropriate in this species.

IV. Summary and Conclusions

This submission contained a second mouse study as the first one was declared invalid primarily due to the high mortality experience of the dosed animals. In the current study there were an additional 36 animals per sex which were studied for plasma levels and were not statistically analyzed.

The carcinogenicity study consisted of two parallel studies in 30 animals per sex per dose group which this reviewer treated as one study. At day 640 the terminal sacrifice was initiated. Among either sex there was no evidence of a significant linear dose relationship in mortality. Among the male mice no statistically significant trends in tumor incidence rates were observed. An evaluation of this study's validity showed that from the statistical point of view there were a sufficient number of animals throughout the length of the study dosed sufficiently high to allow for late developing tumors. The only questions remaining are i) whether the study should have lasted a full two years in this species and ii) whether clinical signs and severe histopathologic effects also support the notion that the high dose was close to the MTD. Among the female mice this reviewer observed two statistically significant tumor trends: adenocarcinoma of the lung, which was not mentioned by the sponsor because adenocarcinomas and multifocal adenocarcinomas were treated as different tumor types, and adenocarcinoma of the mammary glands, which was also reported by the sponsor.

Some additional minor points:

This reviewer does not totally agree with the sponsor's analyses. Using an ordinal scaling of the dose rather than the actual doses influences the trend statistic. It has been the practice of

the Division of Biometrics to use the actual doses as weights in the mortality and tumor analyses.

There is no need to use asymptotic results as StatXact provides the p-values for an exact permutation trend test.

Also, all animals dying after the start of terminal sacrifice were considered sacrificed and Terminal Sacrifice was treated as only one time interval by this reviewer, not as several as done by the sponsor. This resulted in slightly different percentages of animals surviving till terminal sacrifice but had no effect on conclusions or p-values. If an animal was classified as having died of a fatal tumor during the time of terminal sacrifice, this reviewer's program handled the event appropriately as part of the fatal tumor analyses.

Roswitha E Kelly
Mathematical Statistician

Concur:

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Todd Sahlroot, Ph. D.
Acting Team Leader

5/20/96
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Director, DB I

RETURN
MAY 2 1 1996

cc:Archival NDA 20-592, Zyprex (olanzapine), Lilly
HFD-120/Division File
HFD-120/Dr. Atrakchi
✓HFD-120/Dr. Fitzgerald
HFD-344/Dr. Lisook
HFD-710/Chron.
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/Ms. Kelly
HFD-710/RKELLY/05/16/96/wp-zyprex2.rev

Table 1
INTERCURRENT MORTALITY RATES
Second Mouse Study

MALE MICE

Days	0	.05	mg/kg/day 2.0	8.0
0 -365	3/60 (5%)	4/60 (7%)	6/60 (10%)	8/60 (13%)
366-548	6/57 (15%)	10/56 (23%)	6/54 (20%)	9/52 (28%)
549-639	11/51 (33%)	10/46 (40%)	11/48 (38%)	11/43 (47%)
Term. Sac.	40/60 (67%)	36/60 (60%)	37/60 (62%)	32/60 (53%)

FEMALE MICE

Days	0	.05	mg/kg/day 2.0	8.0
0 -365	2/60 (3%)	4/60 (7%)	5/60 (8%)	6/60 (10%)
366-548	12/58 (23%)	15/56 (32%)	10/55 (25%)	8/54 (23%)
549-639	12/46 (43%)	13/41 (53%)	12/45 (45%)	10/46 (40%)
Term. Sac.	34/60 (57%)	28/60 (47%)	33/60 (55%)	36/60 (60%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

Table 2

Results of Intercurrent Mortality Analyes
Second Mouse Study

Males

Groups Compared	Direction	Two-tailed P-Value of Test	
		Cox	Kruskal/Wallis
C,L,M,H	pos	.151	.142
C,L	pos	.479	.349
C,M	pos	.605	.451
C,H	pos	.151	.102
L,M	neg	.989	.904
L,H	pos	.538	.447
M,H	pos	.440	.381

Females

Groups Compared	Direction	Two-tailed P-Value of Test	
		Cox	Kruskal/Wallis
C,L,M,H	neg	.340	.360
C,L	pos	.304	.249
C,M	pos	.950	.828
C,H	neg	.868	.809
L,M	neg	.393	.322
L,H	neg	.171	.136
M,H	neg	.697	.617

Interpretation of Direction of Trend: Trend is labeled positive when survival is poorer (i.e. mortality is greater) in the comparison (right-hand) group than in the reference (left-hand) group; the trend is labeled negative when survival is better in the comparison group than in the reference group.

Table 3: Tumor Trend Tests

MALE MICE STUDY 2

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
ADRENAL	ADRENOCORTICAL ADENOMA	S	0.3653	0.31970	1	0	1	1
ADRENAL	PHEOCHROMOCYTOMA	S	0.4469	0.27400	1	0	0	1
HARDERIAN GLAND	ADENOMA	S	0.6521	0.65565	5	6	9	4
HEART	FIBROSARCOMA	S	1.0000	0.79765	1	0	0	0
KIDNEY	RENAL CELL ADENOMA	S	0.4469	0.27400	1	0	0	1
KIDNEY	RENAL CELL CARCINOMA	S	0.7242	0.73175	0	1	0	0
LIVER	FIBROSARCOMA	S	1.0000	0.79765	1	0	0	0
LIVER	HEMANGIOMA	S	0.9801	0.89750	2	1	0	0
LIVER	HEMANGIOSARCOMA	M	0.8882	0.89120	1	3	3	0
LIVER	HEPATOCELLULAR ADENOMA	S	0.9327	0.92725	8	11	12	4
LIVER	HEPATOCELLULAR CARCINOMA	M	0.9546	0.94455	6	4	5	1
LUNG	ALVEOLAR/BRONCHIOLAR ADENO	S	0.4285	0.42920	12	10	9	10
LUNG	ALVEOLAR/BRONCHIOLAR CARCI	M	0.5380	0.53810	2	3	1	2
LUNG	FIBROSARCOMA	S	1.0000	0.79765	1	0	0	0
MEDIASTINUM	FIBROSARCOMA	S	1.0000	0.79765	1	0	0	0
PROSTATE	FIBROSARCOMA	S	1.0000	0.79765	1	0	0	0
SKELETAL MUSCLE	LEIOMYOBLASTOMA	S	0.4759	0.55175	0	0	1	0
SKIN	FIBROSARCOMA	S	1.0000	0.78725	1	0	0	0
SPLEEN	HEMANGIOSARCOMA	M	0.9121	0.88690	2	1	1	0
TESTIS	HEMANGIOMA	S	0.6334	0.73735	0	1	1	0
TESTIS	INTERSTITIAL CELL TUMOR	S	0.0432	0.01940	1	0	1	3
THYROID	FOLLICULAR CELL ADENOMA	S	0.7242	0.73175	0	1	0	0
URINARY BLADDER	LEIOMYOBLASTOMA	S	0.2903	0.06265	0	0	0	1
WHOLE ANIMAL	FIBROUS HISTIOCYTOMA, MALIG	M	0.8032	0.81620	1	1	1	0
WHOLE ANIMAL	HEPATOCELLULAR CARCINOMA	S	0.7291	0.73490	0	1	0	0
WHOLE ANIMAL	LYMPHOSARCOMA	M	0.1665	0.14985	4	1	1	4
WHOLE ANIMAL	MYELOSARCOMA	S	0.3939	0.23005	1	0	0	1

FEMALE MICE - 2ND STUDY

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
ADRENAL	ADRENOCORTICAL ADENOMA	S	1.0000	0.80415	1	0	0	0
ADRENAL	PHEOCHROMOCYTOMA	S	0.7780	0.78320	1	0	1	0
CERVIX	LEIOMYOSARCOMA	S	0.9827	0.89090	2	1	0	0
DUODENUM	ADENOMA	S	0.5267	0.59745	0	0	1	0
HARDERIAN GLAND	ADENOMA	S	0.5201	0.52290	1	4	6	3
HEART	ADENOCARCINOMA	S	0.2128	0.03115	0	0	0	1
JEJUNUM	HEMANGIOSARCOMA	S	0.5267	0.59745	0	0	1	0
LIVER	HEMANGIOMA	S	0.0585	0.00760	0	0	0	2
LIVER	HEMANGIOSARCOMA	M	0.0459	0.03260	0	1	1	3
LIVER	HEPATOCELLULAR ADENOMA	S	0.5258	0.56040	1	1	2	1
LIVER	HEPATOCELLULAR CARCINOMA	S	0.2135	0.17150	0	0	1	1
LIVER	SARCOMA, UNDIFFERENTIATED	S	0.7333	0.70365	0	1	0	0
LUNG	ADENOCARCINOMA	S	0.0119	0.00340	0	0	1	3
LUNG	ALVEOLAR/BRONCHIOLAR ADENOM	M	0.9292	0.92410	8	10	7	5
LUNG	ALVEOLAR/BRONCHIOLAR CARCIN	M	0.5602	0.57785	3	1	3	2
LUNG	HEPATOCELLULAR CARCINOMA	S	0.5267	0.59745	0	0	1	0
LYMPH NODE	ADENOCARCINOMA	S	0.2128	0.03115	0	0	0	1
LYMPH NODE	FIBROSARCOMA	S	1.0000	0.78120	1	0	0	0
LYMPH NODE	HEMANGIOMA	S	0.4681	0.54610	0	0	1	0
MAMMARY GLAND	ADENOCARCINOMA	M	0.0024	0.00140	0	0	3	5
MAMMARY GLAND	ADENOMA	S	0.2748	0.05675	0	0	0	1
MEDIASTINUM	ADENOCARCINOMA	S	0.2128	0.03115	0	0	0	1
MEDIASTINUM	ALVEOLAR/BRONCHIOLAR CARCIN	S	0.4681	0.54610	0	0	1	0

Table 3 con'd:

FEMALE MICE - 2ND STUDY

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
MENINGES	SARCOMA, UNDIFFERENTIATED	S	0.7610	0.75220	0	1	0	0
OVARY	GRANULOSA CELL TUMOR, MALIG	S	0.5267	0.59745	0	0	1	0
OVARY	PAPILLARY CYSTADENOMA	S	0.9178	0.89960	2	5	0	1
OVIDUCT	LEIOMYOMA	S	0.2128	0.03115	0	0	0	1
PERITONEUM	ADENOCARCINOMA	S	0.2128	0.03115	0	0	0	1
PERITONEUM	FIBROSARCOMA	S	1.0000	0.78110	1	0	0	0
PERITONEUM	LEIOMYOSARCOMA	S	1.0000	0.80415	1	0	0	0
PITUITARY	ADENOMA	M	0.1425	0.11130	1	1	1	3
SKELETAL MUSCLE	HEMANGIOSARCOMA	S	0.4681	0.54610	0	0	1	0
SKELETAL MUSCLE	RHABDOMYOSARCOMA	S	0.5127	0.58065	0	0	1	0
SKELETAL MUSCLE	SARCOMA, UNDIFFERENTIATED	S	0.7333	0.70365	0	1	0	0
SKIN	BASAL CELL EPITHELIOMA	S	0.2748	0.05675	0	0	0	1
SKIN	FIBROSARCOMA	M	1.0000	0.88345	2	0	0	0
SKIN	KERATOACANTHOMA	S	1.0000	0.76095	1	0	0	0
SKIN	NEUROFIBROSARCOMA	S	1.0000	0.80320	1	0	0	0
SKIN	SQUAMOUS CELL CARCINOMA	S	0.2748	0.05675	0	0	0	1
SPLEEN	HEMANGIOMA	S	1.0000	0.78110	1	0	0	0
STOMACH	LEIOMYOSARCOMA	S	1.0000	0.80415	1	0	0	0
THYMUS	ALVEOLAR/BRONCHIOLAR CARCIN	S	0.2128	0.03115	0	0	0	1
URINARY BLADDER	LEIOMYOBLASTOMA	S	0.2749	0.05675	0	0	0	1
UTERUS	ENDOMETRIAL STROMAL TUMOR,	M	1.0000	0.95675	4	0	0	0
UTERUS	HEMANGIOMA	S	0.2748	0.05675	0	0	0	1
UTERUS	HEMANGIOSARCOMA	S	0.2074	0.16580	0	0	1	1
UTERUS	LEIOMYOBLASTOMA	S	0.5267	0.59745	0	0	1	0
UTERUS	LEIOMYOMA	S	0.1774	0.18455	1	0	3	2
UTERUS	LEIOMYOSARCOMA	M	0.9321	0.92770	2	2	2	0
UTERUS	LIPOSARCOMA	S	0.7404	0.75930	0	1	0	0
VAGINA	LEIOMYOMA	S	0.7404	0.75930	0	1	0	0
VAGINA	SQUAMOUS CELL CARCINOMA	S	0.7500	0.75670	0	1	0	0
WHOLE ANIMAL	FIBROUS HISTIOCYTOMA, MALIG	S	1.0000	0.80120	1	0	0	0
WHOLE ANIMAL	HEMANGIOSARCOMA	S	0.5274	0.59295	0	0	1	0
WHOLE ANIMAL	HISTIOCYTIC SARCOMA	S	0.9946	0.96940	3	3	0	0
WHOLE ANIMAL	LYMPHOSARCOMA	M	0.6212	0.62345	14	7	13	11

Figure 1:

C:\DATA\SASFILES\ZYPREX\RAHMAN\LTA.MHS

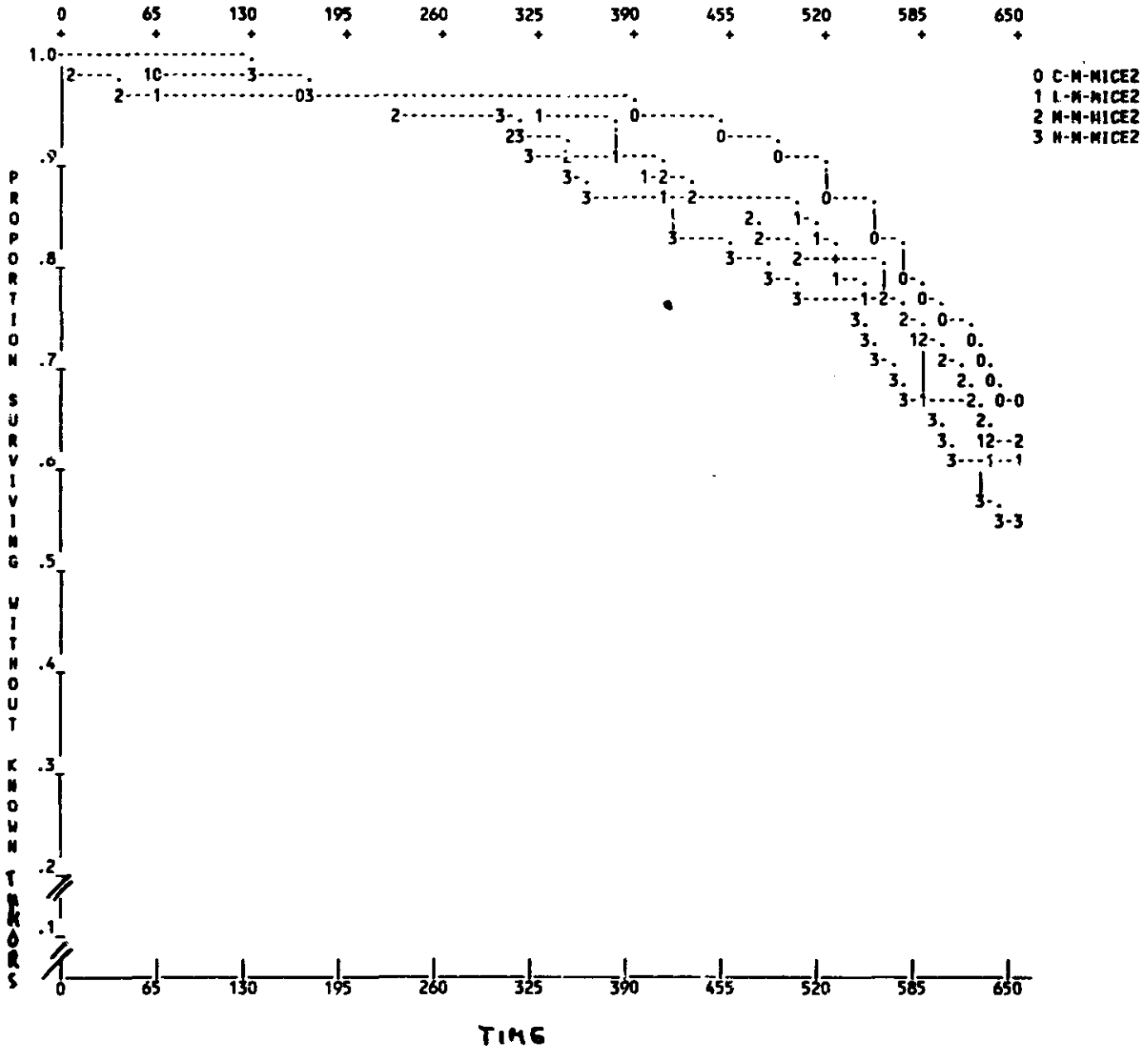
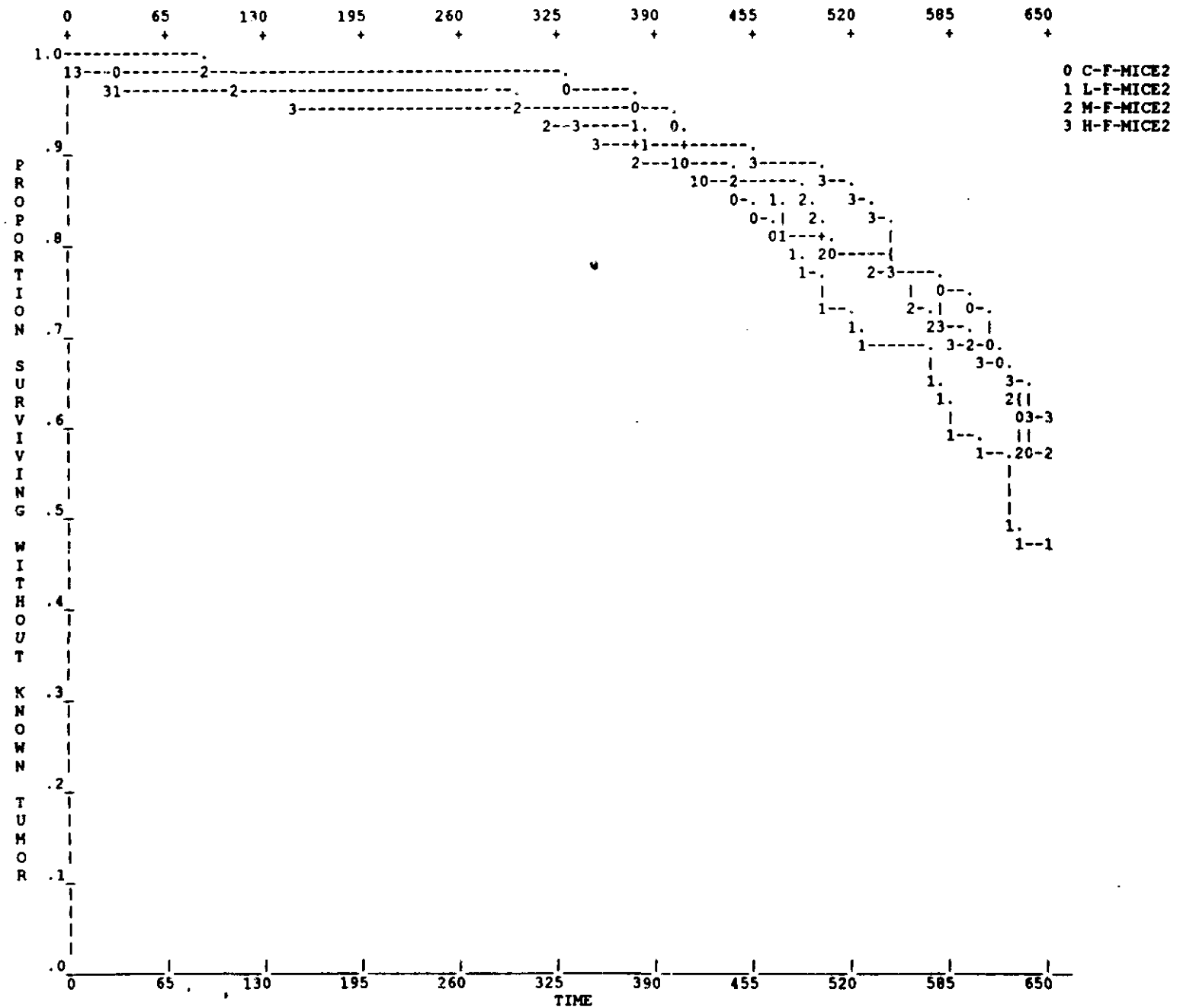


Figure 2: DATASET 1, DSNAME: C:\DATA\SASFILES\ZYPREX\RAHMAN\LTA.FMS



STATISTICAL REVIEW AND EVALUATION

Additional Analyses

DATE: JUL 2 1996

NDA#: 20-592

APPLICANT: Lilly Research Laboratories

NAME OF DRUG: Zyprex (olanzapine)

DOCUMENTS REVIEWED: Statistical Carcinogenicity Reviews of 5/14/96 and 5/20/96.

I. Background

Dr. Atrakchi (HFD-120) requested analyses of pairwise comparisons between controls and medium dose animals and between controls and high dose animals for all lung and mammary gland tumors in any of the three carcinogenicity studies (one rat and two mouse studies). In addition, lymphosarcomas in female mice of the first mouse study were to be compared between control and mid-dose and control and high-dose animals regardless of the locus of this tumor.

II. Results

The findings are summarized in the attached table. The trend test is generally more powerful than a pairwise comparison test and is, in general, associated with a higher level of significance. It is also noted that the levels of significance applied by this reviewer are much more stringent (.025 for rare tumors and .005 for common tumors) than those used by the sponsor (.05). In the accompanying table results with p-values $\leq$ .10 have been recorded to show how they may have contributed to a significant trend, but do not sustain such power in the pairwise comparison.

Applying the above levels of significance for rare and common tumors, the attached summary indicates that only adenocarcinomas of the mammary gland in female mice, in both mouse studies, show significant pairwise comparisons when the fatal and incidental tumors are combined. In particular, in the first mouse study the combined comparisons of C versus M and C versus H with each a p-value of .01 are considered significant as the tumors were rare in these animals. In the second mouse

study, the combined C versus H comparison passed the criterion of $p \leq .025$. The p-value of the corresponding C versus M comparison was not small enough to be called a statistically significant result.

III. Summary

Pairwise comparisons of incidence rates between control animals and their corresponding mid-dose and high-dose groups were performed for all lung and mammary tumors in each of the three rodent studies. In addition, all lymphosarcomas in female mice of the first mouse study were similarly tested.

Using the p-values of .025 and .005 as levels of significance for rare and common tumors, respectively, only adenocarcinomas of the mammary gland in female mice sustained significance: in the first study, both the C vs. M and the C vs. H comparisons of the combined (fatal and incidental) tumors remained significant with $p=.01$; in the second mouse study, only the C vs. H comparison for the combined adenocarcinoma showed significance with $p=.007$. None of the controls had exhibited this tumor.

Roswitha E. Kelly
Mathematical Statistician

Concur:

Todd Sahlroot, Ph. D.
Acting Team Leader

George Chi, Ph.D.
Director, DB I

cc:Archival NDA 20-592, Zyprex (olanzapine), Lilly
HFD-120/Division File
✓HFD-120/Dr. Atrakchi
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HFD-344/Dr. Lisook
HFD-710/Chron.
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/Ms. Kelly
HFD-710/RKELLY/07/01/96/wp-zyprex3.rev

Rat Study	Males	Lung	alveo/bronch adenoma	incidental	C vs M	NS
					C vs H	NS
			osteoma	incidental	C vs M	NS
					C vs H	NS
			C-cell carcinoma	incidental	C vs M	NS
					C vs H	NS
			renal cell carcinoma	incidental	C vs M	NS
					C vs H	NS
			undiff sarcoma	incidental	C vs M	NS
					C vs H	NS
			squamous cell carcinoma	fatal	C vs M	NS
					C vs H	NS
				incidental	none	
		Mammary Gland	fibroadenoma	fatal	C vs M	NS
					C vs H	NS

				incident al	C vs M	NS
					C vs H	NS
				combined	C vs M	NS
					C vs H	NS
			adenocarcinoma	incident al	C vs M	NS
					C vs H	NS
	Females	Lung	alveo/broch adenoma	incident al	C vs M	.11
					C vs H	NS
			adenocarcinoma	incident al	C vs M	NS
					C vs H	NS
			alveo/bronch carcinoma	fatal	C vs M	NS
					C vs H	NS
				incident al	C vs M	NS
					C vs H	NS
				combined	C vs M	NS
					C vs H	NS

			neurofibro-sarcoma	incident al	C vs M	NS
					C vs H	NS
			malignant pheochromo-cytoma	incident al	C vs M	NS
					C vs H	NS
		Mammary Gland	fibroadenoma	fatal	C vs M	NS
					C vs H	NS
					******* C vs L2	.07
				incident al	C vs M	NS
					C vs H	NS
				combined	C vs M	NS
					C vs H	NS
			adenoma	incident al	C vs M	NS
					C vs H	NS
			adenocarcinoma	fatal	C vs M	NS
					C vs H	NS

				incidental	C vs M	.07
					C vs H	NS
				combined	C vs M	.01
					C vs H	NS
			carcinosarcoma	incidental	C vs M	NS
			•		C vs H	NS

First Mouse Study	Males	Lung	any tumor		C vs M	NS
					C vs H	NS
		Mammary Gland	none			
	Females	Lung	alveo/bronch adenoma	incidental	C vs M	NS
					C vs H	NS
			adenocarcinoma	incidental	C vs M	NS
					C vs H	.07
			alveo/bronch carcinoma	incidental	C vs M	NS
					C vs H	NS
					******* C vs L	.07
			basal cell carcinoma	incidental	C vs M	NS
					C vs H	NS
			undiff sarcoma	incidental	C vs M	NS
					C vs H	NS
			squamous cell carcinoma	incidental	C vs M	NS
					C vs H	NS

		Mammary Gland	adenoma	incidental	C vs M	NS
					C vs H	NS
			adenocarcinoma	fatal	C vs M	.10
					C vs H	.08
				incidental	C vs M	NS
					C vs H	NS
				combined	C vs M	.01
					C vs H	.01

First Mouse Study	Females	Whole Animal	Lymphosarcoma	fatal	C vs. M	NS
					C vs. H	NS
				incidental	C vs. M	NS
					C vs. H	.017
				combined	C vs. M	.073
					C vs. H	.017

2nd Mouse Study	Males	Lung	alveo/bronch adenoma	incidental	C vs. M	NS
					C vs. H	NS
			alveo/bronch carcinoma	fatal	C vs. M	NS
					C vs. H	NS
				incidental	C vs. M	NS
					C vs. H	NS
				combined	C vs. M	NS
					C vs. H	NS
			fibrosarcoma	incidental	C vs. M	NS
					C vs. H	NS
		Mammary Gland	no tumors			
	Females	Lung	alveo/bronch adenoma	fatal	C vs M	NS

					C vs H	NS
				incidental	C vs M	NS
					C vs H	NS
				combined	C vs M	NS
					C vs H	NS
			Adenocarcinoma	incidental	C vs M	NS
					C vs H	.10
			alveo/bronch carcinoma	fatal	C vs M	NS
					C vs H	NS
				incidental	C vs M	NS
					C vs H	NS
				combined	C vs M	NS
					C vs H	NS

			hepatocell. carcinoma	inciden tal	C vs M	NS
					C vs H	NS
		Mammary Gland	adenoma	inciden tal	C vs M	NS
					C vs H	NS
			adenocarcinoma	fatal	C vs M	NS
					C vs H	NS
				inciden tal	C vs M	NS
					C vs H	.06
				combine d	C vs M	.04
					C vs H	.007

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS **NDA 20,592**

	letterdate	stampdate	rec'd by chemist	COMPLETED
INITIAL SUBMISSION:	21-SEP-95	25-SEP-95	02-OCT-95	19-JAN-96
AMENDMENT:	~~18~~ 19-JAN-96			22-JAN-96

CHEMIST REVIEW: # 1 **SPONSOR: ELI LILLY**

REVIEW CHEMIST: M.Zarifa, Ph.D **ADDRESS:** **Lilly Corporate Center**
Indianapolis, IN 46285

APR 18 1996

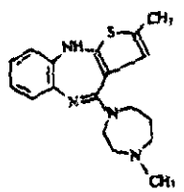
PRODUCT NAME:

Proprietary:	ZYPREX®
USAN:	Same as Chemical Name below
INN:	Olanzapine
Code Name/Number:	**LY170053**

DOSAGE FORM/ROUTE OF ADMINISTRATION: 2.5-mg, 5-mg, 7.5-mg, and 10-mg Tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Manifestations of psychotic disorders

STRUCTURAL FORMULA & CHEMICAL NAME:



$C_{20}H_{20}N_4S$ **Mol. Wt.** 312.43

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine

REMARKS: The drug substance is highly basic, of low solubility in water, soluble in acidic media and highly aromatic. It degrades readily under acidic stressed conditions especially in the presence of light and/or free radicals. Olanzapine is similar to clozapine. Both the n.d.s. and dosage form manufacturing processes and packaging procedures in the NDA indicate adequate controls of moisture, a critical parameter. The drug product has shown good stability for 12-month storage under normal conditions and a 24-month expiry date seems reasonable.

CONCLUSIONS & RECOMMENDATIONS: RECOMMEND THAT **NDA 20-592 FOR ZYPREX TABLETS IS APPROVABLE** CONTINGENT UPON RECEIPT OF REQUESTED INFORMATION ABOUT THE N.D.S. INTERMEDIATE AND STARTING MATERIALS FROM (DMF HOLDER). THE PROPOSED EXPIRY DATE OF 24 MONTHS IS APPROVABLE CONTINENT UPON COMPLETION OF BIOMETRICS ASSESSMENT OF THE STATISTICAL METHODOLOGY AND RECEIPT OF THE UPDATED 18-MONTH ACTUAL STABILITY DATA. **SITE INSPECTIONS WERE SATISFACTORY AND THE EIR RECOMMENDATION IS APPROVABLE.**

Mona Zarifa

Mona Zarifa, Ph.D., Chemist

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/SHardeman
HFD-120/SBlum/MZarifa
HFD-810/CHolberg (cover page, def.list only)

filename: N020592.000

SHB 4/16/96

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS **NDA 20,592**

	letterdate	stampdate	rec'd by chemist	COMPLETED
INITIAL SUBMISSION:	**21-SEP-95**	**25-SEP-95**	**02-OCT-95**	**19-JAN-96**
AMENDMENTS:	**29-JAN-96**	**30-JAN-96**	**31-JAN-96**	**16-APR-96**
	21-MAR-96	**22-MAR-96**	**22-MAR-96**	**16-APR-96**

CHEMIST REVIEW: # 2 **SPONSOR:** **ELI LILLY**

REVIEW CHEMIST: M.Zarifa, Ph.D **ADDRESS:** **Lilly Corporate Center**
Indianapolis, IN 46285

PRODUCT NAME:

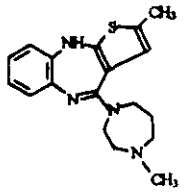
Proprietary:	ZYPREX®
USAN:	Same as Chemical Name below
INN:	Olanzapine
Code Name/Number:	**LY170053**

APR 30 1996

DOSAGE FORM/ROUTE OF ADMINISTRATION: 2.5-mg, 5-mg, 7.5-mg, and 10-mg Tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Manifestations of psychotic disorders

STRUCTURAL FORMULA & CHEMICAL NAME:



$C_{17}H_{20}N_4S$ **Mol. Wt.** 312.43

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine

REMARKS: has provided the pending information about the starting materials (See DMF Review #2). In these amendments the sponsor provides updated (18-month) actual stability data for the drug product, and more detailed specifications for the drug product impurities.

CONCLUSIONS & RECOMMENDATIONS: RECOMMEND THAT **NDA 20-592 FOR ZYPREX TABLETS IS APPROVED.** THE SPONSOR HAS ADEQUATELY RESPONDED TO THE DEFICIENCIES AND PROVIDED ADEQUATE 18-MONTH ACTUAL STABILITY DATA. PENDING INFORMATION FROM DMF HOLDER HAS BEEN PROVIDED. **RECOMMEND APPROVAL OF 24-MONTH EXPIRY DATE.**

Mona Zarifa

Mona Zarifa, Ph.D., Chemist

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/SHardeman
HFD-120/SBlum/MZarifa
HFD-810/CHoiberg (cover page, dmf.list only)
INIT:

MZB 4/29/96

filename: N020592.001

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS **NDA 20,592**

	letterdate	stampdate	rec'd by chemist	COMPLETED
INITIAL SUBMISSION:	21-SEP-95	25-SEP-95	02-OCT-95	19-JAN-96
AMENDMENTS:	14-JUN-96	17-JUN-96	19-JUN-96	20-JUN-96

CHEMIST REVIEW: # 3 **SPONSOR:** ELI LILLY

REVIEW CHEMIST: M.Zarifa, Ph.D **ADDRESS:** Lilly Corporate Center
Indianapolis, IN 46285

PRODUCT NAME:

Proprietary:	ZYPREXA ® (note the change from Zyprex)
USAN:	Same as Chemical Name below
INN:	Olanzapine
Code Name/Number:	**LY170053**

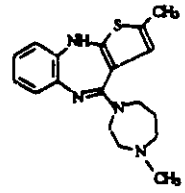
JUL - 9 1996

DOSAGE FORM/ROUTE OF ADMINISTRATION: 2.5-mg, 5-mg, 7.5-mg, and 10-mg Tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Manifestations of psychotic disorders

STRUCTURAL FORMULA & CHEMICAL NAME:

$C_{20}H_{20}N_4S$ **Mol. Wt.** 312.43



2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine

REMARKS: In this amendment the sponsor addresses the three issues in FDA's letter dated May 13, 1996.

CONCLUSIONS & RECOMMENDATIONS: RECOMMEND THAT **NDA 20-592 FOR ZYPREX TABLETS IS APPROVED.** THE SPONSOR HAS ADEQUATELY RESPONDED TO ALL DEFICIENCIES. **PER PREVIOUS REVIEW WE RECOMMEND APPROVAL OF 24-MONTH EXPIRY DATE.**

Mona Zarifa

Mona Zarifa, Ph.D., Chemist

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/SHardeman
HFD-120/SBlum/MZarifa
HFD-810/CHoiberg (cover page, Def. table)
INIT:

AMB 7/6/96

filename: N020592.002

CONFIDENTIAL

SECOND REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-592
Zyprexa™
(formerly Zyprex™)
(Olanzapine)

Tablet

Division of Neuropharmacological Drug Products

(HFD-120)

CENTER FOR DRUG EVALUATION AND RESEARCH

SUMMARY

Eli Lilly submitted an amendment dated 7/22/96 in response to our deficiency FAX dated 7/11/96. Each deficiency was responded to in an appropriate manner. See review notes.

Substantive laboratory work was conducted and the reports written according to GLP.

According to Drs. Mona Zarifa and Stanley Blum of HFD-120, Eli Lilly has recently changed the brand name from Zyprex to Zyprexa. The updated EA does give the correct present trade name.

CONCLUSIONS

Synthetic manufacture, tablet production and packaging, and sale of Zyprexa (Olanzapine) is not expected to have a detrimental environmental effect because:

1. All emissions are said to be controlled in appropriate manner.

2. Olanzapine is expected to biodegrade in the aqueous environmental compartment in a short time, based on laboratory tests.

3. Olanzapine toxicology tests show that, at the maximum expected environmental concentration (MEEC), it is not harmful to a variety of aquatic life forms.

4. Eli Lilly and Company holds the expected licences for each of the production facilities, while Eastman Chemical does the same.

RECOMMENDATIONS

This reviewer recommends that we write the FONSI for this EA.

ENVIRONMENTAL ASSESSMENT REVIEW
(Full)

1. **Date of EA Submission:**

Original EA - June 1995
NDA Clock date - 9/22/95
First Review date - 6/21/96
Deficiencies FAXed - 7/11/96
Amendment under review - 7/22/96

S. Hardeman, CSO

Adequate

2. **Name of applicant/petitioner:**

Eli Lilly and Company

Adequate

3. **Address:**

Eli Lilly Corporate Center
Indianapolis, Indiana 46285

Adequate

RESPONSE TO DEFICIENCIES FROM REVIEW #1

1. It is not clear that the Environmental Assessment as it is currently written is non-confidential. The volume begins with a confidential disclaimer and the MSDS is not to be released without project manager approval. The environmental assessment will be made public by the FDA as required by the Council on Environmental Quality so it must consist entirely of non-confidential information. See Industry Guidance described below.

   RESPONSE Lilly, in their amendment, makes clear what part of the EA is non-confidential and what part is not. The non-confidential part is on pages 2 to

Adequate

2. The current Environmental Assessment does not discuss the disposition of unused product or rejected packaged goods at Eli Lilly nor the disposition of returned goods. This subject should be discussed in CFR Environmental Assessment format item 6 or 4.

RESPONSE Lilly provides the names of the two facilities that will handle substance containing waste and non-substance containing waste.

Adequate

3. The trade name of the drug product was changed to Zyprexa from Zyprex recently. If an FOI Environmental Assessment is submitted (see deficiency 1), it should provide the current correct trade name. If an amendment is provided, the correct name should be confirmed therein.

RESPONSE Lilly confirms the name change and includes it in the amendment.

Adequate

4. have not provided non-confidential statements of compliance with, or being on an enforceable schedule to meet, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the manufacturing operations.

RESPONSE Lilly includes in the amendment appendix 1 the required statements.

Adequate

5 does not explain the effect of approval on compliance with current emissions requirements in the public part of the EA.

RESPONSE Appendix 1 contains a letter from PACO stating they will remain in compliance with all environmental laws and regulations. Adequate

8/1/96

Prepared by
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

Date

8/2/96

Concurred
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Date

Copies:

HFD-120

S. Hardeman, CSO/PM
Original EA Review to NDA 20-592, through S. Hardeman CSO/PM
Division File NDA 20-592

HFD-357

EA File for NDA 20-592
C. Berninger 8/01/96

File Name: c:\eareview\20592e02.rcb

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Zyprexa™
(formerly Zyprex™)
(Olanzapine)

Tablet

Eli Lilly and Company

NDA 20-592

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
(HFD-120)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-592

Xyprexa
(Olanzapine)

Tablet

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Zyprexa, Eli Lilly and Company has conducted a number of environmental studies and prepared an environmental assessment (attached) in accordance with *21 CFR 25.31a(a)* which evaluates the potential environmental impacts of th manufacture, use and disposal of the product.

Olanzapine is a chemically synthesized drug which is administered as a tablet in the long term treatment of schizophrenia and related psychoses in which positive symptoms, and/or negative symptoms are prominent. The drug substance will be manufactured by Eli Lilly S.A., Dunderrow, Ireland, and Eli Lilly and Company, Tippecanoe Laboratories, Shadeland, Indiana. The drug product will be manufactured and packaged by Eli Lilly Industries, Inc., Carolina, Puerto Rico. The product will also be packaged by The finished drug product will be used in hospitals, clinics and/or by patients in their homes.

Drug substance may enter the environment from emissions from substance manufacturing sites, from disposal of pharmacetical waste or from excretion by patients.

Chemical and physical test results indicate that Olanzapine will most likely be restricted to the aquatic environmental compartment and will biodegrade in waste water.

The toxicity of Olanzapine to several aquatic organisms was characterized. In all cases, the no effect concentration was significantly above the maximum expecte environmental concentration, indicating that no detrimental environmental effects are expected.

Disposal of the drug may result from pharmaceutical waste such as out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Pharmaceutical solid waste will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

8/2/96

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

Date

8/2/96

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Date

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet (drug substance)
[Others: list]

Copies:

HFD-120

Steve Hardeman, CSO/PM
Original to NDA 20-592, through Steve Hardeman CSO/PM
Division File for NDA 20-592

HFD-205

FOI Copy

HFD-357

EA File
Docket File
C. Berninger, 8/1/96

ENVIRONMENTAL ASSESSMENT FOR THE USE OF ZYPREX™ IN THE TREATMENT OF PSYCHOTIC DISORDERS

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

2

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4

ENVIRONMENTAL ASSESSMENT FOR THE USE OF ZYPREX™ IN THE TREATMENT OF PSYCHOTIC DISORDERS

1. **DATE** June 1995

2. **APPLICANT** Eli Lilly and Company

3. **ADDRESS** *Lilly Corporate Center*
Indianapolis, Indiana 46285

4. DESCRIPTION OF THE PROPOSED ACTION

Eli Lilly and Company is seeking approval for the use of Zyprex™ in the treatment of psychotic disorders. Zyprex is indicated for the acute and long-term treatment of schizophrenia and related psychoses in which positive symptoms, and/or negative symptoms are prominent. The active ingredient in Zyprex is olanzapine. Olanzapine is an antipsychotic agent of the thienobenzodiazepine class. The compound is a potent 5-$HT_{2A/2C}$, dopamine D_1, D_2, D_4, muscarinic M_1, M_2, M_3, M_4, adrenergic α_1, histamine H_1 receptor antagonist. In animal studies, the compound shows preferential mesolimbic selectivity and does not show the same degree of dopamine receptor occupancy seen with most antipsychotics. Zyprex will be administered orally so that 5 to 20 mg of olanzapine is delivered to a patient each day. For long-term therapy, responding patients should be continued at the lowest dose needed to maintain remission. Zyprex will be available in the form of tablets containing 2.5, 5, 7.5, or 10 mg of olanzapine.

This environmental assessment was developed to address the potential environmental issues associated with the use of this pharmaceutical in the treatment psychotic disorders. Approval of this new drug would authorize the production of olanzapine for sale as Zyprex in the United States. Production would occur at facilities of Eli Lilly S.A. (Dunderrow,

Kinsale, Ireland) in County Cork,

and at Tippecanoe Laboratories of Eli Lilly and Company near Lafayette (Lilly Road, Shadeland, Indiana). Zyprex tablets will be manufactured and packaged at the facilities of Eli Lilly Industries, Inc. in Carolina (Km. 12.5, 65th Infantry Avenue, Carolina, Puerto Rico). Blister packaging of the tablets may also be contracted to

Zyprex will be administered by prescription to patients throughout the United States and could potentially be introduced into the following environments:

a. The environments adjacent to the manufacturing, formulation, and packaging plants. The manufacturing plants in Indiana, Arkansas, and Ireland are located in temperate climates and in rural settings. The facilities in Puerto Rico are located in a subtropical climate and in urban settings.

b. Sewage treatment facilities throughout the United States receiving wastes from hospitals and homes where Zyprex is used.

c. Septic tanks receiving wastes from patients at their homes.

5. IDENTIFICATION OF THE CHEMICAL SUBSTANCE

A. FORMULATION

Zyprex will be available in tablet form and will contain 2.5, 5, 7.5, or 10 mg of olanzapine. Zyprex will also contain inert ingredients and materials generally recognized as safe. Ingredients in this tablet formulation are listed in a confidential attachment (Attachment 1). Chemicals used to manufacture the drug substance are listed in a confidential attachment (Attachment 2).

B. OLANZAPINE

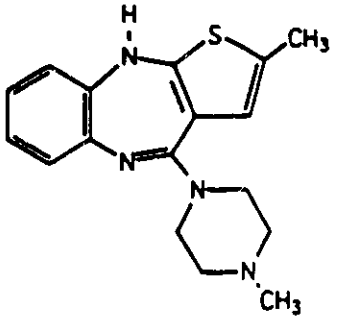
Olanzapine is an off-white to yellow crystalline solid. A multi-step chemical process is used to produce this drug substance. Proposed specifications indicate that the bulk drug substance, when corrected for water content (at most 1%) and residual solvent (at most 0.5%), is not less than 98% olanzapine. The proposed bulk drug specification allows not more than 0.2% of any one related substance and not more than 0.5% of total related substances. Heavy metals will be less than 10 ppm and tin will be less than 100 ppm.

Chemical Name: 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*- thieno[2,3-b][1,5]benzodiazepine

Molecular Formula: $C_{17}H_{20}N_4S$ CAS Registry Number: 132539-06-1

Molecular Weight: 312.4

Structural Formula:



Vapor Pressure: Olanzapine is a nonvolatile solid. Thermogravimetric analysis showed no obvious weight loss until about 200°C, with rapid weight loss and decomposition at 250 °C.

Melting Temperature (Appendix A): Olanzapine melted at 192 ± 0.9 °C

Dissociation Constant in 66% Dimethylformamide (Appendix B): $pKa_1 = 4.69$
$pKa_2 = 7.37$

Ultraviolet-Visible Absorbtion Spectrum (Appendix C): No prominent peak absorption maxima were found at wavelengths greater than 290 nm. Solutions of olanzapine at concentrations of 0.0114, 0.015, and 0.0114 mg/ml were used for this test at solution pH values of 5, 7, and 9, respectively.

Solubility in Water at 25 °C (Appendix D):

Average pH	Equilibrium Solubility (mg/ml)
5	> 87.4 mg/ml (saturation not possible)
7	0.1926 ± 0.0046 mg/ml
9	0.0165 ± 0.0004 mg/ml

Octanol/Water Partition Coefficient (Appendix E):

Solution pH	Octanol/Water Partition Coefficient
5	1.81 ± 0.01
7	48.76 ± 2.28
9	140.80 ± 55.88

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

A. INTRODUCTION OF SUBSTANCES FROM THE MANUFACTURING SITES

1. Facilities Used for Manufacturing, Formulating, and Packaging

The processes for manufacturing olanzapine, the operations for formulating and packaging olanzapine, and pollution control practices at the corresponding facilities are designed and constructed to result in minimal environmental impact. Production of olanzapine will occur at the production facilities of Eli Lilly S.A. (Dunderrow, Kinsale, Ireland) in County Cork, at the production facilities of

and at the Tippecanoe Laboratories of Eli Lilly and Company, near Lafayette (Lilly Road, Shadeland, Indiana). Olanzapine tablets will be formulated and packaged for sale in the United States at the facilities of Eli Lilly Industries, Inc. in Carolina (Km. 12.5, 65th Infantry Avenue, Carolina, Puerto Rico). Blister packaging of the tablets may also be contracted to

These facilities will effectively contain and control the liquid, solid, and gaseous wastes from the production, formulation, and packaging of Zyprex. Production of Zyprex will be done under Good Manufacturing Practices. Eli Lilly and Company will comply with all applicable Federal, State, and local regulations concerning emission control and waste treatment at all production and formulation facilities.

2. Environmental Regulatory Requirements

Treatment, storage, and disposal practices for the facility in Ireland are defined by the regulations administered by the Irish E.P.A., by the Cork County Council, and in other instances, by the Cork Corporation. Licenses and permits are granted under the authorities of the Water Pollution Act of 1977, the Air Pollution Act of 1987, the European Communities (Waste) Regulations of 1979, and the European Communities (Toxic and Dangerous Waste) Regulations of 1982. It is anticipated that in 1995, all environmental

licenses and permits will be incorporated into one integrated pollution control license granted by the Irish E.P.A. Permits related to the planned manufacture of olanzapine and issued by these regulatory agencies for the discharge of wastewater, the treatment, storage, and disposal of materials, and air emissions are listed in Appendix F. A confirmation of intent to comply with environmental regulations governing this facility is also included in Appendix F.

Treatment, storage, and disposal practices for solid, liquid, and gaseous wastes from are defined by the regulations administered, in certain instances, by the U.S. Environmental Protection Agency (EPA) and in other instances, by the of Pollution Control and Ecology °CE). Permits related to the manufacture of olanzapine are issued by these regulatory agencies for the discharge of wastewater (NPDES), the treatment, storage, and disposal of materials (RCRA), and air emissions (AIR). Because of the nature of the environmental permits at facility, no changes were needed for the production of materials related to olanzapine. Listed below are the environmental permits for this facility.

Location	Permit Number	Expiration
		5/31/97
		11/01/99
		No expiration date

Treatment, storage, and disposal practices for solid, liquid, and gaseous wastes from Tippecanoe Laboratories in Indiana are defined by the regulations administered, in certain instances, by the U.S. Environmental Protection Agency (EPA) and in other instances, by the Indiana Department of Environmental Management (IDEM). Permits related to the manufacture of olanzapine are issued by these regulatory agencies for the discharge of wastewater (NPDES), the treatment, storage and disposal of materials (RCRA), and air emissions (AIR). Eli Lilly and Company has made application or will make application for

all necessary environmental permits to manufacture olanzapine. The environmental permits associated with olanzapine are listed below.

Location	Permit Number	Expiration
Tippecanoe	NPDES IN0002861	9/30/92*
	RCRA IND006050967	4/30/93*
	AIR 79-04-90-0382	4/01/90*
	AIR 79-04-90-0383	4/01/90*
	AIR CP 157-2682	Not Applicable **
	AIR CP 157-1980	7/13/97
	AIR CP 157-3546	11/15/99

* Applications have been filed to renew these permits
** This is a registration which has no expiration date.
NOTE: In addition, the Tippecanoe facility also has a facility air identification number OP157-00006 with the Indiana Department of Environmental Management.

Formulation and packaging of Zyprex tablets will be carried out at the Carolina, Puerto Rico facility of Eli Lilly Industries, Inc. All room air will pass through HEPA filters, which will be packaged with solids, particulates, and dust for approved disposal. Air emissions (particulate matter) for olanzapine are regulated by the Puerto Rico Environmental Quality Board. Wash water from the formulations facility will be collected and discharged under a permit issued by the Puerto Rican Aqueduct and Sewer Authority (PRASA) to the Regional Waste Treatment Plant. Treated wastewater from the Regional Wastewater Treatment Plant is discharged into the ocean. Below is a list of the permits that cover the emissions related to the manufacture of olanzapine at Carolina.

Location	Permit Number	Expiration*
Carolina	PRASA GDA-88-112-027	6/95
	AIR PFE-16-0993-1408-I-II-0	5/28/94

* Permits will be renewed for future Zyprex manufacturing processes.

Olanzapine is produced in a multi-step chemical process. The disposition of materials used, consumed, and produced in the process steps used to manufacture olanzapine is also described in a confidential attachment (Attachment 2). Production processes for olanzapine require the use of 10 chemicals on the OSHA Air Contaminants List (Confidential Attachment 3).

3. Wastestream Treatment, Control, and Handling

a. Wastes from Manufacturing

Releases into the environment of wastewater pollutants and liquid and solid wastes resulting from the production of olanzapine will be controlled. *Liquid process waste* streams directly from the chemical synthesis of olanzapine will either be recovered for reuse, will be treated by thermal oxidation, or will be treated by biological wastewater treatment. Solids and particulate filters will also be collected for incineration or disposal at an approved landfill. Dilute wash waters from production processes will be incinerated or treated in biological wastewater treatment facilities. Emission control equipment and treatment systems are or will be in place for these manufacturing operations.

Eli Lilly S.A.

For the Kinsale facility, aqueous waste is either treated by biological treatment or destroyed by incineration. Any waste solids are either regenerated, recycled, or destroyed by incineration at an approved facility.

Aqueous waste streams from processes, tanks, equipment washings, and floor washings will be generated from the manufacture of olanzapine. These aqueous wastes will be pumped to the on-site biotreatment balance tank prior to treatment through a decant vessel which is designed to remove traces of nonmiscible solvents that may get washed into the aqueous waste streams.

All aqueous waste streams received by the treatment plant will be treated in an activated sludge biotreatment system where the organic carbonaceous material present can be broken down by microorganisms to yield end products of carbon dioxide and water plus new cellular material (sludge). The activated sludge system consists of a 1,000 cubic meter holding tank where all incoming wastes will be jet mixed and pH adjustment will be carried out. From this tank, the wastewater will be forwarded to the biotreatment tanks at a rate

based on the strength of the waste (average throughput is estimated to be 300 to 500 cubic meters per day). The wastewater will be forwarded through a tank with pH adjustment to a range of 6.5 to 8.0. Effluent will be routed to clarifiers where biomass in suspension will be allowed to settle. The supernatant from the clarifiers will overflow to final holding tanks before discharge. Solids produced from the treatment plant will be taken off site to an approved facility. All off-gases from the treatment plant will be collected from the roofed tanks and will be routed to a fume incinerator.

The thermal oxidizer wastewater will mainly contain inorganic salt deposits and fine particulate material. This wastewater will be passed through clarifiers and a sump before being discharged to cooling ponds. Before discharge to the cooling ponds, approximately 70% of the effluent will be recycled back to the thermal oxidizer units for reuse.

The final effluent will be collected from clarifier effluent, sludge dewatering effluent, and wastewater from the thermal oxidizer. According to the requirements of the discharge license, the final effluent from the entire facility will be assayed for biochemical oxygen demand (BOD), chemical oxygen demand (COD), pH, total suspended solids (TSS), ammonia as nitrogen, phenol, and cyanide. The effluent will be pumped through a pipeline and diffuser into the Atlantic Ocean at the outer portion of Kinsale Harbour. Surveys have demonstrated that the area has not historically been affected by discharge from this facility. The effluent is treated well before discharge and flushing and dilution rates are high in this area.

The facility will utilize a fume oxidizer, which is a regenerative thermal oxidizer unit. It will be a tertiary treatment device for use to incinerate fumes and control odor. Process and scrubber vents will be ducted from the production buildings and will be routed to the fume oxidizer before discharge to the atmosphere. The fume oxidizer will be operated at about 850 °C. Within the unit, volatile organic compounds, other hydrocarbons and odor-causing constituents will be converted to carbon dioxide and water vapor. Clean air will

pass through a heat exchange system before being released into the atmosphere. During any downtime, emissions to the atmosphere are minimized by scrubbers.

The facility will employ the use of one liquid thermal oxidizer and one solids incinerator at the site to treat solvent and solid waste generated by the production processes. Two types of liquid waste will be fed to the units, primary waste, which will be comprised of flammable solvent and waste material, and secondary waste, which will be comprised of mainly water with small amounts of organics. In addition, the solids unit will be provided with an inclined rotary kiln which will be employed in the burning of solid waste (such as contaminated packaging, fiber drums, etc.) from the site. Solid waste will automatically be charged using a ram feeder. The combustion gas will then be routed through the afterburner of the solids unit.

Both units will be down-fired incinerators with vertical combustion chambers operated at 1,000 °C, with a minimum residence time of 1.5 seconds. Performance tests of the units indicated destruction removal efficiencies greater than 99.99%. The combustion gases leaving the chambers will be quench cooled before ducting to the gas cleaning plant. The liquid thermal oxidizer will consist of a two-stage process comprising a condenser/absorber for acid gas removal and a hydrosonic scrubber for particulate and droplet removal. Both units will be computer controlled and any deviations outside the acceptable limits will result in an alarm. Continuous monitoring of oxygen, water vapor, carbon monoxide, total organic carbon and hydrogen chloride levels will be carried out on the stack gas. The units will also be monitored for hydrogen fluoride, particulates, sulfur dioxide and nitrogen dioxide on a quarterly basis.

Tippecanoe Laboratories of Eli Lilly and Company

For the Tippecanoe facility, aqueous waste is either treated by biological treatment or destroyed by incineration. Solvent wastes are either recovered for reuse or destroyed by incineration. Any waste solids are either regenerated, recycled or destroyed by incineration at an approved facility.

At the Tippecanoe facility, waste gases from the process can be captured by liquid scrubbers, vented to a carbon adsorber, vented to a condenser, or vented to a regenerative thermal oxidizer. Spent scrubber solution can be air stripped, and the resulting gases will be incinerated. The remaining scrubber solution will be sent through biological treatment. Depending on the efficiency of the scrubber used to control the process equipment, trace amounts of solvent may appear in this stream.

The wastewater treatment facility is primarily composed of two air activated sludge tanks having a combined aeration volume of 16.3 million gallons. Trace organics that may enter this system come into contact with the microorganisms in these systems and can be utilized as food and oxidized to carbon dioxide and water. Effluent from these units are processed in clarification systems. Sludges from the clarification units are thickened, dewatered and digested before proper disposal. The Tippecanoe wastewater facility treats the materials that exhibit BOD and COD to well below its NPDES limits. The pH of the discharge is within the range allowed by the NPDES permit , pH 6.0 to 9.0. In general, less than one percent of the daily discharge of wastewater from this facility will be attributed directly to olanzapine manufacturing. The Tippecanoe facility effluent is discharged into the Wabash River.

Liquid thermal oxidizers at the Tippecanoe facility are designed to oxidize primary waste and secondary waste. Primary wastes are mainly spent solvents and are capable of supporting autonomous combustion in the primary combustion chamber. Secondary wastes are mainly water and are injected into the incinerator's main oxidation chamber for thermal destruction downstream from the primary waste, at a distance sufficiently far so as

to not affect the primary burner flame. These thermal oxidizers operate at about 1800 °F or 1900 °F. They are designed to achieve 99.99% destruction and removal efficiencies of materials incinerated. The materials sent for thermal oxidation from olanzapine manufacturing processes could include solvents, unreacted starting materials, byproducts, or intermediates.

The thermal oxidizers are equipped for acid neutralization and removal of particulates and acidic gases from the incinerator exhaust in a gas cleaning system. The gas cleaning system consists of a quench, separator, and venturi scrubber. The exhaust gases after the venturi are directed to the atmosphere through a stack and are monitored for carbon monoxide and oxygen to indicate proper operation of the combustion process.

Air emissions from the manufacture of olanzapine were estimated by calculation. The volatile organic compounds that will be emitted at the Tippecanoe facility were modeled with the air dispersion model SCREEN. The resulting ambient concentration for each compound was found to be below the Permissible Exposure Limits (PELs) by the Occupational Safety and Health Administration (OSHA)

Solids from the olanzapine manufacturing process are incinerated or disposed of at approved solids disposal facilities.

Page
Purged

b. Wastes from Formulating and Packaging Facilities

Eli Lilly Industries, Inc. in Puerto Rico

Formulation and packaging of olanzapine will be carried out at the Carolina, Puerto Rico facility of Eli Lilly Industries, Inc. This facility will follow the standards for Good Manufacturing Practices. Tablets will be manufactured using a fluidized dryer, coating addition machines, and conventional formulation equipment. For the existing fluidized dryer, the air emission control equipment includes a pre-filter (80% control efficiency) and HEPA filters (99.9% control efficiency). For the coating addition machines, the control equipment includes dust collectors followed by HEPA filters (99.9% control efficiency). All solids collected will be packaged appropriately for approved disposal.

Wash water from the formulation and packaging facility will be collected and discharged under a permit issued by the Puerto Rican Aqueduct and Sewer Authority (PRASA) to the Regional Waste Treatment Plant. Wash water will result from the

intermittent rinsing of equipment. These waters will primarily contain suspended solids which may be oxygen-demanding materials. These waters will be processed at the formulation facility in a biological activated sludge system. This wastewater treatment removes the suspended solids, biochemical oxygen demand (BOD), and chemical oxygen demand (COD), to levels of 250 ppm or less, 175 ppm or less, and 300 ppm or less, respectively. The PRASA plant which receives this effluent discharges into the ocean. The highest possible concentration of olanzapine which might occur on an intermittent basis at the discharge point into the ocean is expected to be about 3 µg/L.

The sludge generated in the waste system of the formulation facility will be processed in an aerobic digestion system. The sludge will be dewatered via a belt filter press. The dry solid will be disposed of at a approved landfill facility.

Solid wastes generated at this formulating and packaging facility will generally be cartons, paper, and plastic. Any rejected material, plastic liners, gloves, hair covers, or filters will be collected and disposed of at approved facilties (i.e., landfill or incinerator).

B. INTRODUCTION OF SUBSTANCE FROM THE USE SITES

Use of Zyprex will not be limited to clinical settings. Accordingly, any olanzapine introduced into the environment will have the same general geographical distribution pattern as that which exists for human populations. Most of the population in the United States lives within 100 miles of some coastline.

The recommended daily dosage of olanzapine ranges from 5 to 20 mg. The projected total use of olanzapine in any 1 year in the United States will be less than If all of this olanzapine was administered chronically to patients at a dose of 15 mg/day, about people would be treated with olanzapine each year (kg/person/yr). At this rate, the number of individuals receiving olanzapine would constitute a very small percentage (about 0.18%) of the human population in the United States.

The pharmacokinetics and metabolism of olanzapine have been studied in humans (Kassahun, 1995). The half-life for olanzapine in plasma averaged about 27 hrs, whereas the half-life of total radioactivity from a ^{14}C-labeled dose averaged about 59 hrs. The major metabolic pathways of olanzapine in humans are N-glucuronidation, allylic hydroxylation, 4'-N-oxydation, and N-demethylation. Study results indicate that up to 87% of a ^{14}C-labeled olanzapine dose can be recovered, with 57% in the urine and 30% in the feces. Only a total of about 10% of a dose excreted in urine and feces is the active parent material. The major metabolite excreted is the 10-N-glucuronide, with a total of about 25% of a dose found in the urine and feces. At least 13 radioactive peaks were detected in urine. In addition to olanzapine and the 10-N-glucuronide, the following compounds were identified in urine: N-desmethyl-2-carboxy olanzapine, 2-carboxy olanzapine, N-oxide olanzapine, N-oxide-2-carboxy olanzapine glucuronide, the 4'-N-glucuronide, 2-carboxy olanzapine glucuronide, 2-hydroxymethyl olanzapine, and N-desmethyl olanzapine. Metabolites would be excreted along with small amounts of parent material. All residue would be discharged into municipal sewage treatment systems or into septic tanks.

Primary packaging for Zyprex will be bottles and blister units. Zyprex tablets will be added to amber, high-density polyethylene bottles. The bottles will also hold a desiccant canister and a cotton filler. Tablets may also be packaged in blister units. These units are made from thin laminates of aluminum foil, nylon, and PVC. One tablet will be added per

blister cavitiy, with strips or cards of blisters packaged into cartons. All of these packaging materials are needed to maintain the integrity of Zyprex and provide a surface for written information. In these forms, none of these materials are inherently harmful in the environment. Furthermore, large amounts of this packaging will not be released into the environment because only a very small fraction of the population will actually use Zyprex. Significant effects on the environment are not expected from the disposal of packaging materials for Zyprex.

7. FATE OF EMITTED SUBSTANCE IN THE ENVIRONMENT

Small amounts of olanzapine may be discharged into septic tanks or municipal sewage treatment facilities. Several studies have been conducted to evaluate the characteristics of olanzapine which may influence its fate in the environment. Olanzapine is a nonvolatile crystalline solid, so measureable concentrations are not expected in the atmosphere. Olanzapine does not significantly absorb light at wavelengths between 290 and 800 nm. It is, therefore, unlikely that olanzapine will be directly photolyzed in water. Olanzapine is very soluble in water (at least 97.4 g/L) at pH 5, but only moderately soluble at pH 7 (192.6 mg/L) and at pH 9 (16.5 mg/L). High to moderate water solubility and low to moderate n-octanol/water partition coefficients (1.81 to 140.8) indicate that olanzapine will probably not strongly adsorb to sediment or soil (Kenega and Goring, 1980). Olanzapine does hydrolyze in hot water (Appendix G), but does so slowly at a relevant temperature. At 25 °C and at solution pH values ranging from 5 to 9, the hydrolysis half-life of olanzapine ranged from about 65 to 78 days (Appendix H). Olanzapine does biodegrade. In an aerobic biodegradation study with ^{14}C-labeled olanzapine, only 6.5% of the olanzapine used to start the 28-day study was detectable at the end of the study (Appendix I). The half-life for disappearance of olanzapine was estimated to be about 7.4 days.

A. POTENTIAL CONCENTRATION OF OLANZAPINE IN SEPTIC TANKS

Assuming the average septic tank associated with a private home with four occupants holds about 1000 gallons, and the average person uses 50 gallons of water each day for cleaning, personal hygiene, and drinking, a septic tank could be filled in about 5 days. If it was possible for one occupant of the household to excrete all the residue of a 15-mg/day olanzapine dose as the active parent material during the same day the dose was taken, the concentration of olanzapine in the septic tank could reach about 0.02 mg/L ((15 mg/day)÷((200 gal/day) x (3.785 L/gal))). Since only about 10% of the dose excreted from humans is the active parent material, the highest actual concentration that might occur

in a septic tank is well below 0.002 mg/L. Olanzapine has a biodegradation half-life of about 7.4 days. Olanzapine also hydrolyzes slowly. Any active material that does not biodegrade and is discharged from a septic tank system would probably not adsorb to soil, but would eventually undergo hydrolysis.

B. POTENTIAL CONCENTRATION OF OLANZAPINE IN SEWAGE TREATMENT FACILITIES

Municipal sewage treatment facilities collect water and waste discharged from businesses, government facilities, and homes. Concentrations of olanzapine in the wastewater at sewage treatement facilities would be much lower than those that could be found in septic tanks. The highest continuous concentration of olanzapine possible in a sewage treatment facility can be calculated. If all the olanzapine expected to be produced in a year was administered to each patient at a daily dosage of 15 mg, no more than 0.18% of the population in the United States would receive treatment. In any one community of 100,000 people, only 180 people would be treated with olanzapine. On average, only about 986 gm of olanzapine would be used in a community during a year ((180 people/year) x (5.48 gm/person)), or about 2.7 gm/day. Since about 10% of the residue is excreted as active parent material, about 99 gms of olanzapine would be discharged each year, or about 0.27 g/day. Assuming about 15 million gallons of waste is generated each day by the community, the highest concentration of olanzapine residue that could theoretically occur in the wastewater coming into the sewage treatment facility would be about 0.048 µg/L (2.7×10^6 µg/56.8×10^6 L), or about 0.005 µg of olanzapine/L. After discharge from sewage treatment facilities into surface water, these levels would even be lower.

8. EFFECTS ON THE ENVIRONMENT OF RELEASED SUBSTANCES

A. MAMMALIAN TOXICITY STUDIES

A considerable number of toxicology studies were conducted with olanzapine. The following summarizes those studies that are useful in assessing the effects from potential environmental exposure.

Mutagenicity: The mutagenic potential of olanzapine was studied in a full battery of assays. The tests conducted were the Ames assay (*Salmonella typhimurium* and *E. Coli*), an unscheduled DNA synthesis test with rat hepatocytes, an *in vivo* sister chromatid exchange assay and chromosome aberration assay with Chinese hamsters, an *in vivo* test for induction of micronuclei in the bone marrow of mice, and a mouse lymphoma assay. Where appropriate, each study was conducted with and without metabolic activation. All assays were negative and olanzapine is not considered to be a mutagen.

Acute oral toxicity in mice: The median lethal oral doses in males and females were 211 and 208 mg/kg, respectively.

Acute oral toxicity in rats: The median lethal oral doses in males and females were 174 and 177 mg/kg, respectively.

Acute oral toxicity in dogs and monkeys: No deaths at oral doses of 100 mg/kg.

Inhalation study with rats: The toxicity of olanzapine to rats via an inhalation exposure was determined. A dry powder aerosol of olanzapine at target concentrations of 0.015, 0.03, 0.06, 0.125, and 0.25 mg/L was administered continuously for 4 hours. Mortality and pathology were not observed. No significant changes in body weight or respiratory rate were noted at any concentration. At concentrations ≥0.03 mg/L, changes in ambulatory and nonambulatory activity were observed. The no-effect concentration was 0.015 mg/L.

Dermal toxicity and irritation in rabbits: Dermal toxicity and irritation were evaluated in rabbits by application of olanzapine on the back at a dose of 200 mg/kg. After 24 hours of contact, treatment sites were washed and animals were observed for 14 days. No adverse effects or irritation were seen.

Ocular irritation in rabbits: A standard dose of olanzapine (52 mg, 0.1 cc) produced corneal dullness, slight iritis, and slight to moderate conjunctivitis within 1 hour. All effects cleared within 7 days.

One-year dog study: A chronic study was conducted in which beagle dogs received daily olanzapine doses of either 2, 5, or 10 mg/kg. All dogs survived the treatment period, although three dogs at 10 mg/kg developed treatment-related neutropenia and were removed from treatment. Bone marrow biopsies demonstrated adequate numbers of proliferative cells in neutropenic animals indicating that the neutropenia was not due to bone marrow toxicity. Clinical observations consistent with exaggerated pharmacologic effects included miosis, hypoactivity, and lethargy. Additional ocular observations included decreased tear production, conjunctivitis, ocular discharge, and blepharospasm at the upper two treatment levels. Dogs at the upper two levels also displayed head pressing, tremors, and hind limb stiffness and weakness. High dose dogs had decreased body weights. However, during a one-month reversibility phase, these dogs gained weight and previously mentioned clinical signs were absent. At test termination, immaturity of the uterus and a lack of luteal or luteal remnant tissue in the ovaries of females at the two upper doses indicated a lack of estrous cycling. During the reversibility phase, evidence of estrous cycling was present. Total bilirubin at 5 and 10 mg/kg was increased while decreases in eosinophil counts and increases in thrombocyte counts were observed at 10 mg/kg. No changes in urinalysis parameters or induction of liver enzymes occurred.

One-year rat study: Fisher 344 rats were given oral olanzapine doses of 1, 4, or 16 mg/kg/day for 1 year. Reduced body weight gain, CNS depression, and decreased

ovarian and uterine weights occurred, with effects more pronounced in rats given 4 or 16 mg/kg. Decreased leukocyte counts and bone marrow atrophy in rats given 16 mg/kg were considered a consequence of reduced food intake and a marked effect on body weight. No gross or histopathological tissue alterations were found, except the changes in ovaries, uteri, and mammary glands related to the effect of olanzapine on prolactin.

Mouse carcinogenicity study: The oncogenic potential of olanzapine was studied in CD-1 mice. Initially, daily olanzapine doses of 0, 3, 10, or 30 mg/kg were administered. However on Day 100, the 30 mg/kg dose was decreased to 20 mg/kg due to excessive mortality. Surviving male mice were terminated at 19 months and females were terminated at 21 months. As expected, a dose-related hypoactivity was observed after dosing which disappeared in the lower two doses as the study continued. Male animals at the upper two doses exhibited increased aggressive behavior to cage mates and increased inflammatory lesions of the urogenital tract and other organs. In addition, mice at all treatment groups had decreased circulating white blood cells due to decreased lymphocyte and neutrophil counts. Mammary gland tumors increased in females at the upper two doses and an increased incidence of lymphosarcomas in females was observed at all doses. The increase in mammary gland tumors was not unexpected and was likely due to increased circulating prolactin levels, a secondary pharmacological effect in rodents. The relationship of the increased incidence of lymphosarcomas to olanzapine treatment is unclear. Lymphosarcomas are common in CD-1 mice and the in-house historical incidence in untreated mice is 10 to 22%. In this study, the incidence of fatal lymphosarcomas was not statistically increased and time to onset of these tumors was not reduced by olanzapine. Additionally, lymphosarcomas were not increased in male mice in this study, nor in male or female rats in a separate study. Olanzapine was not genotoxic in a comprehensive battery of tests.

Rat Carcinogenicity Study: The oncogenic potential of olanzapine was assessed in rats by administering daily olanzapine doses of 0, 0.25, 1.0, 2.5, or 4.0 mg/kg for 2 years. On Day 211, the doses of 2.5 and 4.0 mg/kg were increased in females to 4.0 and 8.0 mg/kg. As expected, hypoactivity was observed after dosing, but this became less frequent as the study progressed. Survival was not adversely affected by treatment but body weight gains were depressed in the upper two doses. In addition, females at the upper two doses had increased heart weights, while males at the upper two doses had decreased thyroid weights. The incidence of malignant mammary gland tumors was increased in females at the upper two doses, but the overall incidence of mammary gland neoplasia was not affected. This increased expression of mammary gland tumors in females was not unexpected and was likely related to enhanced circulating prolactin levels, a secondary pharmacologic effect of olanzapine in rodents.

Rat teratology study: Olanzapine was administered to mated female CD rats on gestation days 6 through 15 at doses of 1, 4, and 18 mg/kg. Maternal and embryo/fetal toxicity occurred in animals at the two highest treatment levels. No treatment-related structural abnormalities were observed and no teratogenic effect was associated with olanzapine treatment.

Rabbit teratology study: Mated female New Zealand white rabbits were given daily oral olanzapine doses of 2, 8, or 30 mg/kg on gestation Days 6 through 18. Prenatal survival was not adversely affected, but embryo/fetal toxicity, as indicated by depressed fetal body weights, occurred in the high-dose group. No teratogenic effect was associated with olanzapine treatment.

Female rat fertility study: Female CD rats were administered olanzapine daily at doses of 1, 3, or 10 mg/kg for 2 weeks prior to cohabitation and throughout cohabitation with untreated males, gestation, and lactation. Sedation occurred at all doses. Effects on estrous cycles, which also were expected based on the pharmacology of olanzapine, were noted. Fertility was reduced slightly in females given 3 and 10 mg/kg and pup

viability was affected in offspring of females at the highest treatment level, probably due to lack of maternal care. No effects on reproductive parameters were noted in females at the lowest treatment level. In a follow-up study involving recovery of eggs and embryos from female rats treated with olanzapine at doses of 3 and 10 mg/kg, mating, ovulation, and fertilization of eggs were not impaired.

Two-generation study in rats: A two-generation study was conducted to assess the reproductive performance of rats exposed to olanzapine and that of their progeny. Animals were orally administered olanzapine doses of 0.25, 1.1, or 5 mg/kg/day. Males were treated for 10 weeks prior to mating and throughout two mating trials. Females of the delivery component were treated for 2 weeks prior to mating, and throughout mating, gestation, and lactation. Females for the teratology component were treated for 2 weeks prior to mating and throughout mating and gestation and were killed on gestation day 20. No deaths in the F_0 generation occurred. Some expected effects from exaggerated pharmacology were noted, including a disruption of estrous cycles at the two upper doses. In addition, fewer matings occurred at 5 mg/kg, but the fertility of the animals that mated, and the litter size, survival, and growth of the offspring were unaffected. Developmental retardation, indicated by the presence of wavy ribs or incomplete ossification of skull bones, was observed in the 5-mg/kg dose group of the F_1 generation. At 30 and 60 days of age, respectively, males and females from the F_1 generation exhibited decreased activity levels but were normal when retested between 140-160 days of age. Mating, fertility, and live births were unaffected in the F_1 generation and no treatment-related histopathological findings were observed. The no-effect level for reproductive toxicity and the no-adverse effect level for parenteral toxicity for the F_0 animals was 0.25 mg/kg. The no-effect level for reproductive toxicity and the no-adverse effect level for developmental toxicity for the F_1 animals were 5 and 1.1 mg/kg, respectively.

B. POTENTIAL EFFECTS OF RELEASED SUBSTANCE ON HUMAN HEALTH

1) Production and Formulation of Zyprex

Manufacturing sites for Zyprex are designed for production and formulation of pharmaceuticals according to Good Manufacturing Practices. Olanzapine is toxic, may be irritating to the eyes, and is highly potent. Effective engineering controls will be in place for production and formulation of olanzapine. Controls will be designed to meet a recommended exposure guideline that would only allow olanzapine aerosols to reach a 12-hr average level of only 0.038 mg/m^3. This level would result in exposures substantially below oral doses shown to result in pharmacological response in man. This level is also about 395 times lower than the no-effect aerosol concentration of olanzapine in an inhalation study with rats. Respiratory protection and gloves may be required in certain segments of the production process. Protective clothing will be provided in these facilities and eye protection is required. Considering the extensive engineering controls that will be in place to maintain low aerosol levels of olanzapine and personal protective measures, it can be concluded that workers will not be exposed to significant levels of olanzapine and predictable adverse effects are not expected.

2) Exposure of Humans to Olanzapine via Surface Waters

Significant exposure of humans to olanzapine via surface waters is not expected. Any small amounts of olanzapine that could be discharged from municipal sewage treatment systems will biodegrade and slowly hydrolyze. Based on chemical properties such as water solubility and octanol/water partition coefficient, olanzapine will not bioconcentrate significantly in fish (Kenega and Goring, 1980). The highest total concentration of olanzapine and metabolites in surface waters will be well below 0.048 µg/L, with olanzapine levels below 0.005 µg/L. If an adult drank 2 L of water in a day with 0.005 µg/L of olanzapine, his exposure would be at least 1,000,000 times lower than a therapeutic dose of 10 mg given in a day. Exposure to total residue would be 104,000

times lower than the daily therapeutic dose of olanzapine. Humans are not expected to be adversely affected by any exposure to olanzapine in surface waters.

C. POTENTIAL ADVERSE EFFECTS OF RELEASED SUBSTANCES ON SPECIES IN THE ENVIRONMENT

As with humans, aquatic and terrestrial organisms are not expected to be adversely affected by exposure to any small amount of olanzapine that may be discharged into surface waters. The concentration of olanzapine in surface waters is normally expected to be below 0.005 µg/L. If a terrestrial animal drank 0.2 L of water/kg body weight each day with 0.005 µg/L of olanzapine, it could consume up to 0.001 µg of olanzapine/kg of body weight/day. This oral exposure level is about 2.5×10^5 times lower than the no-effect level of about 0.25 mg/kg/day for doses of olanzapine in a two-generation reproduction study with rats. This oral exposure level is also about 1.7×10^8 times lower than the median lethal dose (174 mg/kg) of olanzapine for female rats. Total olanzapine residue (olanzapine and metabolites) levels would be, at most, 10 times higher than calculated olanzapine levels. Even if it was possible for the total residue to be as active as olanzapine itself, a safety margin of at least 2.5×10^4 would exist for terrestrial mammals. Given the very low concentrations possible in surface waters and the margin of safety demonstrated by mammalian toxicology studies, it is quite unlikely that terrestrial mammals would be adversely affected by olanzapine.

Microbes are relatively insensitive to olanzapine (Appendix J). The minimum inhibitory concentrations (MIC) of olanzapine for *Azotobacter chroococcum* and *Comamonas acidovorans* were >1000 mg/L. *Aspergillus flavus*, *Chaetomium globosum*, and *Nostoc sp.* had MIC values of 1000 mg/L, 400 mg/L, and 255 mg/L, respectively. Possible exposure levels of olanzapine residues in water discharged to municipal sewage treatment facilities (0.048 µg/L) or septic tanks (20 µg/L) are at least 12,750 times lower than the MIC values found for olanzapine.

Rainbow trout (*Oncorhynchus mykiss*) were exposed to average measured olanzapine concentrations ranging from 0.12 to 3.47 mg/L in a 96-hr acute toxicity test (Appendix K). The median lethal concentration of olanzapine was calculated to be 1.74 mg/L in this study. No mortality or other physical signs of toxicity were noted at concentrations up to 0.43 mg/L. This concentration is at least 8900 times higher than the concentration of total olanzapine-related residues (0.048 µg/L) that may be discharged from sewage treatment facilities and at least 8.6×10^4 times higher than the concentration of olanzapine (0.005 µg/L) that may be discharged alone. This acute no-effect level is also about 143 times higher than the highest olanzapine concentration that could be discharged from a production facility.

Daphnia magna were exposed to average olanzapine concentrations ranging from 1.0 to 30.3 mg/L in a 48-hr acute toxicity test (Appendix L). The median effective concentration in this study was 8.0 mg/L. No immobilization or other physical signs of toxicity were noted in this study at olanzapine concentrations up to 2.4 mg/L. This concentration is at least 5×10^4 times higher than the concentration of total olanzapine-related residues (0.048 µg/L) that may be discharged from sewage treatment facilities and at least 4.8×10^5 times higher than the concentration of olanzapine (0.005 µg/L) that may be discharged alone. This acute no-effect level is also about 800 times higher than the highest olanzapine concentration that could be discharged from a production facility.

The green alga *Selenastrum capricornutum* was cultured for 14 days in liquid nutrient media with initial olanzapine concentrations ranging from 0.2 to 14.1 mg/L (Appendix M). Final concentrations ranged from < 0.016 to 10.9 mg/L. Terminal cell count and maximum cell count were significantly lower than control values at initial olanzapine concentrations ≥ 3.4 µg/L (final concentrations ≥ 0.7 µg/L). Average specific growth rates and terminal biomass were significantly reduced relative to control values at initial concentrations ≥ 7.0 mg/L (final concentrations ≥ 4.1 mg/L). Maximum specific growth rate was significantly reduced relative to control cultures at the highest olanzapine concentration tested. The most

conservative no-observed effect concentration for this study was an initial olanzapine concentration of 1.7 mg/L (final concentration of 0.1 mg/L). This concentration is at least 2080 times higher than the concentration of total olanzapine-related residues (0.048 µg/L) that may be discharged from sewage treatment facilities and at least 20,000 times higher than the highest concentration of olanzapine (0.005 µg/L) that may be discharged alone. This acute no-effect level is also about 33 times higher than the highest olanzapine concentration that could be discharged from a production facility.

Since exposure concentrations in the environment are calculated to be extremely low, the proposed action is not expected to affect aquatic or terrestrial species.

9. UTILIZATION OF NATURAL RESOURCES AND ENERGY

Production and formulation of olanzapine will occur at facilities designed for the production and formulation of pharmaceuticals. Formulation and packaging of olanzapine will occur in facilities built to contain any dust. All of these facilities will be operated according to Good Manufacturing Practices.

Endangered and threatened species will not be affected by production of Zyprex. Concentrations of olanzapine that could reach the environment are extremely low and are substantially lower than concentrations that may affect terrestrial or aquatic species.

Properties listed in the National Register of Historic Places will not be affected by the production or use of Zyprex.

In general, process streams from the production of olanzapine only utilize a portion of the waste treatment or recovery facilities already installed for these and other process wastes. Disposal of waste from the manufacturing processes and operations will not require unusual amounts of energy or natural resources.

Estimates of natural resources and energy (electricity, natural gas, coal and oil) used in the production of Zyprex include fixed costs and other miscellaneous energy usage that are not directly related to production, such as adminstrative office use. Activities associated with production, formulation, and packaging of Zyprex will require less than 1% of the total energy-related natural resources used at each of the manufacturing sites for other purposes. Manufacturing Zyprex will have relatively little impact on the use of energy and natural resources at these facilities.

10. MITIGATION MEASURES

As described in Section 8 of this document, the proposed action would not be expected to have any substantial adverse effect on human health or the environment. Strict engineering controls and waste treatment practices described in Section 6A of this document are in place to minimize release of olanzapine and process products at the manufacturing and formulation facilities. Personal protective gear, such as eye protection and protective clothing, is worn to reduce the potential for exposure to olanzapine or process products at these sites. Respirators and gloves may also be worn in certain production operations. Olanzapine is produced under Good Manufacturing Practices. A Material Safety Data Sheet describing olanzapine, its physical properties, toxicity data, general handling precautions, first aid procedures, disposal procedures, and shipping information is available (Appendix N). The manufacturing process for olanzapine involves 10 chemicals on the OSHA Air Contaminants List (Confidential Attachment 3).

11. ALTERNATIVES TO THE PROPOSED ACTION

As described in Section 8 of this document, the proposed action would not be expected to have any substantial adverse effect on human health or the environment. While there are no known environmental benefits from the production and use of Zyprex, there are, likewise, no known significant risks to the environment. Therefore, alternatives to the proposed action do not need to be considered.

12. LIST OF PREPARERS

The following personnel of Eli Lilly and Company are responsible for the preparation of this Environmental Assessment.

Roger D. Meyerhoff, Ph.D.
Head
Environmental Science & Hazard Communications

August 8, 1995
Date

Neil J. Parke, M. A.
Senior Environmental Affairs Representative
Environmental Affairs

August 14, 1995
Date

Daniel E. Brock, M.S.
Assistant Senior Toxicologist
Environmental Science & Hazard Communications

August 8, 1995
Date

Kenneth H. Carlson, M.S.
Head
Toxicology Projects

August 9, 1995
Date

13. CERTIFICATION

The undersigned official certifies that the information presented in this Environmental Assessment is true, accurate, and complete to the best of his knowledge.

Douglas M. Morton, Ph. D.
Vice President
Lilly Research Laboratories

August 9, 1995
Date

14. REFERENCES

KASSAHUN, K. (1995). The disposition and biotransformation of [^{14}C] olanzapine in man. Report of Lilly Research Laboratories. 133 p.

KENEGA, E. E. AND GORING, C. A. (1980). Relationship between water solubility, soil sorption, octanol-water partitioning, and concentration of chemicals in biota. In Aquatic Toxicology, ASTM STP 707 (J. G. Eaton, P. R. Parrish, and A. C. Hendricks, Eds.), pp. 78-115. American Society for Testing and Materials.

Appendix A: Report Summary

Report Title: Determination of the Melting Temperature of Olanzapine

Study No.: N01494

Report Authors: J. S. Teeter and M. Gunnoe, Lilly Research Laboratories, P.O. Box 708, Greenfield, IN 46140

Methods: A melting temperature study with olanzapine was conducted using the Thiele tube technique with a Buchi (model 535) melting point apparatus. The assay was performed in triplicate by increasing the temperature at 1.0 °C/minute. The temperatures at which the compound visually started and completed a physical state change were recorded.

Results: Olanzapine melted at 192.9 ± 0.9°C.

Appendix B: Report Summary

Report Title: The Determination of the Dissociation Constant of Olanzapine in 66% Dimethylformamide-Water by Potentiometric Titration

Study No.: N01794

Report Authors: J.S. Teeter and P. Huang Lilly Research Laboratories, P.O. Box 708, Greenfield, IN 46140

Methods: A dissociation constant study with olanzapine (0.01 M) was conducted using a potentiometric titration in 66% dimethylformamide-water solutions against standardized 0.1 N hydrochloric acid. A calibrated Fisher Accumet 15 pH meter was used to monitor the solution pH in this study. Calculations of pKa were made from information about solution pH, volume of titrant added, concentration of olanzapine, and concentration of titrant. Olanzapine is an organic base and possesses two molecular sites subject to association and dissociation of H^+ in aqueous solution. The molecule should have two dissociation constants.

Results: The mean pKa values for olanzapine were determined to be 7.37 and 4.69.

Appendix C: Report Summary

Report Title: The Ultraviolet-Visible Absorption Spectra of Olanzapine in Aqueous Buffers at pH 5, 7, and 9

Study No.: N01394

Report Authors: J.S. Teeter and M.D. Gunnoe, Lilly Research Laboratories, P.O. Box 708, Greenfield, IN 46140

Methods: An ultraviolet-visible absorption study was performed to determine the absorption spectrum of solutions of olanzapine using a Shimadzu 160 UV-Visible Recording Spectrophotometer. Three solutions of olanzapine at concentrations of 0.0114, 0.015, and 0.0114 mg/mL were prepared in pH 5, 7, and 9 buffers, respectively. Each buffer solution was scanned in the electromagnetic spectral region between 200 and 800 nm. The test was conducted at a temperature of 25±1°C. Reference standard solutions of didymium and holmium oxide were used to demonstrate acceptable performance of the spectrophotometer.

Results: The olanzapine samples produced no absorbance maxima with wavelengths greater than 290 nm. One to three unresolved absorbance maxima were evident for the samples at the pH values tested, however the maxima were all at wavelengths < 259 nm. Therefore, calculation of molar extinction coefficients and band widths was not performed.

Appendix D: Report Summary

Report Title: A Study to Determine the Aqueous Solubility of Olanzapine in Water and pH 5, 7, and 9 Buffers

Study No.: N01194

Report Authors: J.S. Teeter, Lilly Research Laboratories, P.O. Box 708, Greenfield, IN 46140

Methods: The aqueous solubility of olanzapine was determined in buffered solutions at a pH of 5, 7, and 9, and in unbuffered water. Two sets of 12 saturation vessels were used to determine the solubility of the test article in triplicate at pH 5, 7, and 9, and in unbuffered water. One set of vessels was pre-equilibrated at approximately 40 °C for 24 hours to approach equilibrium from the side of oversaturation. The other set of vessels was pre-equilibrated at room temperature to approach equilibrium from the side of undersaturation. The saturation vessels were prepared by placing excess test material and appropriate buffers into the vessels. The vessels were incubated at 25 °C for 24 hours after the pre-equilibration period. At selected time intervals, samples were collected from the vessels and assayed by HPLC for the olanzapine.

Results: Solution pH	Equilibrium Solubility (mean ± std. dev.)
5	> 87.4 ± 4.0 mg/ml (saturated solution at this pH was unobtainable)
7	0.1926 ± 0.0046 mg/ml
9	0.0165 ± 0.0004 mg/ml
unbuffered water (pH 7.55)	0.0541 ± 0.0024 mg/ml

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Appendix E: Report Summary

Report Title: A Study to Determine the Octanol/Water Partition Coefficient of Olanzapine at pH 5, 7, and 9

Study No.: N00295

Report Authors: J.S. Teeter and P. Huang, Lilly Research Laboratories, P.O. Box 708, Greenfield, IN 46140

Methods: An octanol/water partition coefficient study with ^{14}C olanzapine was conducted using the shake flask method at 25 °C. Nominal olanzapine concentrations in octanol were 0.51 or 5.51 µg/ml. Nine vessels were used at each concentration for three replicates at each of the three buffer levels, pH 5, 7, and 9. Replicates at pH 5 and 7 were sampled and each phase was analyzed for radioactivity by scintillation counting at 24, 48, and 72 hours after initiation of the study. Replicates at pH 9 were sampled at selected time intervals and each phase was analyzed for radioactivity by scintillation counting from 24 to 192 hours after initiation of the study. HPLC was utilized to confirm olanzapine concentrations in octanol that were used to start the study.

Results: Partition coefficients were not dependent on olanzapine concentration, but were dependent on pH. Based on the results measured and listed below, olanzapine is not expected to significantly bioconcentrate or readily sorb to organic materials.

Test Sample	Kow (mean ± std. dev.)
pH 5	1.81 ± 0.01
pH 7	48.76 ± 2.28
pH 9	140.8 ± 55.88

Appendix F: Environmental Regulations Affecting the Manufacturing Facility in Kinsale, Ireland and a Letter which Indicates Intent to Comply with these Regulations

Appendix F: Environmental Regulations Affecting the Manufacturing Facility in Kinsale, Ireland.

License Legislation	License	Reference No.	Date of Expiration	Admin. Agency
Air Pollution Control of 1987	Air Pollution Control License	A.P. 3/93(R)	9/1/96	Cork Co. Council
Local Government (Water Pollution) Act 1977	Water Pollution Control License	WP(W) 6/91	11/23/95	Cork Co. Council
European Communities (Toxic and Dangerous Waste Regulations 1982)	Toxic and Dangerous Waste Disposal Permit	2TDW	9/28/95	Cork Co. Council
European Communities (Waste) Regulations 1979	Non Toxic Waste Permit	NTW	12/31/94	Cork Corp.

NOTE: The above licenses will cease to have effect sometime in 1995 as the Kinsale Facility will then be operating under an Integrated Pollution Control (IPC) License issued by the Irish E.P.A. The Kinsale Facility IPC License will have the Reference Number 9. The IPC Licence will last for a period of 3-5 yeras.

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Eli Lilly S.A. – Irish Branch, Dunderrow, Kinsale, Co. Cork.

ELI LILLY S.A. – IRISH BRANCH

Mr. Mark Owens,
Director , Corporate Environmental Affairs,
Eli- Lilly and Co.,
Indiannapolis,
Indiana, 96285.

10/2/95

Dear Mr. Owens,

This letter of confirmation is provided in answer to the request in connection with the Olanzapine submission to the U.S. F.D.A. The request was for official confirmation that our planned facility at Eli-Lilly, Kinsale for the manufacture of Olanzapine will comply with the relevant environmental regulations of Ireland.

We can confirm that our operations in the manufacture of Olanzapine will comply with the requirements set out in our current Environmental licences, namely, Air Pollution Licence A.P. 3/93 (R), Water Pollution Licence W.P. (W) 6/91, Toxic & Dangerous waste permit 2 TDW/1993 and any other Integrated Pollution control licence as issued by the Environmental Protection Agency. It is also our intention that the production of Olanzapine will comply with Good Manufacturing Practices.

Yours Sincerely,

Dr. Kevin Goggin,
Director of Operations & Environmental Control

Tel: (021) 772699
Telex 75900 LILY EI
Fax 776157

Appendix G: Report Summary

Report Title: The Ready Hydrolysis Potential of Olanzapine at 50°C as a Function of pH

Study No.: N01694

Report Authors: J. S. Teeter, Lilly Research Laboratories, P.O. Box 708, Greenfield, IN 46140

Methods: A 5-day hydrolysis study with olanzapine was conducted at test concentrations of 14.7, 14.9, and 4.85 µg/mL in acetate buffer (pH 5), phosphate buffer (pH 7), and borate buffer (pH 9). The temperature of the test solutions was maintained at 50 ± 1°C and the solutions were kept in the dark. Solutions were analyzed by HPLC at the beginning and at the end of the study.

Results: Mean concentrations of olanzapine on Day 5 were 10.12, 11.19, and 1.85 µg/mL at pH 5, 7, and 9, respectively. These results demonstrated that olanzapine hydrolyzed by 31.15%, 24.87%, and 61.85% at the three pH levels tested.

Appendix H: Report Summary

Report Title: A Study to Determine the Hydrolysis Rate of Olanzapine at 25°C at pH 5, 7, and 9

Study No.: N00195

Report Authors: J. S. Tecter, Lilly Research Laboratories, P.O. Box 708, Greenfield, IN 46140

Methods: A 28-day hydrolysis study with olanzapine was conducted at test concentrations of 19.47, 20.11, and 6.12 µg/mL in acetate buffer (pH 5), phosphate buffer (pH 7), and borate buffer (pH 9). The temperature of the test solutions was maintained at 25 ± 1°C and the solutions were kept in the dark. Solutions were analyzed by HPLC at the beginning and at the end of the study.

Results: Olanzapine concentrations at the end of the study averaged 14.42, 15.26, and 4.76 µg/mL at pH 5, 7, and 9, respectively. Linear regression of the log of the measured concentrations over time yielded the following hydrolysis rate parameters:

pH	Hydrolysis Rate Constant (Day^{-1})	Half Life (Days)
5	1.06×10^{-2}	65.3
7	9.12×10^{-3}	75.97
9	8.89×10^{-3}	77.93

Appendix I: Report Summary

Report Title: A Study to Determine the Aerobic Biodegradation of ^{14}C-Olanzapine in Water Using a $^{14}CO_2$ Evolution Test Method

Study No.: N00395

Report Authors: W. Althaus and M. Gunnoe, Lilly Research Laboratories, P.O. Box 708, Greenfield, IN 46140

Methods: ^{14}C-olanzapine was tested for aerobic biodegradability in an aqueous medium at a test concentration of about 15.3 mg/L (10 mg carbon/L) over a 28-day period. Nine reaction vessels, each connected to a series of traps for collection of radiolabeled volatiles and $^{14}CO_2$, were used to evaluate ^{14}C-olanzapine, ^{14}C-sodium benzoate (reference compound), and inoculum control, each in triplicate. All reaction vessels contained a mineral salts medium that was inoculated with an activated sludge suspension from a municipal sewage treatment plant. At periodic intervals during the test, each reaction vessel was assayed for carbon-14 and traps connected to each reaction vessel were assayed for volatile radiolabeled compounds and $^{14}CO_2$. Concentrations of olanzapine were measured by HPLC in the control and test chemical reaction vessels at periodic intervals during the test. At the conclusion of the study, the amount of radioactivity associated with the microbial biomass was determined.

Results: The reference compound, sodium benzoate, was fully metabolized during the study. An average of 81.2% of the radioactivity associated with sodium benzoate was recovered as $^{14}CO_2$. This indicated that microbes in this material could actively metabolize this reference compound.

Olanzapine did biodegrade under the conditions of this study. A small amount (1.47%) degraded to $^{14}CO_2$ or volatile degradation products. Olanzapine remaining in the aqueous portion of the solution in the vessels at the conclusion of the study averaged about 6.5% of the initial concentration. Total radioactivity was accounted for at the end of the study, with most of the radioactivity (58.8%) in the aqueous portion of the test solution. The microbial biomass contained the remaining 41.2% of the radioactivity. Examination of radioactivity in solution at the conclusion of the study showed that olanzapine and several more polar metabolites were present. Two metabolites identified were 2-hydroxymethyl olanzapine and olanzapine-2-carboxylic acid. Extraction of radioactivity from the biomass showed that it did not contain significant quantities of olanzapine or readily identifiable metabolites. The half-life for disappearance of olanzapine was estimated to be 7.4 ± 1.5 days. A regression for reduction in the log of the olanzapine concentration (µg/mL) over time (days) in one of the test vessels was: $y = -0.037x + 1.117$.

Appendix J: Report Summaries

Reports: Microbial Growth Inhibition from Exposure to Olanzapine

Study No.: Z00495, Z00595, Z00695

Report Authors: J. B. Heim and D. E. Brock, Lilly Research Laboratories, P.O. Box 708, Greenfield, IN 46140

Methods: Olanzapine was evaluated for any potential to inhibit the growth of pure cultures of the species *Aspergillus flavus, Chaetomium globosum, Comamonas acidovorans, Azotobacter chroococcum,* and *Nostoc* sp. Olanzapine was incorporated into agar-based media at concentrations of 0, 200, 400, 600, 800, 1000 mg/L for *Aspergillus flavus, Chaetomium globosum, Comamonas acidovorans, and Azotobacter chroococcum.* It was incorporated into agar-based media at concentrations of 0, 51, 150, 255, 345, and 450 mg/L for exposure to *Nostoc* sp. Duplicate test plates were inoculated with pure cultures of each species. Incubation temperatures for *Azotobacter* , *Comamonas* , *Aspergillus,* and *Chaetomium* were about 26 °C. *Nostoc* was grown at an average temperature of 25.6 °C and an average light intensity of 190 $\mu E/m^2/sec$.

Results: The minimum inhibitory concentrations (MIC) of olanzapine for *Azotobacter chroococcum* and *Comamonas acidovorans* were >1000 mg/L. *Aspergillus flavus, Chaetomium globosum,* and *Nostoc sp.* had MIC values of 1000 mg/L, 400 mg/L, and 255 mg/L, respectively.

Appendix K: Report Summary

Report Title: The Acute Toxicity of Olanzapine to Rainbow Trout in a Static-Renewal Test System

Study No.: F00595

Report Authors: D.E. Brock and J.B. Heim, Lilly Research Laboratories, P.O. Box 708, Greenfield, IN 46140

Methods: A toxicity test was conducted to determine the acute effects of olanzapine on rainbow trout (*Oncorhynchus mykiss*). Juvenile trout weighing about 1.1 g each were exposed for 96 hrs to average assayed olanzapine concentrations of 0 (water and acetic acid controls), 0.12, 0.43, 0.73, 1.80, or 3.47 mg/L. A small amount of acetic acid was used to help solubilize the olanzapine. Test solutions were changed every 12 hrs in order to maintain stable test concentrations. Twenty fish were exposed at each treatment level. Water temperature ranged from 11.1 to 12.7°C, pH ranged from 7.0 to 8.1, and dissolved oxygen ranged from 9.6 to 11.7 mg/L. At the beginning of the study, the water quality was characterized by a total hardness of 103 mg/L as $CaCO_3$, a total alkalinity of 120 mg/L as $CaCO_3$, a conductivity of 239 µmhos. Un-ionized ammonia levels at test initiation and termination were ≤0.01 mg/L.

Results: No mortality or other physical signs of toxicity were observed at concentrations ≤0.43 mg/L. Fish displayed signs of hypoactivity, prostration, and mortality at concentrations ≥0.73 mg/L. Based on these observations, the 96-hr median lethal concentration and 95% confidence limits were 1.74 mg/L and 1.35 to 2.25 mg/L. The slope of the concentration mortality curve at 96 hrs was 3.2.

Appendix L: Report Summary

Report Title: The 48-hour Acute Toxicity of Olanzapine to *Daphnia magna* in a Static Test System

Study No.: C00295

Report Authors: D.E. Brock and J.B. Heim, Lilly Research Laboratories, P.O. Box 708, Greenfield, IN 46140

Methods: A toxicity test was conducted to determine the acute effects of olanzapine on *Daphnia magna*. First-instar organisms were exposed for 48 hours to average assayed olanzapine concentrations of 0, 1.0, 2.4, 5.0, 10.0, 20.3, and 30.3 mg/L. Control animals were exposed to dilution water and water containing a small amount of acetic acid, which was used to solubilize olanzapine. A total of 20 organisms were tested at each treatment level. Assessments of toxicity were based on signs of sublethal toxicity and frequencies of immobilization in exposed populations. Temperature of test solutions averaged 20.0 °C and pH ranged from 8.1 to 8.8. Dissolved oxygen concentrations averaged 8.6 mg/L. Total hardness, total alkalinity, and conductivity of the control water at test initiation were 86 mg/L as $CaCO_3$, 86 mg/L as $CaCO_3$, and 176 µmhos, respectively.

Results: No treatment-related immobilization or other physical signs of toxicity were observed in *Daphnia magna* exposed to average assayed olanzapine concentrations ≤ 2.4 mg/L. Hypoactivity, prostration, and immobilization were observed at higher concentrations. The 48-hr EC50 and 95% confidence limits were calculated to be 8.0 mg/L and 9.3 to 10.9 mg/L, respectively.

Appendix M: Report Summary

Report Title: The 14-Day Acute Toxicity of Olanzapine to the Freshwater Green Alga (*Selenastrum capricornutum*) in a Static Test System

Study No.: J00394

Report Authors: D.W. Poage, Lilly Research Laboratories, P.O. Box 708, Greenfield, IN 46140

Methods: A static toxicity test was conducted to evaluate the effects of olanzapine on the green alga, *Selenastrum capricornutum*. Algal cells were cultured under continuous wide-spectrum light (80 $\mu E/m^2/sec$) for 14 days in a liquid nutrient medium that contained olanzapine at initial assayed concentrations of 0 (water and acetic acid controls), 0.2, 0.8, 1.7, 3.4, 7.0, and 14.1 mg/L. Each treatment consisted of three replicate 500-ml Erlenmeyer flasks containing 100 ml of nutrient medium with an initial algal density of 1000 cells/ml. Temperatures of the test solutions ranged from 24.8 to 25.3°C. The pH values of the test solutions ranged between 7.0 to 7.5 at the beginning of the study, and 7.8 to 9.1 at the end of the study. The algal population of each flask was quantified on Days 2, 3, 4, 5, 7, 10, and 14 using a compound microscope and hemacytometer, and algal biomass was measured on Day 14. These measurements were used to determine the no-observed effect concentration.

Results: After 14 days, olanzapine was not detectable (limit of detection was 0.016 mg/L) in the 0.2 and 0.8 mg/L treatments. Analyzed concentrations in the remaining treatments were 0.1, 0.7, 4.1, and 10.9 mg/L. The drops in test concentrations may have been due to biodegradation or hydrolysis. Terminal cell count and maximum cell count were significantly lower than control values at inital olanzapine concentrations $\geq$ 3.4 µg/L (final concentrations $\geq$ 0.7 µg/L). Average specific growth rates and terminal biomass were significantly reduced relative to control values at initial concentrations $\geq$ 7.0 mg/L (final concentrations $\geq$ 4.1 mg/L). Maximum specific growth rate was significantly reduced relative to control cultures at the highest olanzapine concentration tested. The EC50 for the average specific growth rate was calculated to be greater than the highest concentration tested. The most conservative no-observed effect concentration for this study was an initial olanzapine concentration of 1.7 mg/L (final concentration of 0.1 mg/L).

Appendix N: Material Safety Data Sheet for Olanzapine

LILLY RESEARCH LABORATORIES
EXPERIMENTAL COMPOUND
MATERIAL SAFETY DATA SHEET

ELI LILLY AND COMPANY • LILLY CORPORATE CENTER • INDIANAPOLIS, INDIANA 46285

COMMON NAME: Olanzapine
(Lilly Nos.: QA402E, QA406G, LSN170053)
REVISED DATE: April 28, 1995

SECTIONS REVISED: Sections 1, 3, 5, 7, 8, 9

EMERGENCY TELEPHONE: 317-276-2000 CHEMTREC TELEPHONE: 1-800-424-9300

This document provides available information relevant to the handling of the experimental material identified above. Some of the information contained herein is preliminary, and some sections may contain opinions based on available scientific information. All of the information is offered with the good faith belief that it is accurate, but this safety data sheet does not constitute a warranty of any kind, express or implied. This document and the accompanying caution statement have been made available so that proper protective measures can be taken by persons who may be exposed to the material during pre-market research and development activities. In the event of any adverse incident associated with this material, the safety data sheet is not intended to be a substitute for consultation with appropriately trained personnel.

This document is not to be distributed outside of Eli Lilly and Company without the express consent of the project manager.

See attached glossary for abbreviations.

Lilly Lab Labeling Codes: Health: 2 Fire: 1 Reactivity: 1
Special: P

Primary Physical and Health Hazards: Toxic. Irritant (eyes, skin). Highly Potent. Nervous System, Blood, Liver, Hormone Effects.

Caution Statement: Olanzapine is toxic, may be irritating to the eyes and skin, and is highly potent. Effects of exposure may include drowsiness, changes in blood cell count, changes in serum liver enzymes, and increase in serum prolactin.

Lilly Exposure Guideline: 0.038 mg/m3 TWA for 12 hours

COMMON NAME: Olanzapine
(Lilly Nos.: QA402E, QA406G, LSN170053)
REVISED DATE: April 28, 1995

---------- SECTION 1 - MATERIAL IDENTIFICATION ----------

Common Name: Olanzapine

Chemical Name: 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)-

Synonyms/Trade Names: NAIF

CAS Number: 132539-06-1

Molecular Formula: C17 H20 N4 S

Chemical Family: Benzodiazepine

Intended Use: Antipsychotic agent

---------- SECTION 2 - PHYSICAL DATA ----------

Appearance: Off-white to yellow crystalline powder

Odor: Odorless

Boiling Point: NA

Melting Point: 195 C (383 F)

Specific Gravity: NA

pH: 6.1 (saturated aqueous solution)

Evaporation Rate: NAIF

Solubility in Water: Insoluble

Vapor Density: NAIF

Vapor Pressure: NAIF

COMMON NAME: Olanzapine
(Lilly Nos.: GA402E, GA406G, LSN170053)
REVISED DATE: April 28, 1995

---------- SECTION 3 - FIRE AND EXPLOSION INFORMATION ----------

Extinguishing Media: Use water, carbon dioxide, dry chemical, foam, or Halon.

Unusual Fire and Explosion Hazards: Extreme caution should be exercised in handling this compound. As a finely divided material, may form dust mixtures in air which could explode if subjected to an ignition source.

Flash Point: NAIF

Method: NA

UEL: NAIF

LEL: NAIF

---------- SECTION 4 - REACTIVITY INFORMATION ----------

Stability: This material should not be exposed to temperatures above 115 C (239 F). If this temperature is exceeded a rapid build-up of heat and pressure may occur. This temperature is based on a laboratory test and assumes near atmospheric pressures and quantities of less than 500 kg (1100 lb). For additional information refer to the CHL data base on EHSS or contact the Lilly Chemical Hazards Laboratory.

Incompatibility: May react with strong oxidizing agents (e.g., peroxides, permanganates, nitric acid, etc.).

Hazardous Decomposition: May emit toxic fumes when heated to decomposition.

Hazardous Polymerization: Not known to occur.

COMMON NAME: Olanzapine
(Lilly Nos.: QA402E, QA406G, LSN170053)
REVISED DATE: April 28, 1995

SECTION 5 - HEALTH HAZARD INFORMATION

Human - Occupational

Effects, Including Signs and Symptoms, of Exposure: Contact dermatitis has been reported. Based on the clinical dose, Olanzapine is highly potent.

Medical Conditions Aggravated By Exposure: None known.

Primary Route(s) of Entry: Inhalation and skin contact.

Exposure Guidelines: PEL and TLV not established.
LEG 0.038 mg/m3 TWA for 12 hours

Human - Clinical

Clinical Experience: The most frequently reported events in multiple dose studies were drowsiness, agitation, nervousness, constipation, and dry mouth. Laboratory results revealed transient elevations in liver function tests, and minimal elevation in serum prolactin levels at higher doses.

Animal Toxicity Data Single Exposure

Oral: Rat, median lethal dose 177 mg/kg, reduced activity, lethargy, coma, tremors, convulsions, drooping eyelids, salivation.

Monkey, 100 mg/kg, no deaths, sedation, prostration, reduced activity, anorexia.

Skin: Rabbit, 200 mg/kg, no deaths or toxicity.

Inhalation: Rat, 880 mg/m3 for four hours, no deaths, reduced activity, lethargy, labored respiration, prostration.

Skin Contact: Rabbit, nonirritant

Eye Contact: Rabbit, irritant

COMMON NAME: Olanzapine
(Lilly Nos.: QA402E, QA406G, LSN170053)
REVISED DATE: April 28, 1995

---------- SECTION 5 - HEALTH HAZARD INFORMATION (continued) ----------

Animal Toxicity Data Repeat Exposure

Target Organ Effects: Nervous system effects (sedation, reduced activity, salivation, pupil constriction), blood effects (decreased blood cell counts), lymphatic system effects (lymphoid tissue changes), heart effects (increased heart rate).

Reproduction: Decreased mating activity due to sedation. Decreased fertility, abnormal reproductive cycles, and reproductive tissue changes due to elevated prolactin levels. These effects of prolactin are not considered relevant to humans. Embryo and fetal toxicity occurred only at maternally toxic doses.

Sensitization: NAIF

Mutagenicity: Not mutagenic in bacterial or mammalian cells.

Carcinogenicity: Olanzapine produces mammary tumors in female rats and female mice. This is thought to be related to elevated prolactin levels. There is insufficient evidence to extrapolate effects in rodents to humans, with respect to the role of prolactin in human mammary carcinogenesis. An increased incidence of lymphosarcoma has been observed in female mice. The relevance of this finding to humans is not clear.

---------- SECTION 6 - EMERGENCY AND FIRST AID PROCEDURES ----------

Eyes: Hold eyelids open and flush with a steady, gentle stream of water for 15 minutes. See an ophthalmologist (eye doctor) or other physician immediately.

Skin: Remove contaminated clothing and clean before reuse. Wash all exposed areas of skin with plenty of soap and water. Get medical attention if irritation develops.

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COMMON NAME: Olanzapine
(Lilly Nos.: QA402E, QA406G, LSN170053)
REVISED DATE: April 28, 1995

SECTION 6 - EMERGENCY AND FIRST AID PROCEDURES (continued)

Inhalation: Move individual to fresh air. Get medical attention if breathing difficulty occurs. If not breathing, provide artificial respiration assistance (mouth-to-mouth) and call a physician immediately.

Ingestion: Call a physician or poison control center. Drink one or two glasses of water and give 1-2 tablespoons syrup of ipecac to induce vomiting. Do not induce vomiting or give anything by mouth to an unconscious person. Immediately transport to a medical care facility and see a physician.

SECTION 7 - HANDLING PRECAUTIONS

For appropriate handling precautions in specific laboratory or manufacturing operations, consultation with an occupational health and safety or technical services representative is recommended.

Respiratory Protection: Use an approved HEPA-filtered or supplied-air respirator.

Eye Protection: Chemical goggles and/or face shield.

Ventilation: Extensive local exhaust or enclosed process equipment.

Other Protective Equipment: Chemical-resistant gloves and body covering to minimize skin contact. If handled in a ventilated enclosure, as in a laboratory setting, respirator and goggles or face shield may not be required. Safety glasses are always required.

Other Handling Precautions: In production settings, airline-supplied, hood-type respirators are preferred. Shower and change clothing if skin contact occurs.

COMMON NAME: Olanzapine
(Lilly Nos.: QA402E, QA406G, LSN170053)
REVISED DATE: April 28, 1995

---------- SECTION 8 - SPILL, LEAK AND DISPOSAL PROCEDURES ----------

Spills: Contain dry material by lightly misting with water, followed by sweeping up or vacuuming. Vacuuming may disperse dust if appropriate dust collection filter is not part of the vacuum. Be aware of potential for dust explosion when using electrical equipment. Wear protective equipment, including eye protection, to avoid exposure (see Section 7 for specific handling precautions).

Waste Disposal: Dispose of any cleanup materials and waste residue according to applicable federal, state, and local regulations.

---------- SECTION 9 - SHIPPING INFORMATION ----------
(Proper Shipping Name / Hazard Class / UN Number)

DOT: Toxic solids, organic, n.o.s. (olanzapine) / 6.1 / UN2811

ICAO: Toxic solid, organic, n.o.s. (olanzapine) / 6.1 / UN2811

IMO: Toxic solid, organic, n.o.s. (olanzapine) / 6.1 / UN2811

Packing Group: III

For additional information contact: Environmental Science and Hazard Communication: 317-277-4973

GLOSSARY
Abbreviations Used in Material Safety Data Sheets

ACGIH = American Conference of Governmental Industrial Hygienists
BEI = Biological Exposure Index
CAS Number = Chemical Abstract Service Registry Number
CERCLA = Comprehensive Environmental Response Compensation and Liability Act (of 1980)
CHEMTREC = Chemical Transportation Emergency Center
CWA = Clean Water Act
DOT = Department of Transportation
EP = Extraction Procedure as defined under RCRA Regulations
EPA = Environmental Protection Agency
HEPA = High Efficiency Particulate Air (Filter)
HSDB = Hazardous Substance Data Base
IARC = International Agency for Research on Cancer
ICAO = International Civil Aviation Organization
IMO = International Maritime Organization
LEG = Lilly Exposure Guideline
LEL = Lower Explosive Limit
MSDS = Material Safety Data Sheet
NA = Not Applicable, except in Section 9 where NA = North America
NAIF = No Applicable Information Found
NCI/NTP = National Cancer Institute/National Toxicology Program
NIOSH = National Institute for Occupational Safety and Health
NOS = Not Otherwise Specified
OHS = Occupational Health Services
OSHA = Occupational Safety and Health Administration
PEL = Permissible Exposure Limit
PSN = Proper Shipping Name
RCRA = Resource Conservation and Recovery Act
RTECS = Registry of Toxic Effects of Chemical Substances
SARA = Superfund Amendments and Reauthorization Act
STEL = Short Term Exposure Limit
TLV = Threshold Limit Value
TSCA = Toxic Substances Control Act
TWA = Time Weighted Average/8 Hours Unless Otherwise Noted
UEL = Upper Explosive Limit
UN = United Nations

APPENDIX 1

NON-CONFIDENTIAL APPENDIX TO AN ENVIRONMENTAL ASSESSMENT FOR THE USE OF ZYPREXA™ IN THE TREATMENT OF PSYCHOTIC DISORDERS

NOTE (Applicable to the Entire Environmental Assessment):

The final trade name of the drug product is Zyprexa. This name should be used wherever the original name Zyprex is written in the submitted Environmental Assessment.

4. Description of the Proposed Action

This section of the assessment identifies those locations from which materials may be introduced into the environment. It should be noted in this section that returned or rejected drug substance in the United States will be disposed of at the following facility by incineration according to a Resource Conservation and Recovery Act Permit issued by the U.S. EPA under facility identification number IND072040348:

6. Introduction of Substances into the Environment

2. Environmental Regulatory Requirements

This section of the assessment identifies the environmental regulatory requirements for facilities associated with producing, formulating and packaging Zyprexa. Non-confidential statements of compliance for the plant site in and for the packaging plant are provided as attachments to this amendment.

It should also be noted in this section that packaging of Zyprexa tablets will be carried out at the Air from the Zyprexa filling room will pass through HEPA filters, which will be packaged with solids, particulates, and dust for disposal. Air emissions (particulate matter) for Zyprexa are regulated by the Puerto Rico Environmental Quality Board. Wash water from the packaging facility will be collected and discharged to a Puerto Rican Aqueduct and Sewer Authority (PRASA) Regional Waste Treatment Plant. These activities should not affect current emission requirements.

3. Wastestream Treatment, Control, and Handling

b. Solid Wastes from Manufacturing

This section indicates that solid wastes from the production, formulation, and packaging operations will be collected and sent to appropriate solid waste facilities. All solid wastes from the packaging operations for Zyprexa a will be returned to Eli Lilly Industries, Inc., Carolina, Puerto Rico operations for disposal as described below.

Solid wastes that contain the drug substance from the production, formulation, and packaging operations in the United States and Puerto Rico (including) will be sent to the following facility for incineration according to a Resource Conservation and Recovery Act Permit issued by the U.S. EPA under facility identification number IND072040348:

Solid wastes that do not contain the drug substance from the formulation and packaging operations in will be sent to the following regulated non-hazardous waste incineration facility in accordance with any conditions and requirements stipulated for non-hazardous waste disposal:

C

1st Review

CONFIDENTIAL

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-592

Zyprexa™
(formerly Zyprex™)

(Olanzapine)

Tablet

Division of Neuropharmacological Drug Products

(HFD-120)

CENTER FOR DRUG EVALUATION AND RESEARCH

SUMMARY

This full Environmental Assessment, submitted by Eli Lilly and Company, is dated June 1995, so it was written before the Guidance for Industry was released. The product does qualify for Tier 0, but we will review it in the full format.

It is not clear that the Environmental Assessment as currently written is non-confidential. The volume begins with a confidential disclaimer and the MSDS is not to be released without project manager approval. The environmental Assessment will be made public by the FDA as required by the Council on Environmental Quality so it must consist entirely of non-confidential information.

A number of deficiencies were uncovered during the present review. See deficiency letter.

Substantive laboratory work was conducted and the reports written according to GLP.

According to Dr. Mona Zarifa and Dr. Stanley Blum of HFD-120, Eli Lilly has recently changed the brand name from Zyprex to Zyprexa. The updated EA should give the correct present trade name.

CONCLUSIONS

Synthetic manufacture, tablet production and packaging, and sales of Zyprexa (Olanzapine) is not expected to have a detrimental environmental effect because:

1. All emissions will be controlled in appropriate manner.

2. Olanzapine is expected to biodegrade in the aqueous environmental compartment in a short period of time, based on laboratory tests.

3. Olanzapine toxicology tests show that, at the maximum expected environmental concentration (MEEC), it is not harmful to a variety of aquatic life forms.

4. Eli Lilly and Company holds the expected licences for each of the production facilities, while Eastman Chemical does the same.

RECOMMENDATIONS

However, this reviewer recommends that the deficiency letter at the end of this review be communicated to the firm immediately.

ENVIRONMENTAL ASSESSMENT REVIEW
(Full)

1. **Date of EA Submission:**

   June 1995

   S. Hardeman, CSO

   Adequate

2. **Name of applicant/petitioner:**

   Eli Lilly and Company

   Adequate

3. **Address:**

   Eli Lilly Corporate Center
   Indianapolis, Indiana 46285

   Adequate

4. **Description of the proposed action:**

   a. **Requested Approval:**

      "Eli Lilly and Company is seeking approval for the use of Zyprex™ in the treatment of psychotic disorders." Packaging details are not given in this section, but rather in Format Item 6, last paragraph page 20. Zyprexa will be available as 2.5, 5, 7.5, or 10 mg tablets. "The primary packaging for Zyprex will be bottles and blister units. Zyprex tablets will be added to amber, high-density polyethylene bottles. The bottles will also hold a desiccant canister and a cotton filler. The blister units are made from thin laminates of aluminum foil, nylon, and PVC."

      Adequate

   b. **Need for Action:**

      "Zyprex is indicated for the acute and long term treatment of schizophrenia and related psychoses in which positive symptoms, and/or negative symptoms are prominent."

Adequate

c. **Production Locations:**

I. **Proprietary Intermediate(s):**

All manufacturing of substance and intermediates is done at the three sites given below. No other firms or sites are used.

ii. **Drug Substance:**

Eli Lilly S.A.
Dunderrow, Kinsale
County Cork
Ireland

Eli Lilly and Company
Tippecanoe Laboratories
Lilly Road
Shadeland, Indiana

iii. **Finished Dosage Form:**

Manufactured and Packaged by:

Eli Lilly Industries, Inc.
Km. 12.5, 65th Infantry Avenue
Carolina, Puerto Rico

Adequate

d. **Expected Locations of Use (Drug Product):**

The drug will be used in hospitals, clinics, and by patients in their homes.

Adequate

e. **Disposal Locations (Drug Product):**

The drug product will be disposed of in sewage treatment facilities and individual home septic tanks throughout this country.

Adequate

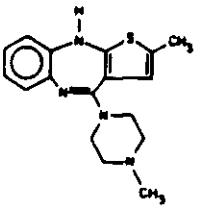
5. Identification of chemical substances that are the subject of the proposed action:

Drug Substance

Established Name: olanzapine INN, USAN
Chemical Name: 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine
CAS #: 132539-06-1
Laboratory Code Number: QA402E, QA406G, LSN170053
Molecular Weight: 314.4
Molecular Formula: $C_{17}H_{20}N_4S$

Structural Formula:

Olanzapine *[1992]* (oh lan' za peen). $C_{17}H_{20}N_4S$. 312.44. (1) 10*H*-Thieno[2,3-*b*][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)-; (2) 2-Methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine. *CAS-132539-06-1*. INN. *Antipsychotic*. (Lilly) ◆*LY170053*



Physical Description: off-white to yellow crystalline solid
Additives: none
Impurities: less than 0.5% total related substances
Other Physical Properties: given in public EA submission page 7-8

Drug Product

Excipients: provided in confidential attachment 1

Adequate

6. Introduction of substances into the environment: For the site(s) of production:

a. Potential Emitted substances:

I. Drug Substance:

Eli Lilly S.A.
Dunderrow, Kinsale
County Cork
Ireland

The Director of Operations and Environmental Control, Dr. Kevin Goggin, certifies that the above facility is and will be in compliance with all applicable Irish environmental laws. See page 46 in the EA.

Our Guidance for Industry states that if further information is needed, the FDA will request it. This reviewer feels that no further information is needed.

Adequate

Olanzapine is produced in a multi-step chemical process. The disposition of materials used, consumed, and produced in olanzapine manufacture is described in Confidential Attachment 2. Production processes for olanzapine require the use of 10 chemicals on the OSHA Air Contaminants List; see Confidential Attachment 3. See DMF 10,738 for further information.

Eli Lilly and Company
Tippecanoe Laboratories
Lilly Road
Shadeland, Indiana

Olanzapine is produced in a multi-step chemical process. The disposition of materials used, consumed, and produced in olanzapine manufacture is described in Confidential Attachment 2. Production processes for olanzapine require the use of 10 chemicals on the OSHA Air Contaminants List; see Confidential Attachment 3.

Adequate

ii. **Finished Dosage Form:**

Manufactured and Packaged by:

Eli Lilly Industries, Inc.

Km. 12.5, 65th Infantry Avenue
Carolina, Puerto Rico

Emitted materials are waste substance, tablets, and packaging materials.

Emitted materials are the same as above.

Adequate

b. **Controls (Air, Liquid Effluent, Solid):**

I. **Drug Substance:**

Control of Air Emissions

Air emissions from the batch manufacturing area are treated in two Regenerative Thermal Oxidizer units.

Control of Liquid Effluent

Liquid effluent is treated in a biological waste-ater treatment system.

Control of Solid Waste

Incineration is used for any hazardous (solid) waste.

Eli Lilly and Company
Tippecanoe Laboratories
Lilly Road
Shadeland, Indiana

Controls for Air

Waste gases from the process can be captured by liquid scrubbers, vented to a carbon absorber, vented to a condenser, or vented to a regenerative

thermal oxidizer.

Controls for Liquid Effluent

Aqueous waste is either treated by biological treatment or destroyed by incineration. Solvent wastes are either recovered for reuse or destroyed by incineration.

Controls for Solid

"Any waste solids are either regenerated, recycled or destroyed by incineration at an approved facility."

Adequate

ii. **Finished Dosage Form:**

Manufactured and Packaged by:

Eli Lilly Industries, Inc.
Km. 12.5, 65th Infantry Avenue
Carolina, Puerto Rico

Control of Air Emissions

"All room air will pass through HEPA filters, which will be packaged with solids, particulates, and dust for approved disposal."

For the fluidized dryer, and the other machines involved in tablet manufacture, the final air treatment is HEPA filters of 99.9% control efficiency.

Adequate

Control of Liquid Effluent

The site has a biological activated sludge treatment plant that removes suspended solids, biological oxygen demand (BOD), and chemical oxygen demand (COD). That waste water goes to the Regional Waste Treatment Plant permitted by the Puerto Rican Aqueduct and Sewer Authority (PRASA).

Adequate

Control of Solid Waste

Solid wastes generated at this plant will be

collected and disposed of at approved landfill or incinerator facilities.

The submission states that "Any rejected material, plastic liners, gloves, hair covers, or filters will be collected and disposed of at approved facilities (i.e., landfill or incinerator)". See page 19 of the EA.

Deficient

Disposition of unused product or rejected packaged goods, including those at contract packagers, should be discussed in this format item 6.b., if it has not been described in EA format item 4.e. Firm has not complied with the above guidance.

The . dated October 1995, contains a short EA. This documents states that, in effect, appropriate controls are used and is in compliance.

Adequate

c. **Compliance with Federal, State and Local Emission Requirements:**

"Eli Lilly and Company will comply with all applicable Federal, State, and local regulations concerning emission control and waste treatment at all production and formulation facilities."

I. **Drug Substance**

Deficient

has not provided a public statement of compliance with environmental laws.

EASTMAN CHEMICAL BATESVILLE			
Emission	Authorizing Agency	Permit #	Expiration Date
discharge of waste water	both EPA and Arkansas Department of Pollution Control and Ecology	NPDES AR0035386	5/31/97
materials	"	RCRA ARD089234884	11/01/99
air emissions	"	AIR 1085-AR-0	no expiration date

Eli Lilly and Company
Tippecanoe Laboratories
Lilly Road
Shadeland, Indiana

Permit information is provided along with a list of applicable laws.

Adequate

ii. **Finished Dosage Form:**

Manufactured and Packaged by:

Eli Lilly Industries, Inc.
Km. 12.5, 65th Infantry Avenue
Carolina, Puerto Rico

Permit numbers, and licencing authority is given.

states that the firm is in

compliance with all applicable environmental rules and regulations in their DMF.

Deficient

must certify this in the public part of the EA. See Deficiency Letter.

d. **Effect of Approval on Compliance with Current Emissions Requirements:**

I. **Drug Substance:**

states "Because of the nature of the environmental permits at the Eastman Chemical facility, no changes were needed for the production of materials related to olanzapine". Thus, we can conclude that approval will not effect the state of compliance. See page 10 of the EA.

Eli Lilly and Company
Tippecanoe Laboratories
Lilly Road
Shadeland, Indiana

Eli Lilly states that "In general, less than one percent of the daily discharge of wastewater from this facility will be attributed directly to olanzapine manufacturing. Thus we can conclude that approval will not effect state of compliance. See page 15 of the EA.

Adequate

ii. **Finished Dosage Form:**

Manufactured and Packaged by:

Eli Lilly Industries, Inc.
Km. 12.5, 65th Infantry Avenue
Carolina, Puerto Rico

From the discussion of the facilities on page 10 of the submission, it is reasonable to conclude that approval of this NDA will not effect state of compliance.

Adequate

Deficient

does not explain the effect of approval on compliance with current emissions requirements in the public part of the EA.

e. **Expected Introduction Concentrations**

1. **Expected Introduction Concentrations from Use**

"The projected total use of olanzapine in any 1 year in the US will be less than " Thus, the concentration in the waste water must be considerably less than 1 ppb, since corresponds to

See the next section for several calculations.

2. **Expected Introduction Concentrations from Disposal**

See the next section.

Adequate

7. **Fate of emitted substances in the environment:**

The studies in which the following data was generated, were conducted according to GLP.

Impurities are not discussed in the EA document, but since this is a synthetic substance the impurities are minimal and not of concern.

Atmospheric Ecosystem

Olanzapine is a nonvolatile crystalline solid, so measurable concentrations are not expected in the atmosphere.

Aquatic Ecosystem

"Olanzapine does not significantly absorb light at wavelength between 290 and 800 nm." It is therefore

unlikely that olanzapine will be directly photolyzed in water. Olanzapine does hydrolyze in hot water (Appendix G), but does so slowly at a relevant temperature. At 25 C and at solution pH values ranging from 5 to 9, the hydrolysis half-life of olanzapine ranged from about 65 to 78 days (Appendix H)."

Olanzapine does biodegrade, since in an aerobic biodegradation study with ^{14}C-labeled substance, only 6.5% of the olanzapine used to start the 28-day study was detectable at the end of the study (Appendix I). The half-life for the substance in the biodegradation study was estimated as 7.4 days.

MEEC

The firm states that no more than _ of olanzapine will be used per year in this country. That amount would suggest an unadjusted MEEC of

The firm calculated the MEEC as 0.048 ppb, assuming 10% of the dose is excreted. Their calculation assumes different numbers than ours. In any case the MEEC is low enough to qualify for Tier 0.

Terrestrial Ecosystem

"Olanzapine is very soluble in water (at least 87.4 g/L) at pH 5, but only moderately soluble at pH 7 (192.6 mg/L) and at pH 9 (16.5 mg/L). High to moderate water solubility and low to moderate n-octanol/water partition coefficients (1.81 to 140.8)* indicate that olanzapine will probably not strongly adsorb to sediment or soil."

* log of these results is much less than 3.5.

Adequate

8. **Environmental effects of released substances:**

Eli Lilly provides a summary of Mammalian toxicity studies, of which there are quite a number. See information starting on page 24 of the submitted EA.

Exposure of humans to the olanzapine in drinking water is discussed and a reasonable conclusion is that no detrimental effect will take place. According to the way Eli Lilly computes the concentration after treatment, the olanzapine MEEC will be 0.048 ppb or below.

ENVIRONMENTAL ORGANISM TESTING AND RESULTS				
Organism	EC_{50}	LC_{50}	MIC	NOEC
Azotobacter chroococcum			>1000mg/L	
Comamonas acidovarans			same	
Aspergillus flavus			1000mg/L	
Chaetomium globsum			400mg/L	
Nostoc sp.			255mg/L	
Rainbow Trout (*Oncorhynchus mykiss*)		1.74mg/L		0.43mg/L (96h)
Daphnia magna	8.0mg/L			2.4mg/L
Green Alga (Selenastrum capricornutum)				1.4mg/L

The NOEC is in all cases more than 1000 times greater than the MEEC.

Adequate

9. **Use of resources and energy:**

   a. **Production:**

      The firm estimates that energy use at each of the production sites will be less than 1% of the total energy use.

   b. **Effect on Endangered/Threatened Species:**

      The firm states that there will be no effect on such species.

   c. **Effect on Properties Listed/Eligible for National Register of Historic Places:**

      Firm states that such properties will not be effected.

Adequate

10. **Mitigation measures:**

Mitigation measures include waste treatment controls, personal protective gear is required, product is under GMP, and MSDS is available.

Adequate

11. **Alternatives to the proposed action:**

Firm states that since there is no anticipated adverse environmental effect, alternatives are not needed.

Adequate

12. **List of preparers, & their qualifications (expertise, experience, professional disciplines) and consultants:**

Adequate

13. **Certification:**

Adequate

14. **References:**

Adequate

15. **Appendices:**

The Eli Lilly Appendices include some 12 report summaries, non-confidential, for such physical properties as Octanol/Water Partition Coefficients.

The MSDS is included.

Adequate

DEFICIENCY LETTER

The following deficiencies have been and need immediate correction. The applicant may either mit an updated EA incorporating the additional information or provide an amendment (non-confidential) that FDA will attach to the original EA submission.

1. It is not clear that the Environmental Assessment as it is currently written is non-confidential. The volume begins with a confidential disclaimer and the MSDS is not to be released without project manager approval. The environmental assessment will be made public by the FDA as required by the Council on Environmental Quality so it must consist entirely of non-confidential information. See Industry Guidance described below.

2. The current Environmental Assessment does not discuss the disposition of unused product or rejected packaged goods at Eli Lilly nor the disposition of returned goods. This subject should be discussed in CFR Environmental Assessment format item 6 or 4.

3. The trade name of the drug product was changed to Zyprexa from Zyprex recently. If an FOI Environmental Assessment is submitted (see deficiency 1), it should provide the current correct trade name. If an amendment is provided, the correct name should be confirmed therein.

4. have not provided non-confidential statements of compliance with, or being on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the manufacturing operations.

5. does not explain the effect of approval on compliance with current emissions requirements in the public part of the EA.

In the future, submission of an index tabbed volume would expedient review of the submission.

Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements is now available by FAX on Demand. Call 1-800-342-2722 and follow the instructions to request document number 0803. Because of expected demand, it may take up to 24 hours for the FAX to arrive.

This guidance document may also be downloaded in WordPerfect format from the Food and Drug Administration CDER Gopher. Open the FDA World Wide Web Page and select the "search" facility. Go to the "Industry Guidance" directory.

6/21/96

Prepared by
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

6/21/96

Concurred
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Copies:

HFD-120

S. Hardeman, CSO/PM
Original EA Review to NDA 20-592, through S. Hardeman CSO/PM
Division File NDA 20-592

HFD-357

EA File for NDA 20-592
C. Berninger 6/19/96, 6/20/96

File Name: c:\eareview\20592e01.rcb

Pharmacology Review
NDA# 20592
Olanzapine ; LY170053
Zyprex

Sponsor: Eli Lilly & Co.

Reviewer:	Aisar H. Atrakchi, Ph.D.
Teeam Leader:	Glenna Fitzgerald, Ph.D.
CSO:	Steve Hardeman
Rev Date:	Apr 29 1996

Table of Content

Overall Summary and Evaluation

Olanzapine is an *Atypical* antipsychotic drug shown to have similar pharmacological profile in animals to colzapine. The former is a thienobenzodiazepine derivative whereas, the latter is a dibenzodiazepine derivative. Both drugs seem to produce minimal or no extrapyramidal side effects compared with *Typical* antipsychotics. Radioreceptor binding assays in vitro showed olanzapine to have high affinity to a number of receptors including 5HT2A/2C, D4/3/1/2, M1, alpha1 adrenergic, and H1 receptors. Note that the highest affinity was to muscarinic M1 receptors. Olanzapine did not show selective binding to the dopamine receptors except low affinity was seen for D5 (Ki 51nM vs. 11&16nM for D1&D3, 26nM for D4 and 31nM for D1). From the table below, it can be seen that olanzapine has higher affinity to D1&2 than does clozapine.

in vitro Receptor Binding Profile for Olanzapine [Ki (nM)]

receptor	[^{3}H] radioligand	cell/tissue	Olanzapine	Clozapine	Haloperidol	Risperidone
Dopamine						
D_1	SCH 23390	rat striatum	31 ± 0.7	85 ± 0.7	25 ± 7	75 ± 8
D_2	Raclopride	rat striatum	11 ± 2	125 ± 20	1 ± 0.04	3 ± 0.1
Serotonin						
$5HT_{1A}$	8-OH-DPAT	rat cortex	>1000	770 ± 220	7930 ± 800	490 ± 10
$5HT_{1B}$	5HT	rat cortex	1355 ± 380	1200 ± 170	<50% at 10µm	1325 ± 130
$5HT_{1C}$	5HT	beef striatum	800 ± 190	980 ± 110	6950 ± 950	100 ± 11
$5HT_{2A}$	Ketanserin	cortex	4 ± 0.4	12 ± 3	78 ± 22	0.6 ± 0.2
$5HT_{2C}$	Mesuriergine	human cortex/ beef caudate	11 ± 1	3 ± 0.8	3085	26 ± 5
$5HT_3$	LY 278584	rat cortex	57	89	>1000	<50% at 10µm
Muscarinic						
m_1	Pirenzepine	cerebral cortex	1.9 ± 0.1	1.9 ± 0.4	1475 ± 300	<50% at 10µm
	NMS	CHO-K1	2.5 ± 0.3	1.4 ± 0.3	n.d	<50% at 10µm
m_2	NMS	rat heart	18 ± 5	10 ± 1	1200 ± 190	<50% at 10µm
m_3	NMS	salivary gland	25 ± 2	14 ± 1	1600 ± 305	<50% at 10µm
	NMS	CHO-K1	13 ± 0.8	7 ± 1	n.d	<50% at 10µm
m_4	NMS	rat striatum	13 ± 2	18 ± 5	<50% at 10µm	<50% at 10µm
	NMS	CHO-K1	10 ± 0.6	6 ± 0.5	n.d	<50% at 10µm
m_5	NMS	CHO-K1	6 ± 0.6	5 ± 1.2	n.d	<50% at 10µm
Adrenergic						
α_1	prazosin	whole brain	19 ± 1	7 ± 4	46 ± 6	2 ± 0.1
α_2	Rauwoscine	whole brain	230 ± 40	8 ± 3	360 ± 100	3 ± 0.7
β	DHA	whole brain	<50% at 10µm			
histamine H_1	pyrilamine	whole brain	7 ± 0.3	6 ± 2	3630 ± 85	155 ± 35
$GABA_A$	Muscimol	cortex	<50% at 10µm			
benzodiazepine	flunitrazepam	whole brain	<50% at 10µm			

olanz D4 27nM, clozapine 11.55 nM

A similar binding profile was observed using human neuronal tissue (see below). Olanzapine did not bind to $GABA_A$, Bzd, or beta adrenergic receptors.

Inhibition of radioligand binding by olanzapine:

Receptor	IC_{50} (nM)
D1	25±4
D2	10±2
$5HT_{2A}$	7±2
$5HT_{2C}$	71±8
M1	2±0.1
Alpha1	70±14
alpha2	280±20
beta, $GABA_A$, and Bzd	>1000

In vivo biochemical studies were conducted to support the in vitro receptor binding (see below table from sponsor). Similar to clozapine, olanzapine showed preferential effects at 5HT (ED_{50} 0.57mg/kg i.p.) relative to dopamine sites (ED_{50} 3mg/kg i.p.) As demonstrated by the decr in corticosterone level. The latter is elevated in response to D2 or 5HT2 (or 5HT1c) receptor agonists. Olanzapine in male rats elevated serum prolactin level after 0.3-10mg/kg oral doses. This finding is in contrast to early clinical trials where olanzapine did not have a sig effect on prolactin (Beasley et al., 1995).

In Vivo Biochemical Pharmacology Studies

Study Title	Species, Strain	Group/ Sex/Age (weeks)	Dose (mg/kg)/ Route[a]	Results
Effect of LY170053 given orally on prolactin levels in male rats.	Rat, SD	10/M/10	0.3-10 p.o.	Olanzapine produced a significant increase in prolactin concentrations in rats.
The effect of LY170053 on dopamine and dopamine metabolite concentrations in the corpus striatum and mesolimbic system of the rat.	Rat, W	6/M/ 8-10	2.5-20 p.o.	Olanzapine produced a significant increase in dopamine metabolite levels in both the striatum and mesolimbic areas.
The effect of LY170053 on 5-hydroxytryptamine and 5-hydroxyindoleacetic acid concentrations in frontal cortex, mesolimbic area and corpus striatum of the rat brain.	Rat, W	6/M/ 8-10	2.5-20 p.o.	Olanzapine produced a dose-related elevation in 5-HT and 5-HIAA levels in rat brain.
Neuroendocrine evidence for antagonism of serotonin and dopamine receptors by olanzapine (LY170053), an antipsychotic drug candidate.	Rat, SD	5/M/4-6	0.3-3 i.p.	Olanzapine antagonized the quipazine-induced elevation of serum corticosterone in rats with an ED_{50} of 0.57 mg/kg i.p., while antagonizing the pergolide-induced increase with an ED_{50} of 3 mg/kg.
Effects of olanzapine on catecholamine metabolism in rat brain regions.	Rat, SD	5/M/4-6	0.03-10 i.p.	Olanzapine produced dose-related increases in DOPAC and HVA and MHPG and blocked the increase elicited by quipazine. These changes support the view, that olanzapine antagonizes dopamine D_2, α_2 and 5-HT_2 receptors in rat brain.
Antagonism by olanzapine of ^{3}H-arachidonic acid release in cell lines transfected with m_1, m_3 and m_5 muscarinic receptors.	Rat, SD	4/M/ 9-11	0.3-10 i.p.	In vivo, olanzapine did not produce salivation in rats and failed to antagonize oxotremorine-induced salivation.

Behavioral Pharmacology Tests Relevant to Proposed Clinical Indication:

- apomorphine-induced climbing behavior to test D1&D2 receptor response. Olanzapine blocked the response with ED_{50} of 5mg/kg; clozapine was half as atcive with ED_{50} of 10mg/kg.

- 5-hydroxytryptophan-induced head twitches in mice, to test 5HT2 receptor response. Both olanzapine and clozapine induced a dose-response decr in head twitches with ED_{50} values of 2&3mg/kg respectively.

- Oxotremorine-induced tremor in mice, a test for anticholinergic activity. Olanzapine and clozapine antagonized the tremorgenic effect of oxotremorine with ED_{50} values of 3 and 12mg/kg respectively.

- Inhibition of conditioned avoidance response (CAR), a test to predict antipsychotic behavior in rats and induction of catalepsy (CAT) is a reflection of extrapyrmidal symptoms. Olanzapine induced catalepsy with ED_{50} of 23mg/kg which is 4x higher than the dose that blocked the CAR (5.6mg/kg). For both effects, olanzapine was less effective than clozapine that had ED_{50s} of 0.74 and 0.28mg/kg for the CAT and CAR respectively. [i.e. olanzapine produced minimal extrapyramidal signs than clozapine].

- Schedule-controlled behavior in rat or pigeon/conflict test; a test for anxiolytics. Olanzapine, clozapine, and chlordiazepoxide, produced the expected changes in rate of responding. However, the 3 drugs, had little or no effect on the high rate of responding produced in the reward component but the rates in time-out and the conflict period were incr.

- amphetamine-induced hyperactivity and stereotypy were reduced by 10mg/kg p.o. to Wistar rats. But olanzapine potentiated stereotypy at later time points. Olanzapine did not antagonize hyperactivity in Lister Hooded rats induced by amphetamine but it sig reduced cocaine-induced hyperactivity at 2.5-10mg/kg p.o. These differential effects of olanzapine in Lister Hooded rats were stated to be perhaps related to olanzapine preferentially reducing mesolimbic activity mediating cocaine effect, rather than the striatal activity that mediates amphetamine hyperactivity.

Other tests included rotarod in rats where a sig decr in performance was observed after 20mg/kg oral olanzapine. Olanzapine orally dosed at 20mg/kg protected against PTZ-induced convulsions but lowered the threshold for electroshock in another test at 10mg/kg p.o. Olanzapine causes marked sedation, this effect was examined by monitoring the sleep/wake cycle in the rat. Olanzapine at 1&5mg/kg p.o. incr slow wave sleep and decr REM duration, specially at the HD.

Electrophysiology:

Studies have shown that typical antipsychotic tend to decr the spontaneous firing of A9&A10 dopaminergic neurons after repeate dosing whereas, atypical antipsychotic tend to decr the activity of A10 but not A9 neurons. Therefore, it has been hypothesized that A10 neurons may underlie the extrapyramidal side effects. After s.c. administration for 21d, olanzapine produced a dose-dependent decr in the number of spontaneously firing A9&A10 neurons but only at the LD (10mg/kg). No effect of repeate dosing on firing rate of either type of neurons. Olanzapine following a single administration (10&20mg/kg s.c.) However, incr the number of spontaneously firing A10 neurons, but decr the rate of firing of A10 at low dose.

Effect on Neurotransmitters:

Effects of olanzapine on brain regional levels of dopamine metabolites DOPAC & HVA/nucleus accumbens, and NE metabolite MHPG sulfate/hypothalamus were studied in SD rats. Olanzapine at 0.03-10mg/kg i.p. produced a dose-dependent incr in DOPAC and HVA (upto 4x). The MHPG level was incr 1.4-2x but the incr was not consistent (incr seen at 0.03, 0.3 and 10mg/kg, but not at 0.1, 1.0, or 3mg/kg). Olanzapine inhibited quipazine-induced incr in MHPG sulfate in rats dosed 0.3-3mg/kg i.p.; this is an indication of antagonistic effects at 5HT2 receptors. A dopamine antagonism (D2) was demonstrated by olanzapine's blockade of pergolide-induced inhibition of GBL-induced incr in dopa levels in rats dosed with pergolide, GBL, and a decarboxylase inhibitor.

Cardiovascular Studies:

Effects of olanzapine on the CVS were examined in anesthetized rat, dog, cat, and g. pig. In anesthetized **rat**, mean BP was reduced dose-dependently (12-46% of cont values) without reaching statistical sig. The decr at higher doses was accompanied by dec in HR and incr in respiration rate (doses 0.1, 1, and 10mg/kg). The sponsor indicated (data not presented) that responses elicited by standard agonists were minimally affected except for histamine and DA that were decr at 1&10mg/kg bolus i.v. In one rat, 20mg/kg was injected as a bolus and the animal failed to recover from a massive hypotension that followed the injection. In anesthetized **cat**, MBP was dose-dependently reduced at 0.1 and 1mg/kg/min (infusion) and respiration rate was sig incr at the 1mg/kg/min dose; no effect on EKG. In 2cats (1m&1f), infusion of 1mg/kg/min caused arousal after 10min of infusion that was suppressed by 1% chloralose or pentobarb. Some of the responses on MBP elicited by standard agonists were modified by doses ≥0.1mg/kg/min. The pressor response by adrenaline and depressor effect of histamine were further reduced by all 3 doses of olanzapine (0.01, 0.1, and 1mg/kg/min)(36-63% of cont). The depressor response to isoprenaline, Ach, and histamine were also reduced by olanzapine at ≥0.1mg/kg/min. The responses to NE and phenylephrine were unmodified. Note that the pressor response to adrenaline was actually converted to a depressor response in 3/4 cats in the 2 highest doses. In anesthetized **dog**, infusion of olanzapine caused HR to sig incr in 2HD (49&59BPM over the cont). No effect on respiration rate, EKG, or MBP; arousal noted in 1m and 1f at HD. Similar to the cat, the pressor response to adrenaline was reversed to a depressor response at 0.1&1mg/kg/min. The depressor response to Ach was reduced at HD, the pressor responses to phenylephrine was reduced in the 2HD. The pressor response to DA was biphasic in 3/4 HD dogs and converted to a depressor at 0.01mg/kg/min and completely blocked at 1mg/kg/min. Following i.v. bolus to these dogs, no effect on EKG, but mean SBP and DBP were reduced starting at 0.1 and upto 20mg/kg dose. In the male dog, the fall in BP was accompanied by a small decr in respiration at 0.1 and 1mg/kg but a rise and fall in respiration noted at 10 and 20mg/kg. The pressor response to adrenaline was converted to a depressor at bolus doses ≥0.1mg/kg, the response to Ach was reduced or blocked at ≥1mg/kg, and the responses to phenylephrine and tyramine were reduced or blocked at 10&20mg/kg bolus. In the dog, olanzapine conc were measured in plasma after i.v. infusion to 2 dogs. ^{14}C-olanzapine was administered to these dogs and was detectable 1hr post infusion of 0.1mg/kg/min. From the table below it can be seen that unchanged olanzapine was 30-50% less than total radioactivity indicating rapid and extensive metabolism. There was no difference in conc between sexes. In **anesthetized g.pig**, MBP was reduced by 20-31mmHg at all 3 doses (0.1, 1, 10mg/kg i.v. bolus). Responses to agonists were all reduced or blocked and response to bronchoconstriction due to 5HT was highly susceptable to 0.1mg/kg olanzapine

The concentration of LY170053 in plasma, urine and bile in data of two dogs after intravenous infusion

Male Dog 9.0 kg	Determination by chromatographic assay	
Infusion concentration lasting 1 hour	Sample collection time (min)	Plasma Level[1]
0.01 mg/kg/min	20	0.07
	60	0.13
0.1 mg/kg/min	20	0.76
	60	0.91
1 mg/kg/min	20	8.22
	60	12.96

Female Dog 7.4 kg		Determination by chromatographic and radioactive methods	
Infusion concentration lasting 1 hour	Sample collection time (min)	Plasma Level	
		Chromatographic[1]	Radioactive[2]
0.01 mg/kg/min	25	0.04	N.D.
	60	0.05	N.D.
0.1 mg/kg/min	25	0.50**	N.D.
	60	0.82	1.51
1 mg/kg/min	25	5.10	7.92
	60	12.10	20.2
Terminal urine	--	N.T.	160.5
Terminal bile	--	N.T.	290.0

[1]Each figure represents μg/ml of LY170053 (Appendix 1)
[2]Each figure represents μg ^{14}C equivalents (Appendix 2)

N.T. = not tested
N.D. = not detected

the CVS effect of olanzapine was also examined in the conscious SHR. Olanzapine injected i.p. into these rats caused a decr in MBP (-9±2%) at 1mg/kg dose with statistical sig at 30 and 90min postdose. No sig change in HR. In the pithed SHR, the same dose of 1mg/kg shifted to the right by 2 fold, the dose response curve of the pressor alpha1 agonist methoxamine. At a 100x lower dose of 0.01mg/kg, there was a 3 fold shift in the 5HT pressor response relationship in these pithed SHR and 0.1mg/kg caused 300 fold shift. These findings indicate that in conscious SHR, the small antihypertensive effect is likely due to modest blockade of alpha1 receptors than to the great inhibition of effect of 5HT. This is based on the finding that peripheral 5HT2 receptors play a minor role in maintenance of BP in this model.

Effect on the Immune System:
Olanzapine at oral doses between 0.8-25mg/kg/d for 10d had no effect on the immune response in mice. Mice received ten daily doses of olanzapine and 3 days later, these mice were challenged with sheep RBC antigens. Mice were killed 7days post injection of the Ag and blood collected via cardiac puncture. Two HD mice died and some dosed 12.5 and 25mg/kg were lethargic. The effect of olanzapine was compared to 3 immunosuppressive drugs, this test required cooperative functioning of macrophages, T-lymphocytes, and B-lymphocytes.

ADME & TK:
The pharmacokinetics of olanzapine was studied in CD-1 mice, Fisher 344 rats, Beagle dogs, and Rhesus monkeys after single and repeate administration by the oral and parenteral routes. A validated HPLC method with dl of 1ng/ml was used to quantitate plasma conc. Metabolites of olanzapine have been detected in plasma, urine, and bile using LC/MS-MS methods.

Olanzapine was well absorbed following single oral doses to mice, rats, dogs, and monkeys. In the rat, absorption was greatest from the small intestine and colon. The **absolute oral bioavailability** of olanzapine was determined in the **rat at 47%** in contrast to absorption of radioactivity of 79%. These findings indicate good absorption and significant first pass effect/metabolism. Peak plasma concentrations were reached between **0.5hr in the mouse to 3hr in the dog (T_{max} in humans is 5hr)** indicating rapid absorption. Plasma concentrations of olanzapine were much lower than total plasma radiocarbon in all species examined which indicated extensive metabolism. Concentrations of olanzapine were approximately 10x higher in portal than that in systemic circulation which reflected extensive 1st pass effect. Mean **plasma $t_{1/2}$** ranged between **3hr in rodents and monkeys to 9hr in dogs**, plasma elimination half life in **humans was 27hr. Terminal plasma elimination $t_{1/2}$ of total radioactivity was 11hr in mice, 30hr in rats, 28hr in dogs, and 98hr in monkeys; the corresponding value in humans was 59hr.**

To set exposure limits for safe-handling of olanzapine in the work place, rats were exposed via inhalation to single and multiple doses of olanzapine. Single dose inhalation studies showed linear kinetics between plasma levels and increasing exposure concentration to olanzapine aerosol that ranged between 6-250ug/L. In multiple dose studies, rats were exposed for 4hrs/d for 12days to 1.2, 6, and 30mg/m^3 olanzapine. Drug did not accumulate in plasma when measured on day10 under these experimental conditions. Mean plasma levels of olanzapine measured 15-20min postdose were 3, 40, and 253ng/ml for 1.2, 6, and 30mg/m^3 doses respectively.

In multiple dose studies in m[illegible]d rats, there was no gender differences in plasma drug levels. Plasma levels and exposure (AUC) increased with increasing dose and there seemed to be no drug accumulation. The incr in [illegible] was generally linear at low doses and tended to be non-linear with incr in dose and duration.

Olanzapine widely distributed to various tissues following administration. Maximum radioactivity in rats after a single oral dose was detected in the following tissues/organs: the Harderian gland>liver>lungs>kidneys>jejunum. Maximum radioactivity was reached between 2-6hr postdose.

Moderate to high radioactivity was also detected in adrenals, bone marrow, duodenum, ileum, pituitary, spleen, and thyroid. Lowest levels were in the plasma/blood, eye, cerebellum, medulla, spinal cord, muscle, and white fat. In terms of percent of radioactive dose, the liver accounted for the highest value of 11% of total recovered radioactivity measured at 2hr postdose. Radioactivity was detected in the brain 2-6hr postdose and levels at both time points were higher than those in the blood. In a 21d tissue distribution study, the urinary profile of metabolites was not altered over the duration of the study.

Olanzapine was detected in milk and plasma samples obtained from lactating rats administered radioactive drug at 5mg/kg as a single oral dose and pregnant rats dosed on gd12 at 18mg/kg oral dose. Radioactivity was detected in all tissues by 1hr of dosing with max levels reached between 1-3hr. Highest activity was in maternal tissues: adrenals, bone marrow, GI, Harderian gland, kidney, liver, mammary glands, ovary, pancreas, salivary glands, spleen, urinary bladder, placenta, and yolk sac. By 24hr postdose, radioactivity was still detectable in all except maternal blood, fetal tissue, pancreas, and placenta. These studies clearly indicate placental transfer of the drug into the fetus.

Olanzapine in all species tested (mouse, rat, dog, and monkey) was extensively metabolized as indicated by the higher plasma conc of total radioactivty over the parent drug. However, olanzapine was most extensively metabolized in the monkey and least metabolized in the rat. The degree of metabolism in mice, dogs, and humans lies between that of the monkey and the rat. **In no one species the metabolic profile was similar to that of the humans i.e. direct glucuronidation to form the 10-N-glucuronide.** This metabolite was found in trace amounts in dog urine. In vitro studies from liver slices and microsomes from human donors, the P450 enzyme subfamilies responsible for olanzapine metabolism were CYP2D6 (to form 2-OHCH3), CYP1A2 (to form N-desmethyl and 7-OH), and Flavin-containing monooxygenase (to form the N-oxide). Studies with liver microsomes from mice showed no effect in mice treated for 3mo on any enz activity tested. In rats treated for 6mo with 1mo recovery, generally the changes in enz activity were slight. There was a sig incr in CYP1A in male rats dosed 4 and 16mg/kg, also, total P450 content was reduced in males and females. In dogs treated at 2, 5, and 10mg/kg/d for 1yr, small and statistically insignificant increases in enzyme activities were observed in CYP1A, CYP2B, and CYP3A. The only sig incr noted at end of 4wk recovery period was in female dogs dosed 10mg/kg in CYP1A at 1.5x cont; P450 content was unaffected. It can be concluded that the **overall effect of olanzapine on enzyme activity is slight** in animals tested for long periods upto 1yr. **Because of the multiple metabolic pathways, olanzapine is not expected to interact or affect the metabolism of other drugs specially those that are metabolized by CYP1A2.** Olanzapine had no effect on GSH content when tested in rats at 5 and 25mg/kg.
In mice, the major urinary metabolite is the **7-OH glucuronide (13%** of 20mg/kd administered dose). The major metabolites accounted for 70% of the urinary activity. In rats, the main urinary metabolite was the **2-OHCH3** olanzapine followed by N-desmethyl-hydroxy-olanzapine-glucuronide (tentative). In bile, a GSH adduct was identified (N-acetylcysteine adduct; tentative). Urinary radioprofiles after single or repeate dose seem to be relatively constant. In dogs, the major urinary metabolite is **7-OH-N-oxide** olanzapine (8% of administered dose). Also in urine, cysteine adducts were tentatively identified and accounted for 1-2% of dose. Therefore, detection of these putative cysteine cpd suggests formation of GSH conjugates. The major metabolites including unchanged olanzapine accounted for 60% of urinary activity. In monkeys, the main urinary metabolite was **N-desmethyl-2-carboxy-olanzapine** accounted for 17% of dose or 36% of urinary activity. In addition to unchanged olanzapine, some of the urinary metabolites were also present in plasma of mice, rats, and dogs including the GSH conjugates detected in rat bile. **The metabolic pathways of olanzapine in animals included aromatic hydroxylation, alkyl oxidation, N-dealkylation, N-oxidation, in addition to conjugation with glucuronide and GSH. Only in the dog, both aromatic and N-oxidation reactions were found (7-OH-N-oxide).** The monkey differed from the rat, mouse, and dog, in that oxidation of the benzene ring was absent. The metabolism of olanzapine differs between humans and animals in 2 ways:

1. Direct glucuronidation is absent in animals (except for a trace amounts detected in dog urine); its the main pathway in humans forming the 10-N-glucuronide.

2. Absence of aromatic oxidation in any of the human biological fluids, however, much of this pathway was found in animals.

The monkey does not form the 10-N-glucuronide but seemed to have a similar oxidative metabolism as humans.

Seven metabolites were identified in rat bile after oral administration of 8mg/kg of labelled olanzapine. The 7 metabolites and olanzapine represented 75% of radioactivity in bile and 39% of administered dose. The major metabolite was glutathione adduct of olanzapine that accounted for 34% of biliary radioactivity and N-acetylcysteine adduct at 17%; unchanged olanzapine accounted for 2% of biliary radioactivity.

Major route of elimination of olanzapine in **rodents and dogs is by feces.** Rats dosed a single i.v. of labelled olanzapine showed the same pattern of elimination as that after oral dosing. **Monkeys similar to humans, mainly excrete olanzapine by urine.** In rats as indicated above, most of fecal elimination came via the bile and enterohepatic recirculation.

Certain metabolites and/or impurities/degradation products of olanzapine were tested for receptor binding and pharmacological activity. The 2-CH3OH and N-desmethyl metabolites showed similar affinities to DA2, H1, 5HT2, and alpha1 as those for olanzapine with the former having the most similar profile to olanzapine with respect to these receptors.

			K_i (nM)			
Cpd	DA2	5HT2	H1	α1	M	DA1
olanzapine	20	10	7	15	67	119
2-CH3OH	22	18	6	12	500	66
N-desmethyl	9	23	22	80	333	203

The rank order of affinity of the above cpds is as follows:
olanzapine: H1>5HT2>alpha1>DA2>M>DA1>alpha2
2-CH3OH: H1>alpha1>5HT2>DA2>D1>M>alpha2
N-desmethyl: DA2>H1>5HT2>alpha1>DA1>M>alpha2

The N-oxide has similar binding profile to that of olanzapine but at much lower affinity. The lactam and the N-glucuronide do not bind (very poor affinity) to any of these receptros.

Therefore, the 2-CH3OH and N-desmethyl metabolites could have physiological-pharmacological activity if their conc achieved after administration of olanzapine is adequate to do so. These 2 cpd though have affinity, their conc after olanzapine administration is low and their binding (receptor occupancy) is expected to be less than 1/10th the receptors occupied by olanzapine. It is concluded that these metabolites can not produce any physiologic effect unless their conc are incr sig over that of olanzapine. The N-desmethyl, N-oxide, and 2CH3OH metabolites were tested in vivo animal models depictive of dopaminergic activity. None of these 3 metabolites showed any effect. Fisher rats dosed orally with olanzapine at 16mg/kg for 2wk. Olanzapine contained 3 degradation products formed during storage. These were 301664, 343344, and 343345 present at 1.02-1.05% of this daily dose of olanzapine. These impurities did not induce any toxicity different from those of olanzapine.

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Toxicology:

The acute LD_{50} values (mg/kg) were:

Species	Route	M	F
Mouse	p.o.	211	208
Rat	p.o.	174	177
	i.p.	112	107
Dog	p.o	>100	>100
Rhesus Monkey	p.o.	>100	>100

The potential toxicity of olanzapine was examined in rodents and dogs dosed repeatedly at durations that ranged from 2wks to 1yr. Doses tested in **mice were 3 to 45mg/kg/d**, doses in **rats were 0.25 to 54mg/kg/d** and those in **dogs were 2 to 40mg/kg/d**. Common clinical signs in rodents and dogs included hypoactivity, lethargy, and miosis (except in mice). Other signs included catatonia in mice that lasted for several hrs postdose, in rats incr lacrimation, and some animals of high doses showed hyperirritability and mydriasis, dogs showed restlessness, tremors, and head pressing. The main drug related findings included **hematology, ophthalmology, organ wt changes, and histopath of uterus, mammary glands, and ovaries.**

Olanzapine affected the **hematopoietic system in mice, rats, and dogs of both sexes, the mechanism appear to be via an immunological effect and not bone marrow site.** Male B6C3F1 **mice** dosed 5, 15, 45mg/kg/d for 3mo showed 36, 65, and 70% decr in lymphocytes and neutrophils relative to the cont with individual data in all drug grs being lower than the normal range. WBC count was also reduced in female mice mainly in high dose at 53% less than the corresponding cont values. CD1 male mice showed dose-dependent reduction in WBC count at end of 3mo dosing with 3, 10, and 30mg/kg/d with 52-68% decr in lymphocyte and 48-80% decr in neutrophils. CD1 females dosed 30mg/kg showed a sig decr in lymphocytes at end of study. These females only at 2mo, had sig decr in RBC count, Hb, and PCV. In a 2wk tox study in CD1 mice, dose-dependent decr in lymphocytes and neutrophils with total depletion of leukocytes, was measured in males and females dosed at ≥45mg/kg/d. Olanzapine had no effect on any hematology parameter in **rats** dosed for 2wks at 2, 6, 18, and 54mg/kg/d. However, a sig decr in lymphocyte count was measured in rats dosed 22.5mg/kg/d for 3mo and a dose-dependent incr in Hb, MCV, & MCHC values noted in females dosed 2.5, 7.5, and 22.5mg/kg/d. Male rats dosed 16mg/kg/d for 6mo, showed a 27% decr in WBC count due to a decr in lymphocytes (29%) and neutropnil (20% of the cont). This decline in WBC persisted through 1mo recovery period. Reticulocyte count was also reduced in males dosed 4&16mg/kg (3-14%) and females dosed 16mg/kg (12%). Dose-dependent incr noted in male and female rats dosed 4&16mg/kg in MCV, MCHC (only in males), and MCH. In a 1yr tox study, the WBC count was reduced in male and female rats dosed 16mg/kg/d but without a sig change in cell type distribution. There were 5 of 20 male rats in this gr with WBC values lower than the normal range. In this 1yr study, the mean values of Ht, PCV, MCV, and MCH were consistently elevated in both sexes measured at 6 and 12mo without an effect on RBC count. **Histopath finding included dose-dependent bone marrow hypocellularity in rats dosed 4&16mg/kg/d for 1yr with >70% of these rats showing this pathology.** In **dogs**, erythrocyte parameters and erythroid precursors of bone marrow were depressed in males and females dosed 40mg/kg/d for 2wks. These dogs and those dosed 10 and 20mg/kg/d had lymphoid depletion of the thymus. In a 3mo study, 1 male dog dosed 10mg/kg/d developed **severe neutropenia, thrombocytopenia, and bone marrow erythroid hypoplasia** on day34 of treatment. Treatment was stopped and the dog recovered. This dog was re-challenged twice with 10mg/kg and a 3rd time with 2mg/kg olanzapine; the hematologic findings were reproduced within 4-9days of each re-challenge. Immunological investigation showed **incr in soluble immune complex levels and in the amount of ^{14}C-olanzapine bound to serum immunoglobulin.** These results suggested that olanzapine-induced neutropenia and thrombocytopenia were immune-mediated and not

a drug effect on the myloid component of the bone marrow. In a 6mo study, the effects of olanzapine were compared to those of cpd 170222, an analog that differs from olanzapine by having an ethyl instead of a methyl gr at position 2 of the thieno ring. Cytopenias occurred in dogs dosed with either cpds. In 2 female dogs dosed 3mg/kg olanzapine's cytopenia was observed at 6mo of dosing, one dog showed hemolytic anemia with decr RBCs and erythroid hyperplasia of bone marrow, the 2nd dog had neutropenia, thrombocytopenia, and myeloid hyperplasia of bone marrow. Liver and spleen smears showed extramedullary hematopoiesis but without apparent bone marrow toxicity as indicated by the absence of inhibition of cloning activity of CFU-GM or CFU-MK progenitor cells in bone marrow. The results from platelet-associated and neutrophil-associated IgG assays were equivocal and negative respectively. These results suggested that olanzapine-induced cytopenia is due to an effect of the drug on peripheral blood rather than a bone marrow toxicity. The findings in dogs dosed cpd 170222 were similar to those of olanzapine but slightly more severe. **Histopathology for both cpds showed extramedullary hematopoiesis in liver and spleen and incr hematopoietic activity in bone marrow.** In a 1yr study, one dog dosed 10mg/kg/d showed **2 episodes of hemolytic anemia with reticulocytosis and sluggish bone marrow response**. Following the 1st episode, there was **persistent monocytosis, leukocytosis, incr RBC sedimentation rate, incr in total serum immunoglobulins, and mild-moderate bilirubinuria.** The 1st episode had long induction period of 5mo whereas the 2nd had a short one at 6wks with relatively rapid erythrogenic recovery of bone marrow. The sponsor concluded that based on these differences in the properties of the 2 episodes, olanzapine-induced hemolytic effects are immune-mediated. In a 2nd 1yr dog study, olanzapine effects were re-examined using the same doses of 2, 5, and 10mg/kg/d. Similar to the other studies, drug-related hemolytic findings (neutropenia in this case) were observed in **4 dogs dosed 10mg/kg/d**. Two females and 1m developed neutropenia with or without thrombocytopenia after 6-8wks of treatment. Upon rechallenge with escalating doses of olanzapine, all 3 dogs again developed neutropenia; bone marrow tox was excluded. Another dog dosed 10mg/kg developed neutropenia after 10-11mo, but treatment continued and neutrophil count improved with time. **A female dosed 2mg/kg developed hemolytic anemia after 10mo of dosing which progressed to myelofibrosis.** A male dog dosed 5mg/kg also developed anemia and bone marrow changes at end of study and later was diagnosed with hepatic amyloidosis but serum chemistry analyses revealed chronic inflammation that was unrelated to the drug. **In all 4 dogs, there seemed to be no correlation between plasma levels and the hematological findings except in 1 dog where blood levels were 7-10x the values measured 24hr postdose of unaffected dogs.** Immunological tests were done and the sponsor concluded that olanzapine-induced neutropenia is likely caused by destruction of peripheral neutrophils with possible effect on neutrophil maturation/storage compartment in bone marrow. Histopath exam of the female dog dosed 2mg/kg and male dog dosed 5mg/kg that had hemolytic anemia, revealed bone marrow hypercellularity and marrow fibroplasia. The sponsor indicated that these 2 conditions are consistent with **beagle dog myelofibrosis**. The anemia was persistent despite termination of dosing, administration of transfusions, and steroid therapy and had properties of an autoimmune reaction with agglutination of RBC in Coomb's test. The sponsor consulted 2 pathologists one of which Dr. Bell, was associated with Marshall farms where these dogs were purchased. Dr. Bell indicated that Marshall farms had previously identified a cohort of **pregnant or lactating dogs with regenerative anemia caused by myelofibrosis of unknown origin,** similar to what is reported here. These animals were eliminated from the breeding program. Dr. Bell stated in his report that Marshall farms **had never seen** a case of myelofibrosis in nonpregnant dogs or males and **concluded that the finding in Lilly's study is different from the Marshall farm dogs.** On the other hand, Dr. Moncnef concluded after reviewing the medical records for the affected dogs in Lilly's study, that these cases are similar to **idiopathic anemia which is suspected to be of immune-mediated mechanism.** He also **concluded that anemia and myelofibrosis are unrelated to drug treatment** since it occurred in low dose and have been previously described in beagle dogs. It is the opinion of the reviewer that olanzapine-induced hematological findings are drug related since they have been identified in more than one species and in both sexes.

In a separate report (#68) the sponsor further investigated the 1yr dog findings to determine whether serum Ab specific for olanzapine can be detected in dogs with neutropenia. Serum samples from all dog grs including the cont were collected and analyzed by ELISA for development of Ab against olanzapine. Olanzapine IgM Ab was detected in 6/16 cont, 12/28 noncytopenic drug dogs, and 3/3 cytopenic drug dogs. In the cont untreated dogs the level of IgM ranged from bql of ≤2.4 rel.ug/ml to 30rel.ug/ml, in the treated grs without the 3 dogs with cytopenia, the IgM level ranged from bql of ≤2.4rel.ug/ml to 76rel.ug/ml. In the 3 cytopenic dogs, the level was from bql to 238rel.ug/ml. This finding was shown to be specific to olanzapine when fixed conc of free olanzapine inhibited portion of the binding. Olanzapine IgG Ab was detected only in sera from 1 dog with cytopenia. This activity was inhibited to 58% with addition of free olanzapine. Also in this dog, high levels of IgM (upto 238rel.ug/ml or 5-6x the preexisiting level in other dogs) were detected. This effect was inhibited to 26-48% with free drug. The sponsor indicated that the relatively high level of olanzapine IgM and presence of olanzapine IgG suggests a qualitative difference in the type of Ab produced by this dog. It was concluded that the cytopenia observed in at least 1 dog of the 3, may be contributed to olanzapine-specific Ab.

The ophthalmological findings were seen in dogs treated for 2wks, 6mo and 1yr at doses between 2-40mg/kg/d. In the 2wk study, miosis occurred in all drug grs but could not be correlated with dose. There was dose-dependent and sig reduction in lacrimal flow 6hr postdose. These dogs had normal pupil reflexes but pupils of dogs dosed 40mg/kg did not dilate completely in response to application of dilating agents. The mechansim of miosis in this study could not be deduced. No effect on ophthalmology was noted in a 3mo tox study in dogs dosed 2, 5, or 10mg/kg. In a 6mo tox study, dose-dependent miosis hyperreactivity to pupillary light response, and reduced response to mydriatic drug were seen in dogs dosed 4&8mg/kg/d. Similar to the 6mo study, dogs dosed 2,5, 10mg/kg for 1yr showed dose-dependent miosis, altered pupillary light reflex, and reduced tear production. In HD dogs blepharospasm was also noted. Other findings included conjunctivitis and discharge; tear production was reduced and was irreversible by end of study. The doses used in the 1yr were the same doses used in the 3mo study where no ophthalmological findings were observed. The sponsor related the ophthalmological results to the anticholinergic effect of the drug.

In a 3mo oral gavage mouse study, histopath exam showed **lymphoid depletion of the spleen and moderate multifocal lymphoid necrosis in all drug grs (3, 10, 30mg/kg/d) in addition, non dose-dependent mammary gland acinar hypertrophy, ductal ectasia, and ductal epithelial hypertrophy were seen in these 3 drug grs.** Rats orally dosed for 3mo at 2.5, 7.5, and 22.5mg/kg/d had dose-dependent reduction in relative wts of the ovaries and uteri; without histopath findings. Dogs orally dosed at 10, 20, 40mg/kg/d for 2wks had **lymphoid depletion of the thymus in all drug grs without histopath findings**. The relative wt of the testes was sig reduced in rats dosed 10mg/kg/d for 3mo and histopath exam showed **hypospermatogenesis**. The decr in testes wt in this study might have been secondary to wt loss in this gr. The absolute and relative wt of the ovaries were reduced in female rats dosed 4&16mg/kg/d for 6mo and uterine wt remained depressed in rats dosed 16mg/kg through the 1mo recovery period. Also in this study, the **relative wt of the adrenals in male rats dosed 16mg/kg/d was incr and histopath showed decr in vacuolation of cortical cells that persisted through the 1mo recovery period at which time the vacuolation was also observed in males dosed 4mg/kg/d.** Histopath exam showed mammary gland changes in males and females in this 6mo study. In males dosed 4&16mg/kg/d tissue morphology was changed from the normal lobuloalveolar to tubuloalveolar pattern and secretions were present in female rats dosed 16mg/kg/d. The **incidence and prominance of mucoid metaplasia of vaginal epithelium** were incr in females dosed 4&16mg/kg/d and **ovarian follicular prominance** was also incr in females dosed 16mg/kg/d. These mammary gland changes reversed during the recovery period. Uterine hypoplasia was observed in females dosed 4&16mg/kg/d at end of study and in females dosed 16mg/kg/d at end of recovery. There was thecal prominance in the ovaries of females dosed 4&16mg/kg/d. The findings in the ovaries and uteri were considered secondary to reduced wt in these animals. In a 1yr oral study in

rats, the absolute and relative wt of the adrenals were incr in rats (m+f) dosed 16mg/kg/d and the relative wts of the ovaries and uteri were decr in females of this dose; there was no histopath findings. Dogs treated for 6mo showed a sig decr in absol and rel wts of the ovaries in animals dosed 4&8mg/kg/d. A sig incr noted in the rel wt of the adrenals in male dogs dosed 8mg/kg/d; no histopath findings. Similarly, in a 1yr dog study, the **absol and rel wt of the ovaries was dose-dependently reduced** (doses 2, 5, 10mg/kg/d); no histopath findings. In a repeate 1yr dog at the same doses, in contrast to the 1st study, there were no marked changes in any organ wt. However, there was a reversible dose-related delay in estrous in half of the dogs dosed 5mg/kg and all dogs dosed 10mg/kg; no histopath.

The mammary gland findings and effects on ovaries and uteri are probably related to incr in prolactin level observed in presence of DA anagonists. A dose-dependent increase in prolactin palsma level occurred after single dose administration of olanzapine to rats. Doses ranged between 0.1-2.5mg/kg; values in females were higher than those in males at all doses and all time points, remaining elevated upto 6hr postdose. Similar to single dose findings, repeate dose studies in rats for 3mo at 1 to 4mg/kg in males or upto 8mg/kg in females, showed dose-dependent incr in prolactin level. This incr was higher and lasted longer when measured at 3mo than the values at 1mo. Also, at the lowest dose of 0.25mg/kg in males, a sig incr noted at 3mo measurement but not at the 1mo.

Toxicokinetics in mice, rats, and dogs were measured concurrently with the tox studies. Plasma levels incr with increasing dose, the incr was non-linear as the dose increased. Some indication of drug accumulation was noted as plasma levels measured later in the study were higher than those measured earlier (e.g. day30 vs. Day1). Olanzapine in all of the subchronic and chronic studies was administered orally (gavage in rodent and capsule in dogs). In all species there was no sex difference (except in mice dosed 45mg/kg/d for 3mo) in plasma conc. In mice mean plasma levels ranged between **35-431ng/ml in males and 52-861ng/ml in females** at doses 5, 15, and 45mg/kg/d. Peak level were reached 0.5-1hr postdose and PK followed 2 compartment model with rapid phase half life of <1hr and slow phase half life of ≥12hr. Rats dosed for 3mo, mean plasma levels ranged between **0.1-4ug/ml** with means between **0.13 to 2ug/ml** at 2.5, 7.5 and 22.5mg/kg doses. Mean max conc in rats dosed for 6mo at 1, 4, 8, and 16mg/kg/d were **24, 241, 802, and 2076ng/ml respectively, the corresponding values for AUC were 222, 1282, 6579, and 29109ng.hr/ml.** Mean Tmax reached between 0.5-8hr and, elimination half life ranged between 1-48hr. Mean max conc in dogs dosed for 1yr at 2, 5, and 10mg/kg were **114, 245, and 456ng/ml respectively, and the corresponding AUC values were 912, 2164, and 5133ng.hr/ml.** Mean Tmax was 2-3hr and mean elimination half life ranged between 6-24hr. Some degree of acummulation was noted with time and high doses. Dogs dosed for 14days, peak plasma levels at 40mg/kg/d reached **1.7ug/ml on day 14 and 0.9ug/ml on day1** indicating some accumulation.

Carcinogenicity:

Life-time bioassays were conducted in CD-1 mice and Fisher 344 rats. Dose selection was based on dose-range finding studies in both species:

Mice: 2wk oral study at 45, 70, and 100mg/kg
two 3mo studies: 3, 10, 30mg/kg and 5, 15, and 45mg/kg.

Rats 2wk study at 2, 6, 18, 54mg/kg
3mo study at 2.4, 7.5, 22.5mg/kg

Mouse:

Two life-time bioassays were conducted in CD-1 mice. The 2nd study was conducted because the sponsor felt the HD in the first study exceeded the MTD therefore, lower doses were examined in the 2nd study. Doses for the carcinogenicity study were appropriately selected, based on 3-mo dose-

range finding studies. The doses tested in the first carcinogenicity study were **3, 10, 30/20mg/kg/d** and those in the 2nd study were **0.5, 2, 8mg/kg/d**. Both studies lasted for 19mo in males and 21mo in females and olanzapine was administered by oral gavage. The 30mg/kg dose was reduced to 20mg/kg on d100 due to the high mortality particularly in males and **incr in the incidence of neutropenia** in these mice. In both studies, clinical signs were those observed in other toxicity studies and are extensions of the pharmacological actions: **hypoactivity and sedation** mainly at the higher doses in males and females, rough hair coat and soiling. Other signs included distended penises in males and palpable abdominal masses and in females, high incidence of nodules. Survival was markedly reduced in mice dosed 30mg/kg with male more affected (22% vs. 68% in cont) than females (32% vs. 58% cont). There was no drug effect on survival in any other gr of either study. Mean wt and/or wt gain was comparable to the cont at end of study in all groups, and a sig increase over the cont was observed in females dosed 2&8mg/kg/d in the 2nd study (6-30%) and females dosed 3&10mg/kg/d (upto 12%) in the 1st study. Although the final mean wt and wt gain were similar to the cont, reduction in these parameters occurred at one point or the other throughout the study duration in males and females usually those administered the HD. Food consumption in general, was increased over the cont in all drug groups and similar to the cont at lower doses. The hematology findings in both carcinogenicity studies, included **dose-dependent decr in WBC (32-70%) in males mainly due to decr in lymphocytes and neutrophils.** The eosinophil count in both studies was also sig reduced in males dosed 8, 10, and 30/20mg/kg, and the monocyte count was also sig reduced in males dosed 10 and 30/20mg/kg. Such effects were not observed in treated females, females dosed 30/20mg/kg, a sig increase and not a decr in WBC count, was observed. Note however, in the complementary PK study that accompanied the 1st carcinogenicity study, the **WBC count was reduced dose-dependently in males and females at 3, 6, and 12mo but not at 15mo.** Also the count of eosinophils and monos was reduced in both sexes dosed 10 and 30/20mg/kg at several times during the study reaching statistical significance when measured at 3, 6, and 12mo. Drug related effects on clinical chemistry parameters included a **dose-dependent increase in BUN and enzyme levels (AST & CPK)** and some electrolyte changes, these findings noted at 8, 10, and 30/20mg/kg doses. There was no sex difference in drug plasma levels and conc increased linearly at the low doses but generally non-linear as the dose and duration increased. This indicated some level of accumulation with time. Plasma levels measured over 15mo of dosing ranged from BLQ (dl of 1ng/ml) to **614ng/ml at doses between 3-20mg/kg.** Maximum conc was reached between 0.5-1hr of dosing. The effect on organ weights was inconsistent and variable and non-dose dependent. In general, liver and kidney absolute and relative wts incr in males or females dosed 2&8mg/kg without reaching statistical significance. Gross exam did not reveal any drug related finding. **Non-neoplastic lesions** included dose-dependent increase in incidence of **mouse urologic syndrome** (MUS) in males, **kidney dilation** in males (dose-dependent; doses 0.25, 2, 8mg/kg), **vaginal changes** (dose-dependent at 2&8mg/kg), **heart degeneration** (dose-dependent at 2&8mg/kg), **seminal vesicle inflammation** (dose-dependent at 2&8mg/kg), **eye keratitis** (dose-dependent at 0.25, 2, 8mg/kg), and **mammary gland hyperplasia** (at 2&8mg/kg). **Neoplastic lesions** included a sig increase in incidence of **fatal lymphosarcomas** in female mice (non-dose dependent), **mammary gland adenocarcinomas and adenomas** at 10&30/20mg/kg dosed females, and **lung alveolar/bronchiolar carcinomas** in female mice (non-dose dependent).

- The lymphosarcoma was analyzed as a whole-animal finding rather than a tissue-specific finding. There was a sig incr in the combined incidence (fatal+incidental) of lymphosarcoma in all 3 female drug groups (17, 15, 17% and 7% in cont; and the adjusted incidence was 24, 24, 36% for 3, 10, 30/20mg/kg respectively and 9% in the cont). The sponsor contributed this high incidence to low incidence in the cont which was lower than the sponsor's own historical data, 8-15%, and the adjusted rate was 10-22%. Note that analysis of fatal incidence alone did not reach statistical sig. Also, the sponsor indicated that this lesion was not found in male mice or in male or female rats (see discussion later). Also, the sponsor indicated that these incidences in drug groups lied within the range published in the literature with values between 3-31% for cont female and the fact that lymphosarcomas are

spontaneously occurring tumors in female mice, therefore, concluding that this tumor is not drug related. Although the reviewer agrees with the sponsor that this tumor is spontaneous and prevalent in female mice and it was not seen in male mice or in either sex of the rat, nor was it significantly increased in the repeate mouse carcinogenicity study, the response however, **was dose-dependent at the 2 higher doses in females with a 4 fold incr at the HD compared with the cont, and drug had an effect on the lymphoid tissues of the spleen and/or thymus also hematological findings (decr in WBC count; neutropenia, thrombocytopenia) in mice and/or rats and dogs** (reported in previous sub- and chronic toxicity studies). Another issue, is the usefulness of historical data, as was discussed in Dr. Freed's memo of Mar 7th 1994 from articles by Wogan (1982) and McConnell et al., "all primary tumors of the lymphoid system (i.e...lymphomas and lymphocytic leukemias) should be considered together for statistical analysis". From the data provided, it seems that the sponsor analyzed these tumors separately. Lymphosarcoma contributed to 11% of all fatalities in the 1st carcinogenicity study.

- The combined incidence (fatal+incidental) of mammary gland adenocarcinoma (adenomal+adenocarcinoma) in female mice was 0, 2, 4, and 5 of 60 mice in each gr for cont, 3, 10, 30/20mg/kg respectively, and the corresponding combined mortality-adjusted rate was 0, 11, 18, and 24%. The prevalence rate however, did not reach statistical sig in any gr. In the repeate study unlike the 1st one, the rate increased sig and dose-dependently for the combined (fatal+incidental)(5&100% at 2&8mg/kg and the mortality adjusted incidence was 10&17% and 0% for the cont), as well as the prevelance rate of HD (8mg/kg)(13%) was also sig increased but not for the fatal incidence.

- The combined incidence of carcinoma+adenomas of lung alveolar/bronchiolar tumors was sig incr in 3mg/kg female mice at 25% and 10% in the cont. The mortality adjusted rate was 33% vs. 12% in the cont. The significance of this finding is unclear since it occurred in LD and not in other doses and only in females.

It is concluded that olanzapine induces lymphosarcoma and mammary gland adenocarcinoma in female mice dosed at >8mg/kg. These tumors occurred at mean plasma level of 162ng/ml and 484ng/ml (for 8 and 20mg/kg doses in females).

The above conclusion maybe modified awaiting the results/conclusions of tumor analyses by the in-house Biometric Division. Also the carcinogenicity studies have not been submitted to the CAC as of this date.

Rat:
Dose selection for the carcinogenicity study was appropriately based on 3mo dose-range finding study. Olanzapine was orally administered to F344 rats for 2yrs at 0.25, 1, 2.5, and 4mg/kg; the 2 higher doses in females were increased on day 100 to 4 and 8mg/kg respectively because of small drug effect on B.wt. Olanzapine did not affect rate of survival in any gr. Clinical signs included **hypoactivity** in all drug grs increasing in severity with dose and **convulsions** occurred in 11/60 females dosed 4/8mg/kg after 11mo of dosing. The latter sign was not observed previously following repeate dosing. **A sig decr in mean wt and wt gain was observed in rats dosed ≥2.5mg/kg.** The decr in wt in the 2 high doses in males began as early as months 1&2 of dosing and continued till end of study. At termination, HDm had 12% decr in wt gain relative to the cont and in the 2 high dose females grs the decr was 18&33% respectively. Food intake and EFU were sig reduced in treated male and female gr throughout the study. At termination, the decr in EFU for the 2 HDf grs was 15&30% of the cont; the decr in EFU of males was not sig different from the cont at termination There were some small but statistically sig and dose-dependent changes in blood parameters of both male and female drug grs measured at 6, 12, and 18mo. In general, the parameters affected included

Hb, PCV, MCV, and RBC count ususally in the 2 high doses. **At 2yrs, the incr in RBC, Hb, and PCV** was 12-14% of the cont in HDm (4mg/kg) and 3-6% in MD&HDf (4&8mg/kg). The effect on **WBC parameters was variable and non-dose dependent** such as incr and decr in thrombocytes, lymphocytes, and leukocytes. Drug effect on clinical chemistry parameters was also inconsistent, in general there was an incr in liver enzyme activity such as ALP, AST, and ALT in all 3 high dose female grs at 18mo (11-42% of cont), **BUN incr throughout the duration** except a decr (9-47%) noted on mo24, changes in electrolyte levels throughout the study, and a consistent finding was a decr in bilirubin noted during months 6,12, 18, and 24 ranged between 15% to 47% at 24mo. There was no effect on urinalysis. The following organ wts were incr sig in both males and females of MD&HD: **heart** (5-21%), **adrenal** (25-78%), and **thyroid/parathyroid**. The wt of the liver was incr only in MDf (20%), the kidney wt incr in MD&HDf (18%), spleen wt incr in HDf (14%), and the brain wt incr dose-dependntly in MD&HDf (13&25%). The sponsor contributed the incr in adrenal wt to non-specific mechanisms operating during stress, however, the incr in heart wt which usually remains constant, maybe drug related. The wt of uterus was decr dose-dependently in the 3 high doses and the testes wt was also decr in HDm. Organ wts were also calculated relative to the brain and the results were similar to those noted relative to B.wt for the kidneys (decr 12% HDm, 6% HDf), adrenals (incr MD&HDm 24&5%), throid/parathyroid (decr MD&HDm 27%, MD&HDf 15&18%), testes (decr 21%), and uterus (decr 42%). There were no remarkable gross findings.

Plasma conc incr with dose, the incr was linear at 6mo but non-linear thereafter; there was no sex difference in plasma levels. Plasma conc ranged from below 5ng/ml (detection limit) to 910ng/ml.

Since terminal mean wt was sig reduced in males and females of HD incidences of non-neoplastic and neoplastic lesions were actually reduced relative to the cont. The non neoplastic lesions included progressive glomerulonephritis and benign pheochromocytoma in males (sig less than the cont; Peto trend test). In females of HD, the incidences of mononuclear cell leukemia, and pituitary adenoma and C-cell adenoma were also reduced relative to the cont (Peto trend test). The only sig incr in neoplastic lesions was the number of **mammary gland adenocarcinoma** in MD (9/37) and HDf (7/50) compared to 2/39 incidences in the corresponding cont (Peto trend test). These mammary tumors occurred at plasma levels that are 1-12x the max clinical plasma level of 60ng/ml measured after 60mg dose.

Similar to the mouse studies, the in-house statistical analyses have not be completed at this time and these studies have not been submitted to the CAC.

Reproductive and Developmental Studies:
Rats and rabbits were used in standard tests to evaluate the reproductive and developmental toxicity potential of olanzapine. The doses tested ranged between **0.25-22.5mg/kg in the rat and in the rabbit, between 2-30mg/kg**. These doses represent in the **rat 0.13-11x and in the rabbit 2-30x the max recommended human dose on a mg/m^2 basis.**

In a combined Segment I&III study in rats, the main drug related findings were as follows:
- all F0&F1 animals survived.
- mean wt, wt gain, food intake, and EFU were reduced (7-10% of cont) in F0 males and females during gestation and postpartum periods for females and pre-mating period in males; these findings occurred in HD of 5mg/kg and somtimes in MD of 1.1mg/kg.
- prolonged diestrous in females dosed 1.1 and 5mg/kg.
- mating index reduced and precoital period incr at 5mg/kg, fertility was unaffected upto 5mg/kg.
- an incr in no of early resorptions, total number of resorptions/litter, and sum of litters with resorptions in females dosed 1.1mg/kg without an effect on number of live fetuses per litter; none of these findings reached statistical sig.
- slight growth retardation in F0 fetuses from females dosed 5mg/kg seen as an incr in number of fetuses with incomplete skeletal ossifications and/or wavy ribs.
- in F1 postweaning pups, activity was reduced in 30d old males and in 60d old females dosed between 0.25-5mg/kg however, activity was comparable to the cont when these animals were re-tested at ages 140-160days. There was no drug effect on auditory startle responses.

The NOEL for F0 parental toxicity and reproductive toxicity is 0.25mg/kg. The NOEL for developmental tox in F1 generation is 1.1mg/kg and for reproductive tox of F1 is 5mg/kg.

In a male rat fertility study, the **NOEL for male fertility was 22.5mg/kg**; note that mating index was reduced at this dose (10/10 males did not mate) but activity was normal when treatment was discontinued. In a female 10wk fertility study, fertility index was reduced dose-dependently (upto 30%) but the mating index was unaffected. Some rats in all 3 dose groups had acyclic periods and at 10mg/kg, gestation period was prolonged. The **NOEL for female fertility was 1mg/kg.** In a follow-up study, the underlying cause for female fertility was further investigated. Female rats were orally dosed with olanzapine at 3 or 10mg/kg for 2wks pre-mating, during mating, and to postmating day1. Oviducts removed and eggs and embryos were collected. There was a non-significant incr in precoital interval and in number of females failing to mate. In females that mated, there was a 21% decrease in ovulated eggs/rat at 10mg/kg gr. In a female rat teratology study, mean wt gain and food intake at 18mg/kg were reduced and clinical signs were those observed in other tox studies (ptosis, hypoactivity, lethargy, chromorrhinorea, and chromodacryorrhea). At 18mg/kg, embryo/fetal resorptions were incr, fetal wt decr, and incidence of male fetal runts and skeletal variations was incr. **The NOEL for maternal and fetal tox was 1mg/kg and that for teratogenicity was 18mg/kg.**

Rabbits treated during organogenesis at doses up to 30mg/kg, showed clinical signs similar to those observed in rats. Mean wt gain and food intake were reduced at 8 and 30mg/kg groups. There were 2 late abortions in 30mg/kg gr, one dam was not eating and the 2nd lost wt, the sponsor indicated that decr food intake and wt loss can induce abortions therefore, these abortions were not drug related. Mean fetal wt was reduced at 30mg/kg dose gr. **The NOEL for maternal tox was 2mg/kg, that for embryotox was 8mg/kg, and the NOEL for teratology was 30mg/kg.** In a Segment II study in rabbits, olanzapine caused late abortions in one rabbit each in 8 and 30mg/kg dose gr. The sponsor contributed these abortions to dosing accident in one case and to Pasteurella multocida which is frequently present in the rabbit respiratory tract and is responsible for reproductive tract illnesses such as abortions and mertitis. It is unclear if this organism was infact detected in the respiratory tract of the aborted rabbit; if such an organism was not identified, then a drug effect can not be ruled out. Mean wt gain was reduced throughout gestation in 30mg/kg dose gr so did food intake. An incr was observed in early resorptions at all drug gr (2, 8, 30mg/kg) reaching statistical sig in the MD&HD grs

Also incr but nonsig in all 3 drug grs was, total resorptions per litter, litters with resorptions, and no. of litters with nonlive implants (at 8 and 30mg/kg gr). The sponsor indicated that the calculations for these findings were done using all litters including those from 2 dams one each in cont and mid dose that had undetected abortions. However, when calculations were made without the litters from these 2 dams and with litters with at least one live fetus, there were no differences in these parameters. Mean fetal wt was sig reduced at 30mg/kg, no. of fetal runts/litter and no. of fetuses/litter with malformations were incr in HD and MD&HD respectively. The **NOEL for fetal developmental tox was 8mg/kg and for maternal tox 2mg/kg.**

The mutagenicity potential of olanzapine was evaluated in 2 in vitro and 2 in vivo assays: the MLP/TK forward mutation and the UDS for the in vitro tests and bone marrow MN in mice and bone marrow SCE in Chinese hamsters for the in vivo assays. **Olanzapine was non mutagenic in any of these assays** under these experimental conditions.

cc.
/Div File/Orig NDA# 20-592
/G. Fitzgerald/A. Atrakchi/S. Hardeman

Carcinogenicity Labelling:

Carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice for 19-21 months at oral doses of 3, 10, 30/20mg/kg, which are equivalent to 0.8-5 times the maximum recommended human dose on a mg/m2 basis. In a second mouse carcinogenicity study, olanzapine was administered at oral doses of 0.25, 2, 8mg/kg/d which are equivalent to 0.06-2 times the maximum recommended human dose on a mg/m2 basis. Olanzapine was also administered to rats for 2 years at oral doses of 0.25, 1, 2.5, 4mg/kg/d in males and 0.25, 1, 4, 8mg/kg/d in females which are equivalent to 0.13-2 and 4 times the maximum recommended human dose on a mg/m2 basis respectively. In female mice dosed at ≥2mg/kg/d and in female rats dosed at ≥4mg/kg/d, the incidence of mammary gland adenocarcinomas and adenomas was significantly increased over the control. These tumors occurred in mice at plasma level equivalent to 0.4 times the maximum plasma concentration in humans and in rats at plasma level equivalent to 2 times the maximum plasma concentratin in humans. Olanzapine like other antipsychotics, increases plasma prolactin levels following repeate administration to rodents. Increase in prolactin level has been linked to increased incidence of mammary gland neoplasia in rodents. The role of prolactin in human breast cancer however, is not conclusive. Also, at doses ≥10mg/kg/d, the incidence of lymphosarcoma was significantly increased in female mice over the control. A significant effect of olanzapine has been noted on the lymphoid tissue in various species including rodents and dog. A decrease in circulating lymphocytes and neutrophils in mice was noted at doses ≥0.5mg/kg that produced a mean concentration equivalent to 0.07 times the maximum plasma concentration in humans. In rats, the decrease in WBC count was noted at 16mg/kg/d or 3ug/ml plasma concentration which is equivalent to 50 times the maximum concentration measured in humans. It is noted that the incidence of lymphosarcomas was not significantly increased in male mice or male and female rats.

Labelling for Reproductive and Developmental Studies:

Pregnancy Category C; Reproduction studies performed in rats at doses 2.5x the maximum recommended human dose on a mg/m2 and in rabbits at 30x the maximum recommended human dose on a mg/m2 basis did not show evidence of teratogenicity.

Olanzapine administered to the rat at doses that are 11x the maximum recommended human dose on a mg/m2 basis decreased male fertility and at doses equal to or >0.5x decreased female fertility. Precoital period was increased and mating index was reduced in female rats dosed at 2.5x the maximum recommended human dose on a mg/m2 basis. Diestrous and prolonged gestation periods were noted at doses that are ≥0.6x the maximum recommended human dose on a mg/m2 basis. Maternal toxicity as reflected by reduced weight gain and food intake, occurred in rats at doses ≥0.5x the maximum recommended human doses on a mg/m2 basis. Early resorptions and sum and percent of litters with nonlive implants occurred in rats dosed at 0.5x the maximum recommended human dose on a mg/m2 basis and developmental retardation noted at doses 2.5x the maximum recommended human dose on a mg/m2 basis.

In rabbits dosed at ≥8x the maximum recommended human dose on a mg/m2 basis, maternal toxicity was observed as decreased food intake and weight gain. Fetal toxicity was observed in females administered doses 30x the maximum recommended human dose on a mg/m2 basis and noted as a decreased fetal wt , increased number of fetal runts/litter, and increase in number of fetuses per litter with malformations. Olanzapine has not been studied in pregnant women.

SPECIAL STUDIES

- Effect of time, temperature, and butylated hydroxytoluene on extraction of radioactivity from plasma containig ^{14}C-olanzapine/Report# 4/Lilly Labs, IN/Feb 1995.

During analysis of plasma samples from animals administered olanzapine, the contractor lab noted inconsistencies in the analytical method when applied to animal plasma samples. The sponsor suspected stability problems when olanzapine left at room temp. The contractor carried out an exp with dog plasma spiked with olanzapine and left at room temp for 1.5hr. Results showed markedly smaller peak heights compared with samples processed immediately. Based on this finding, the sponsor conducted the present exp. Plasma from rats, dogs, mice, monkeys, and humans were spiked with ^{14}C-olanzapine at 2 conc 500 and 5000ng/ml, and left at room temp for 1, 1.5, or 24hr. Plasma radioactivity was measured by liquid scintillation counting. In other studies using only dog plasma, effect of temp, antioxidant (butylated hydroxytoluene), and protein denaturation was tested. The results showed no effect on radiocarbon extraction from rat, mice, monkeys, or humans, however, dog plasma extractability was reduced after 24hr at room temp specifically at the lower conc of 500ng/ml. The sponsor was able to attenuate this effect by storing samples at zero degree or addition of antioxidatns (BHT) with the latter approach being more appropriate.

PROLACTIN STUDIES:

- Study of effects of inhaled olanzapine on prolactin levels in F344 rats to help establish safe handling procedures in the industrial environment/Report# 27/Tox Study# R39693: measurement of plasma conc of olanzapine/Lilly Labs, IN/Jan 1995.

This acute study was conducted to determine safety exposure limits for olanzapine in the work place. Female Fischer rats (n=8) were exposed to 5 aerosolized conc of olanzapine at 0.0002, 0.0012, 0.006, 0.03, and 0.06mg/l for 4hr. Blood was sampled 20min after end of exposure to measure plasma drug levels and prolactin levels were analyzed during exposure using an implanted atrial cannula. Mean plasma conc were:

Conc (mg/l)	mean±s.d. in ng/ml (Range)	
0.0002	11±7	(3-24)
0.0012	9.6±8	(1.4-18.6)
0.006	3±1.4	(1.6-5.4)
0.03	105±26	(79-149)
0.06	223±81	(87-298)

Large interanimal variation was observed (note conc range above). Plasma level incr with conc at the 2 highest conc (0.03 and 0.06mg/l) in a linear manner but, conc at both 0.0002 and 0.0012 were higher than that recorded for the 0.006mg/l. There was no explanation for this finding except the sponsor speculated that shallow breathing might have contributed to the reduced conc at 0.006mg/l and the large interanimal variability. However, such decr in plasma level was not recorded at the 2 higher conc.

Comment: results for prolactin plasma level was not provided in this report.

- Plasma conc of prolactin in Fischer 344 rats after a single gavage dose of olanzapine/Report# 60/Study# R38090/Lilly Labs, IN/Jun 1995.
Lot# 58962.

Fischer 344 rats (5/sex/dose) were administered a single oral gavage dose of olanzapine at 0.1, 0.5, 1.1, and 2.5mg/ml with the control gr receiving the vehicle (10% w/v aqueous acacia solution). Blood was collected at 0, 0.5, 0.75, 1, 1.5, 2, 4, and 6hr postdose. Prolactin was assayed in these plasma samples using a double Ab radioimmunoassay. Corticosterone plasma levels were also measured but a great deal of variability in the data prevented utilization of the results. ANOVA and Dunnett's at the 0.05 level were used for quantitative analysis of the data. **In males, a sig dose-dependent incr in prolactin levels was recorded starting at 0.1mg/kg at the 1hr samples and in the 1.1 and 2.5mg/kg at the 0.5 and 0.75hr samples (table below).** In the HDm prolactin remained sig elevated ($p<0.05$) till 2hr postdose and non-sig till the 6hr sample. The female control values were much higher than those recorded in males with some values above the dl of the assay. **Prolactin levels in females was also incr sig and dose-dependently** in the 3 top doses starting at the 0.75hr through 1.5hr samples, and in the 2 high doses at 0.5-2hr (see table below). In the 2HDf, values remained elevated upto 6hr postdose (though without reaching statistical sig). Values below are means±s.e. (ng/ml); n=5; all values below differed sig from the cont; () are female values.

		Dose (mg/kg)			
Time (hr)	cont	0.1	0.5	1.1	2.5
0.5	7±1 (29±9)	NS (NS)	NS (45±5)*	15±2 (50±0)	37±4 (45±5)
0.75	7.5±1 (19±5)	NS (NS)	NS (39±7)	18±1 (50±0)	35±1.4 (50±0)
1	5±0.6 (16±3)	7.6±0.7 (NS)	9±2 (33±7)	17±1 (48±2)	27±2 (50±0)
1.5	5±1.6 (12±3)	NS (NS)	NS (33±7)*	NS (48±2)	21±3 (50±0)
2	3±0.4 (13±4)	NS (NS)	NS (NS)	NS (31±6)	14±2.3 (50±0)

* not sig from the cont value.
The values of 50±0 represent those conc that were >50 which is the highest reference standard tested. At 4&6hr prolactin level was sig incr in HDf (0.3&2 fold respectively).

It is concluded that a single oral dose of olanzapine to rats caused a sig and dose-dependent incr in prolactin levels in males and females that occurred as early as 0.5hr of dosing in females and 1hr in males. This incr lasted for a period of 2-6hr in HDm and the 2 high doses in females. The incr in plasma prolactin is expected because of olanzapine's antagonism of DA-induced inhibition of prolactin secretion.

- Plasma conc of prolactin in Fischer rats after 1 or 3 mo of gavage doses of olanzapine/Report# 61/study# R13392/Lilly Labs, IN/Jun 1995
Lot# 58962.

Fischer rats were administered olanzapine by oral gavage for 1 or 3mo at 0.25, 1, 2.5, and 4mg/kg (males, 12/gr) and 0.25, 1, 4, and 8mg/kg (females, 12/gr). The cont gr received the vehicle (10% w/v acacia sol.). Blood was collected from 6/sex/dose at 1 and 3mo starting at 20min and upto 6hr postdose as well as at time 0 (pre-dosing). Note that some animals died due to technical errors during sampling from the cannula making the no. of animals less than 6/gr. Prolactin was assayed by Ab RIA. Statistics was done using ANOVA and Dunnett at $p<0.05$.

1 month:
plasma prolactin levels were sig incr in males and females. In males, a sig incr noted at 40min and upto 2hr postdose in the 2 high doses and in females, prolactin incr as early as 20min till 2hr in the 3 high doses and remained sig elevated in the 2 high doses upto 4hr postdose (see below). **Note that in males values in the 2 high dose groups were moderately high, though did not reach sig, at time zero compared to the cont values (range 12-73ng/ml vs. 15-30ng/ml in cont), with half of the rats in each drug gr showing values above the max value in the cont; these findings were not explained.**
Values below are means±s.e. (ng/ml); n=4-6; all values below differed sig from the cont; () are female values.

Time	Dose (mg/kg)				
	Cont	1	2.5	4	8
20min*	(11±2)	(87±27)	NA	(308±45)	(252±79)
40min	21±5 (13±4)	NS (137±19)	49.5±4 (NA)	59±7 (365±47)	NA (292±49)
1hr	12±2 (10±2)	NS (113±7)	39±3 (NA)	38±4 (241±29)	NA (187±56)
2hr	7±2 (17±4)	NS (68±9)	27±5 (NA)	31±3 (280±31)	NA (186±43)

NS not sig, NA not applicable, i.e the dose was not tested in this sex.
* no effect in males at this time in any dose.

In females, prolactin level remained elevated in the 2 high doses upto 6hr postdose (sig at 4hr)(range conc at 4hr: 59-180ng/ml for 8mg/kg and 50-152ng/ml for 4mg/kg both relative to the cont range of 16-49ng/ml and, at 6hr: 39-243ng/ml for 8mg/kg and 75-421ng/ml for 4mg/kg both relative to the cont range of 26-85ng/ml.

3 months:
At 3mo, prolactin conc in general, in males or females at any time point, were higher than the corresponding values measured at 1mo. Also in males dosed 1mg/kg, prolactin was not incr at the 1mo at any time point however, a sig incr over the cont was measured at 3mo starting at 20min postdose and upto 2hr and the HDm, a sig incr in prolactin was measured at 20min, a finding not seen at 1mo. In females dosed 0.25mg/kg, no sig incr or change was noted in prolactin level measured at

1mo but a sig incr was seen at 3mo at 20min and 1hr samples. Therefore, all female drug groups showed a sig incr in prolactin level at 3mo and the incr persisted in the 2 highest doses through the 6hr sampling period.

Time	Dose (mg/kg)				
	Cont	1	2.5	4	8
20min	21±4 (7±1)	44±3 (152±30)	79±10.5 (NA)	85±7 (390±58)	NA (298±80)
40min	17±2 (10±3)	39±4 (337±48)	81±5 (NA)	86±4 (415±55)	NA (439±31)
1hr	16±3 (7±1.4)	33±3 (161±13)	63±4 (NA)	71±7 (382±65)	NA (311±60)
2hr	14±3 (11±3)	NS (166±56)	57±11 (NA)	54±4 (394±40)	NA (328±47)
4hr*	12±2 (26±7)	NS (63±14)	36±10 (NA)	NS (284±49)	NA (192±29)
6hr*	(43±13)	(199±88)	(NA)	(272±68)	(186±28)

* values incr sig only for females and the single value at 2.5mg/kg in males.
Also in females, a sig incr in prolactin was observed at 0.25mg/kg dose at the 20min and 1hr periods.

It is concluded that repeate oral administration of olanzapine to rats, caused a sig incr in prolactin with levels higher and lasting longer when measured at 3mo vs. 1mo. In females, all 4 drug groups showed a sig incr in prolactin at some timepoint at 3mo, similarly in males, the 0.25 and 1mg/kg dose gr did not incr prolactin levels at 1mo but a sig incr was seen with 1mg/kg during the 3mo.

Summary of Prolactin Studies

A dose-dependent increase in palsma level occurred after single dose administration to rats. Doses ranged between 0.1-2.5mg/kg; values in females were higher than those in males at all doses and all time points, remaining elevated upto 6hr postdose. Similar to single dose findings, repeate dose studies in rats for 3mo at 1 to 4mg/kg in males or upto 8mg/kg in females, showed dose-dependent incr in prolactin level. This incr was higher and lasted longer when measured at 3mo than the values at 1mo. Also, at the lowest dose of 0.25mg/kg in males, a sig incr noted at 3mo measurement but not at the 1mo. The elevation of plasma prolactin is expected since the drug is a DA antagonist and maybe considered an extension of pharmacological activity.

PROTEIN BINDING STUDIES:

- In vitro binding of olanzapine to plasma proteins in mice, rats, dogs, monkeys, and humans/Report# 33/Lilly Labs, IN/June 1995
Lot# label V866ME267.

Plasma protein binding of olanzapine was determined in vitro. Plasma was obtained from male ICR mice, male F344 rats, male beagle dogs, rhesus monkeys, and humans. Conc of olanzapine tested was 100ng olanzapine/ml based on tox and PK studies (reports# 43(mouse), 39(rat), and 23 (dog)). Binding of ^{14}C-olanzapine was determined from 5 samples/species at 37C by ultracentifugation method and amount of free unbound drug was determined by LSC. Results showed similar binding in humans and monkey at a mean of 93 and 91% respectively, and slightly less binding in mouse (81%), rat (83%), and dog (81%). This indicated that amount of free unbound circulating drug (pharmacologically active form of the drug) is less in the mouse, rat, and dog than that in monkey and humans. However, studies in humans (report# F1D-LC-HGAW), showed that the extent of binding was unaffected by a wide range of conc. Non-specific binding of radioactivity ranged between 1-8% which was determined using saline instead of plasma.

- In vitro plasma protein binding of olanzapine in rat plasma by ultracentrifugation with analysis by reverse phase HPLC-UV detection/Report# 44/Lilly Labs, IN/Jan 1995.

Blood was collected from anesthetized male Fischer 344 rats by cardiac puncture; plasma was prepared. Three conc of olanzapine were selected from a validated conc-curve (100, 250, 1000ng/ml). Rat plasma was incubated with olanzapine for 1hr at 37C. Plasma conc were measurable for these 3 conc with approximately 40-50% unbound olanzapine of the spiked sol. (percent bound therefore was 50-60)

STUDIES WITH IMPURITIES AND DEGRADATION PRODUCTS:

- A subchronic tox study in Fischer 344 rats given olanzapine with impurities (T00534)/Report# 63/Study# R13695/Lilly Labs, IN/July 1995/GLP.

Lot# 2753-67 contains the following:

	lot#	%Potency
olanzapine	029JD3	99
301664	AK9OZF274-1	97.7
343344	X353324-36	80.6
343345	X35332437	84

These cpds are degradation products of olanzapine form during storage.

Olanzapine was administered to male and female Fischer rats (106±3g m and 89±4g f) by oral gavage at **16mg/kg/d for 14days.** This dose provided the following daily dose for the impurities: 168ug/kg of 301664, 163ug/kg of 343344, and 165ug/kg of 343345 (representing 1.02-1.05% of the dose). There were 5/sex in the control (10% acacia), and 8/sex for olanzapine gr. No mortalities; clinical signs included hypoactivity in all drug grs decr in severity with time but remaining till end of study, also for the 1st 5d: sternal recumbancy, lethargy, and lacrimation. All rats were normal within 24hr of dosing. Mean wt and wt gain were significantly reduced in both sexes of drug gr throughout the study. By day 4, mean wt gain in males and females was 92 and 73% less than that of the control and by termination, the mean wt gain was 60 and 38% of the control in males and females respectively. The decline in wt in males correlated with a sig decr in food intake as seen from a sig decr in mean cummulative food intake at end of study (10%); for females however, a slight but sig incr noted in mean daily intake (9%) relative to the corresponding controls. The cummulative Efficiency of Food Utilization (EFU) was sig reduced throughout the study both in m&f and by end of study it was 56&43% less than the controls in males and females respectively. Blood was collected from the orbital plexus prior to necropsy for hematology and clinical chemistry. A sig 6-10% incr in RBC, Hb, and PCV of treated males and a non sig 3-5% incr also noted in females. A marked decr in leukocytes (19-21%), lymphocytes (24-27%), and thrombocytes (29-30%) recorded in treated males and females relative to the controls. The clinical chemistry parameters affected included: incr in BUN (20-24%; sig only in m), incr in AST (20-23%; sig only in m), ALT (6% in m, 29% in f; sig only in f), CPK (17% in m, >200% in f; not sig in either sex/large interanimal variation), incr in Cl (2-3%; sig in both sexes), Ca decr (3-5%; sig in both sexes), sig decr in inorg P only in m (14%;), sig decr in total Bili in m (23%), incr in Chol (18% in m, 8% in f; sig only in m), sig decr in TG only in m (41%), sig decr in Glob (9-13%; sig in m&f), the Alb was sig incr in f only (3%), the A/G ratio was therefore, decr in m (sig; 25%) and incr in f (sig; 33%). Changes in organ wts were secondary to decr in mean wt and wt gain, the absolute wt of the ovaries was sig reduced as well as that relative to B.wt and brain wt. Histopathology was limited to bone marrow hypocellularity observed in 3f and 1m characterized by incr in fat cells and a decr in hematopoietic tissue with the non-erythroid elements (myeloid, megakaryocytes, and perhaps lymphocytic) more affected than the erythroid elements. The sponsor indicated that these changes were non-specific and secondary to the decr in B.wt. Other histopath findings were minimal and common to rats including kidney mineralization and some females with under-developed corpora lutea.

It was concluded that the effects of administration of olanzapine + impurities to rats for 14ds is similar to previously reported findings of olanzapine minus these impurities. The 3 impurities reported in the present study result from degradation of olanzapine during storage and were present at 1.02-1.05% of the administered dose.

Note that blood was collected for measurement of plasma conc but samples were destroyed inadvertantly, therefore, plasma levels of olanzapine and the 3 impurities remain unknown.

- In vitro receptor profile of olanzapine and 5 of its analogues, 170055, 170238, 290411, 301664, and 10-N-glucuronide for adrenergic (alpha 1,2, and beta), muscarinic, DA1 and DA2, H1, 5HT2, $GABA_A$ and benzodiazepine (Bzp) receptors/Report# 73/Lilly Labs, IN/Apr 1995/GLP.
Lot# for olanzapine 029JD3

290411 = 2-CH3OH
170055 = N-desmethyl
170238 = N-oxide
301664 = lactam byproduct of degradation

Frozen rat whole brain tissue was used to assay for Bzp H1, and adrenergic receptors, cortex for GABA, muscarinic, and 5HT, and corpus striatum for DA. Affinity constant (K_i) and IC_{50} were determined for each assay, values are the means±s.e. of at least 2 experiments. Olanzapine showed high affinity to H1> 5HT2> alpha1>DA2>muscarinic>DA1>alpha2 (263nM). Olanzapine had no affinity to Bzp, beta adrenergic, or GABA upto 10uM conc. The 2-CH3OH and N-desmethyl metabolites showed similar affinities to DA2, H1, 5HT2, and alpha1 as those for olanzapine with the former having the most similar profile to olanzapine with respect to these receptors. The affinity (Ki) to muscarinic receptors were about 7x lower for the 2-CH3OH than the Ki for olanzapine but the 2-CH3OH had higher affinity for DA1 than that of olanzapine (Ki 66 vs. 119nM respectively).

	K_i (nM)					
Cpd	DA2	5HT2	H1	α1	M	DA1
olanzapine	20	10	7	15	67	119
2-CH3OH	22	18	6	12	500	66
N-desmethyl	9	23	22	80	333	203

The rank order of affinity of the above cpds is as follows:
olanzapine: H1>5HT2>alpha1>DA2>M>DA1>alpha2
2-CH3OH: H1>alpha1>5HT2>DA2>D1>M>alpha2
N-desmethyl: DA2>H1>5HT2>alpha1>DA1>M>alpha2

The N-oxide has similar binding profile to that of olanzapine but at much lower affinity. The lactam and the N-glucuronide do not bind (very poor affinity) to any of these receptros.

Therefore, the 2-CH3OH and N-desmethyl metabolites could have physiological-pharmacological activity if their conc achieved after administration of olanzapine is adequate to do so. Based on the receptor occupancy theory, both high affinity and adequate conc must be presented for the receptor for binding tooccur. These 2 cpd though have affinity, their conc after olanzapine administration is low and their binding (receptor occupancy) is expected to be less than 1/10th the receptors occupied by olanzapine. It is concluded that these metabolites can not produce any physiologic effect unless their conc are incr sig over that of olanzapine.

- In vivo pharmacology of potential olanzapine metabolites and degradation products*/Report# 80/Lilly Labs, IN/Oct 1992, Mar 1994, Apr 1995.
* N-desmethyl, N-oxide, 2-CH3OH, and lactam.

The following in vivo animal tests predictive of DA activity were examined using olanzapine and 3 of its metabolites and one degradation product: apomorphine induced climbing in mice, cocaine induced hyperactivity in Lister Hooded rats, conditioned avoidance in Lister Hooded rats, and conditioned avoidance in Squirrel monkeys. Dosing for the apomorphine test included oral, i.v. and s.c., for the cocaine induced hyperactivity i.p (only the desmethyl was tested with olanzapine), for the conditioned avoidance in rats oral or i.v., and conditioned avoidance in monkeys s.c.

Apomorphine-induced climbing: Olanzapine induced a sig and dose-dependent decr in climbing response in mice at 0.625, 1.25, 2.5, and 5mg/kg s.c. dose and at 1mg/kg i.v., and 2.5, 5, and 10mg/kg orally. Metabolites N-desmethyl, 2-CH3OH, and the lactam cpd failed to antagonize the climbing response at doses <20mg/kg, the N-oxide on the other hand was active in decr the climbing behavior at a mini effective dose 12.5mg/kg s.c. compared with 0.625mg/kg s.c. olanzapine.

Cocaine induced hyperactivity in rats: Olanzapine antagonized the cocaine induced hyperactivity at 1.25-5mg/kg i.p. whereas, the N-desmethyl had no effect upto 25mg/kg.

Avoidance response in rats: olanzapine produced a dose-dependent decr in this response at 0.25-1mg/kg i.v. and 2.5-10mg/kg oral dose; none of the metabolites or the lactam cpd had any effect upto 25mg/kg oral dose.

Avoidance response in monkeys: olanzapine produced a marked decr in response (0.3-1mg/kg s.c.) as did N-desmethyl at 10-17.5mg/kg s.c., however, the desmethyl was 33x less active than olanzapine.

It was concluded that none of these metabolites or the degradation product have any significant pharmacologic activity in vivo. It is interesting to note that the N-oxide had some effect on apomorphine induced climbing when this cpd showed very poor affinity to DA receptors in vitro thouhg it had similar binding profile to olanzapine. The N-desmethyl showed affinity to DA receptors and in in vivo had small effect as seen in the avoidance response in monkeys.

- Effect of olanzapine impurities (170055&301664) on induction of reverse mutation in Salmonella and E. Coli using the Ames test/Report# 58/Studies 950131AMS3902, 950201AMS3904, and 950208AMS3904/Lilly Labs, IN/May 1995/GLP.

The above 2 impurities of olanzapine were tested using Salmonella strains TA1535, TA1537, TA98, and TA100in and in E.coli WP2uvrA in presence or absence of S9. Concentrations tested were based on a preliminary tox test for each impurity using TA100. note that it is recommended that all strains of Salmonella be tested in the preliminary tox assay and not just one strain. The conc selected for the actual assay ranged between 250-1800ug/plate of cpd 170055 in -S9 and 250-3000ug/plate in +S9 and for cpd 301664 the conc in + and -S9 ranged between 62.5-1000ug/plate; higher conc could not be tested due to precipitate at 1000ug/plate. A positive response was that when the no. of revertants increases by at least 2x for strains TA98 and 100 and WP2uvrA or at least 3x for TA1535 and TA1537 in 2 successive conc of the cpd.

Impurity 170055 was not mutagenic (did not incr the no. of revertant colonies) at any conc tested in +/- S9. Impurity 301664 was not mutagenic in -S9 but mutagenic in +S9 at 62.5 and 125ug/plate for TA100 and at 62.5, 125, 250, and 500ug/plate for E.coli strain with >2x (2.1-2.5x for TA100 and 2-4x for WP2uvrA strain). This assay was repeated using the same conc and conditions; the results were negative.

It is concluded that cpds 170055&301664-impurities of olanzapine, were non mutagenic in the Salmonella and E.coli assay at the conc tested in presence or absence of S9. The positive response noted in cpd 301664 in +S9 was not dose-dependent and negative in the repeate assay therefore, it can be concluded that this cpd did not incr the no. Of revertants in the Ames test.

- Effect of olanzapine with impurities on induction of reverse mutation in Salmonella and E. coli using the Ames test - Plate incorporation assay/Report# 64/Study# 950626AMS3964/Lilly Labs. IN/July 1995/GLP

The degradation products were the lactam (301664), ketolactam (343344), and the ketothiolactam (343345)

Bacterial strains tested were TA1535, TA1537, TA98, and TA100 as well as E. coli strain WP2uvrA. The assay was done in +/- S9, the positive controls were MNNG, 2NF, and 9AmAc in - S9 and 2AA in + S9. Criteria for a positive mutagen were: at least a 2x incr in revertants over the cont value for strains TA98, TA100, and WPuvrA and, at least a 3x incr over the cont value for strains TA1535 & TA1537. The conc used in this assay were selected based on previous Ames test (Report# 7); the solvent used in this assay was DMSO. Precipitate noted at 4000 and 5000ug/plate in - and + S9 respectively. Olanzapine + impurities did not induce/incr No. of revertants when tested at conc ranging between 250-4000ug/plate in - S9 or at conc between 312.5-5000ug/plate in + S9. The positive controls produced the anticipated response. It was concluded that olanzapine + impurities of degradation was non-mutagenic in the Ames assay.

- Effect of olanzapine with impurities given orally for 2 consecutive days on induction of MN in bone marrow of ICR mice/Report# 65/Study# 950620MNT3964/Lilly Labs, IN/July 1995/GLP.

Olanzapine + impurities (301664, 343344, 343345) was administered by oral gavage to male and female ICR mice at 11.6, 23, or 46mg/kg/d for 2d. Doses were based on a preliminary study where 100% lethality occurred at 62.5mg/kg. The HD selected was approximately 50% of the median lethal dose and was the HD in previous tox study (Report# 33). In the definitive study, 5 mice/sex/dose were used and killed 24hr post the 2nd dose. Bone marrow (femur) was isolated and processed. One thousand PCEs were counted per mouse and the numbers of PCE with and without MN and the number of NCE were recorded. Bone marrow tox was assesssed by the PCE/NCE ratio. Olanzapine at either dose did not induce MN formation compared with the control, the positive control CP gave a positive response as expected.

Clinical signs included hypoactivity, squinting, lethargy, and hunched posture.

SUMMARY AND CONCLUSION:

Based on the 2-wk subchronic tox study in rats and the in vitro bacterial Ames mutagenicity tests and in vivo bone marrow induction of MN in mice, presence of the 3 impurities with olanzapine produced effects consistant with those previously reported with olanzapine in absence of these impurities. Therefore, presence of these impurities with olanzapine does not impose a safety hazard. These impurities were present at 1.05% the administered dose in rats. In a max clinical dose of 20mg (0.33mg/kg at 60kg) when each of these impurities present at 0.5%, the doses tested in rats thus represented a 100x safety margin.

In vitro receptor binding assay for olanzapine and its metabolites the N-desmethyl, N-oxide, and the 2-CH3OH plus the lactam a degradation product showed the N-desmethyl and the 2-CH3OH to have similar profile and affinity to olanzapine but neither cpd showed higher affinity than the parent at any neurotransmitter site tested. The N-oxide had also a similar profile to olanzapine but the affinity was very poor. The N-desmethyl had higher affinity to DA2 than did olanzapine (9 vs. 20nM) but its conc from administration of olanzapine is not expected to be high enough to produce any physiologic effect. In vivo pharmacology using animal tests predictive of DA activity, did not show any sig finding with these metabolites relative to olanzapine. The only finding was that of the N-oxide in decr the apomorphine climbing at a dose 20x less than that for olanzapine.

ADME

ABSORPTION

Rat

- In vivo intestinal absorption of ^{14}C-olanzapine in Fischer 344 rats/Report# 9/Lilly Labs, IN/Jan 1995.

This study was done to identify the segment of the GI where olanzapine is best absorbed when administered in aqueous sol. Absorption was determined by disappearance of radioactivity from stomach, duodenum, jejunum, ileum, and colon, and the apppearance of radioactivity in plasma 2hr post single intraluminal dose of 8mg/kg. A specified vol of the dose sol was injected into the selected segment of the gut and left for 2hr after which time the GI loop was flushed with water into scintillation vials and radioactivity quantified. The difference between amount injected and that remainig at the end of the 2hr in a segment represented extent of absorption. Radioactivity was also measured in plasma and urine. Max radioactivity retained in decreasing order was: stomach (48%)>duodenum (24%)>jujenum (11%)>colon (3%)>ileum (1%). This indicated that olanzapine was best absorbed from the ileum and the colon (least radioactivity), and the poorest absorption was from the stomach (high radioactivity). Good absorption was also evident from plasma with radioactivity between 1.6-2.8ug.Equiv/ml (least in stomach at 0.5ug.Equiv/ml). Radioactivity was also detected in urine 2hr postdose providing further evidence of good absorption.

- Plasma conc of olanzapine in the portal and systemic circulation of male Fischer rats given a single oral dose of ^{14}C-olanzapine at 8mg/kg/Report# 15/Lilly Labs, IN/Apr 1993.

Two studies were conducted: one to measure conc of radioactivity in portal and systemic plasma and the 2nd to measure conc of olanzapine in portal and systemic plasma by HPLC method. Male Fischer 344 rats (4/time point/exp) were administered 8mg/kg olanzapine (cold and label) by oral gavage. Starting at 0.5hr and upto 24hr postdose, animals were anesthetized and blood collected from the portal vein and inferior vena cava. Olanzapine seemed to be well absorbed as indicated by the high radioactivity and olanzapine conc in the portal circulation at 0.5 and 1hr postdose. Max conc of radioactivity in portal plasma was 2338$\pm$297ng.Equiv/ml reached at 0.5hr of dosing and conc in systemic plasma was 1229$\pm$434ng.Equiv/ml. The reduced radioactivity in systemic vs portal plasma as early as 0.5hr of dosing may indicate biliary excretion, metabolite formation, or retention of radioactivity by the liver. In the above study (report# 11) after 8mg/kg oral dose max radioactivity excreted into the bile occurred within 24hr of dosing at 15% and 10% recorded during the 1st 6hr of dosing. By 3hr post dose, radioactivity continued to decline and was comparable in portal and systemic plasma indicative of absence of uptake or retention by the liver. Max conc of olanzapine in portal plasma was 2159$\pm$852ng/ml at 1hr and that in systemic plasma was 212$\pm$67ng/ml at 1hr. Mean plasma elimination half life of radioactivity was 6-6.5hr (calculated between 6-24hr) which is longer than that of olanzapine at 2.3hr (calculated between 3-12hr). Mean AUC of radioactivity was 8073 and 10,104ng.hr/ml for systemic and portal plasma respectively, the corresponding AUC values for olanzapine were 1418 and 8546ng.hr/ml respectively. This study demonstrated extensive first pass effect and liver uptake of olanzapine following single oral dose to rats.

- Plasma conc of olanzapine in male and female Fischer rats receiving different doses by oral gavage for upto 6mo/Tox stdy# R22593&R22693/Report# 31/Lilly Labs, IN/Sep 1993.

Fischer 344 rats (3/sex/dose) were dosed olanzapine at 1, 4, 8, or 16mg/kg for 6mo by oral gavage. Blood was collected on day 0, 2&6mo at 0 (except day0), 0.5, 3, 5, 8, 12, 24, and 48hr postdose. Plasma conc and AUC were incr with dose in a non-linear fashion at all doses, conc were not

detectable on day0 at 1mg/kg at ≥3hr postdose and 4mg/kg at ≥5hr postdose and in the 2 high doses, the drug was not detected by 24hr. Nevertheless all animals seemed to have been exposed to the drug at some point. There was no sex difference in drug conc at all doses and time points.

Day0 Dose (mg/kg)	C_{max} (ng/ml)	AUC_{0-t} (ng.hr/ml)
1	13±3	-
4	74±5	247
8	298±36	1439
16	1123±72	5656
Month 2		
1	11±2	52
4	173±30	851
8	576±91	5289
16	1754±355	21191
Month 6		
1	24±6	222
4	241±30	1283
8	802±58	6579
16	2076±130	29109

values are for m+f combined and are means±s.e.; n=2-5

Mean T_{max} ranged between 0.5-8hr and plasma elimination half life was 1-9hr. It was noted that at the 6mo period for the 1, 4, and 8mg/kg doses, conc could not be detected at 24hr but were measurable at 48hr (dl 1ng/ml), also there seemed to be some degree of drug accumulation with time at all doses with similar finding noted for AUC (see above table).

Mouse

- Plasma PK of radiocarbon and olanzapine following administration of a single oral dose of ^{14}C-olanzapine at 15mg/kg to CD-1 mice/Report# 35/Lilly Labs, IN/Jul 1994.

Blood was collected from male CD-1 mice starting at 0.5 and upto 72hr post oral dosing of 15mg/kg of labelled olanzapine. Plasma conc were measured by a validated HPLC-EC, and radiocarbon content was determined by liquid scintillation counting. Plasma conc of olanzapine ranged between 13ng/ml at 24hr to 421mg/ml at 0.5hr postdose (T_{max}), and the drug was non-detectable by 48hr of dosing (quantification limit(ql) 1ng/ml). Total radioactivity (ng.Equiv/ml) was more or less similar in plasma and whole blood with peak values at 0.5 and 4hr:

	0.5hr	4hr
plasma	2200±104	2260±45
blood	1750±132	1540±18

Having 2 peak radioactivity in plasma and blood at 0.5 and 4hrs may indicate enterohepatic recycling of radioactivity.

Max conc of olanzapine as indicated above was **421ng/ml at 0.5hr**, max mean conc of radioactivity in plasma was 2260ng.Equiv/ml at 4hr and in blood 1750ng.Equiv/ml at 0.5hr. Exposure (AUC_{0-t}) was slightly higher in plasma at 15,201ng.hr/ml than in blood at 13,206ng.hr/ml; **olanzapine's AUC was 1522ng.hr/ml** approximately 10x lower than radioactivity in plasma and 9x lower than radioactivity in

blood. At all times radioactivity in plasma and whole blood were higher than those of plasma olanzapine. Max conc of olanzapine was 19% and 24% of C_{max} of plasma and blood radioactivity indicating good absorption and marked metabolism. **Plasma elimination half life of olanzapine was 3.2hr** when calculated between 7-12hr, **half life of radioactivity in plasma and blood was 11&16hr** calculated between 7-48hr respectively. These data in mice were similar to those reported for rats, dogs, and monkeys following single oral dose of labelled olanzapine (reports 14, 18, 28). In conclusion, single oral dose of labelled olanzapine to mice showed plasma conc and half life lower than those of radioactivity in plasma and blood at all time points, radioactivity showed 2 peaks in plasma and blood indicating enterohepatic recirculation of radioactivity.

- Plasma conc of olanzapine in CD-1 mice given daily oral gavage doses for upto 1yr/tox study# M09593/Report# 37/Lilly Labs, IN/Aug 1993.

Plasma olanzapine conc was determined in mice (6/sex/dose) used in 1yr tox study. These mice were administered olanzapine at oral doses of 0.5, 2, or 8mg/kg; blood was collected at 0.5hr postdose at 6 and 12mo; samples from 2 mice were pooled resulting in total of 3 samples/dose/sex. There was no sex difference in conc at all doses except at the HD/6mo. At the 6mo, HDm had plasma conc that fell outside the range of the standard curve and values had to be extrapolated (see table below from sponsor), also sample size was small (n=3). Note however, that there was no difference between the 6&12mo conc and no sex difference in conc at the 12mo. Therefore, the relevance of the statistically sig difference in conc between sexes at 6mo is not clear. The conc incr linearly with dose except between the HD and the LD&MD where values were several folds higher than would have been predicted. Again, small sample size and analysis at only one time point, could have affected this outcome. In previous mice studies, 18mo tox study and 2-wk TK (reports# 20&43), there were no clear sex difference in conc with time.

Table 37.1 Mean Plasma Concentrations of LY170053 in CD–1 Mice Dosed Daily (Oral; Gavage) with LY170053 at 0.5, 2 or 8 mg/kg for up to One Year (Toxicology Study M09593)

Dose mg/kg	Gender	6 Months		12 Months	
		Mean ng/ml plasma [a]	±SD	Mean ng/ml plasma [a]	±SD
0.5	M	4.82	0.31	8.43	2.28
	F	4.04	0.30	4.93	0.64
2	M	24.23	5.38	37.57	13.74
	F	20.50	4.50	29.83	5.66
8	M	258 [b] *	9.85	227.33	33.31
	F	162	25.87	169.67	31.56

[a] = mean (n = 3 ± SD) plasma concentrations approximately 30 minutes after dosing

[b] = extrapolated value: original values outside of range of standard curve (1 to 100 ng/ml)

Limit of Quantitation = 1 ng/ml

* Values were statistically different between ♂ & ♀ at this time.

Dog

- PK of radioactivity and olanzapine in female dogs after a single oral dose of ^{14}C-olanzapine at 5mg/kg/Report# 18/Lilly Labs, IN/Oct 1993.

See report#17 for urine and feces data. Following single oral dose of ^{14}C-olanzapine to dogs, radioactivity was measurable in all 4 dogs upto 168hr in both blood and plasma. Radioactive conc was similar in blood and plasma indicating good distribution into RBCs. Mean radioactive conc half life was 28-31hr (calculated between 24-96hr) which is similar to that reported for rats (report 6). Olanzapine conc was also measurable in all 4 dogs but only upto 48hr of dosing. Mean max conc of olanzapine was 172±69ng/ml reached at 1-6hr which is 18% of max conc of total radiocarbon at 949ng.Equiv/ml for total radiocarbon reached at T_{max} of 1hr. $AUC_{0.5-48hr}$ of olanzapine was 14% (1923±325ng.hr/ml) of the total radiocarbon in plasma over 0.5-48hr (AUC for total radiocarbon was 13404.6ng.Equiv.hr/ml). Plasma elimination half life of olanzapine was 7.5-11hr (mean 9hr).

- Plasma conc of olanzapine in Beagle dogs administered orally at 2, 5, or 10mg/kg for 1yr/Report# 23/Tox study# D02093)/Lilly Labs, IN/Mar 1995.
Lot# 029JD3.

Male and female beagle dogs were orally dosed olanzapine for 1yr at 2, 5, or 10mg/kg/d and plasma drug levels evaluated on day 0 and months 3,6,12 with collection times between 0-24hr postdose. Validated HPLC method quantitated olanzapine's conc with dl of 1ng/ml.

	Dose(mg/kg)	Mean C_{max} (ng/ml)	AUC_{0-t}(ng.hr/ml)	Mean $t_{1/2}$ (hr)
Day0	2	54	426	4.5
	5	153	1376	4
	10	235	2539	9
Mo3	2	51	443	5
	5	151	1531	5.6
	10	286	2864	5.7
Mo6	2	67	681	5
	5	203	1922	5
	10	299	2884	5
Mo12	2	65	696	6
	5	205	2155	6
	10	315	3396	6

Mean T_{max} was 5-8hr; mean plasma elimination half life of m+f was 5.8±1.2hr.

There seem to be no accumulation of the drug with time. Conc and exposure incr linearly with dose and there was no difference between sexes. Mean combined plasma C_{max} (adding and averaging the m+f data throughout the study) was 59±7.8, 178±30. and 284±35ng/ml at 2, 5, and 10mg/kg respectively. T_{max} was consistent throughout the study irrespective of dose, time or sex. There were 3HD dogs (2f, 1m) that exhibited abnormal hematology (cytopenia) that haulted temporarily drug administration. These dogs were re-challenged after hematology parameters were normalized, using escalated doses at 2,4,8, and 10mg/kg. One male and one female were titrated back to10mg/kg however, the other female dog was titrated up to only 2mg/kg with plasma level of 8ng/ml 24hr post 2-wk re-challenge.

Plasma conc in these dogs where cytopenia was observed were:

plasma conc from HDf with cytopenia (rechallenged with 2mg/kg)	262 and 8ng/ml
plasma conc from HDf displaying normal hematology	24-38ng/m
plasma conc from HDf with cytopenia (rechallenged with 2,4,8,10mg/kg)	24ng/ml
plasma conc from HDf displaying normal hematology	5.5-60ng/ml
plasma conc from HDm with cytopenia (rechallenged with 2,4,8,10mg/kg)	24-26ng/ml
plasma conc from HDm with normal hematology	10-35ng/ml

Following the rechallenge of the male and female dogs, plasma levels were comparable to those dosed 10mg/kg with normal hematology. The female that could only be titrated up to 2mg/kg before abnormal hematology noted again, had mean plasma level of 8ng/ml at 24hr after the rechallenge. This was compared with the original value of 262ng/ml when dosing was haulted due to the cytopenia. **Therefore, a correlation between hematology abnormalities and plasma conc could not be made.** Also, the metabolic profile was found similar in dogs with normal hematology and those with abnormal hematologyt (by HPLC/MS). Note that details for hematology findings were not provided.

Olanzapine was not detectable in plasma 72hr after 4-wk recovery period from 1-yr dosing.

In summary, male and female dogs dosed olanzapine for 1yr at 2, 5, 10mg/kg showed linear incr in plasma conc with dose. There was no sex difference, no accumulation of drug with time, and consistent plasma elimination half life and T_{max}.

METABOLISM

- Metabolic profile of olanzapine in plasma of rats, mice, and dogs/report#22/Study#s 111R93&114R93 (rat); 018M93 (mice); 029D93&033D93 (dog)/Lilly Res Labs, IN/Mar 1994. Lot# for unlabelled drug: Dista 552PP2 dispensed from 552PP2F; for radiolabel: V86-6ME-267.

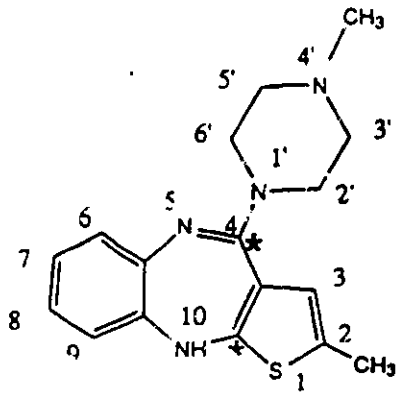
Plasma conc of parent and metabolites were analyzed by HPLC/MS/MS after a single oral dose of olanzapine at 8, 15, and 5mg/kg in rats, mice, and dogs respectively. These doses were selected based on PK and tox studies. Measurements were made at 1&6hr postdose in rats, 1hr in mice, and at 3&12hr in dogs. Fischer male rats (4 rats for each sampling time point); CD-1 mice (10 male mice); and Beagle dogs (3 females per sampling point).

Results & Discussion:
The metabolic profile was more or less **qualitatively similar in all 3 species** tested. The common metabolites included the **parent, 2-hydroxymethyl, and the desmethyl**. The **N-oxide and 7-hydroxy** olanzapine metabolites were found in the **rat and dog plasma** samples but not in the mouse. The metabolic profile in rat plasma was somewhat similar to that in urine with the major urinary metabolite being the 2-hydroxymethyl and the parent drug, was the major entity in plasma. **Two glutathione conjugates** were detected in **mouse plasma** and not found in the rat or dog. One of these conjugates seemed to be similar to that seen when olanzapine was incubated with reduced GSH in presence of horseradish peroxidase and the other, resembled that seen in rat bile. In the dog at 12hr postdose, the plasma profile was similar to that at 3hr except for 2 observations: the conc of the N-oxide at 12hr was markedly lower than the 7-hydroxy derivative and, glucuronide conjugate of the hydroxy derivative could no longer be detected at 12hr. **In all 3 species, the parent cpd accounted for the major radioactivity and in the plasma of all 3 species, hydroxylated glucuronide conjugates were detected** (the exact i.d. of these cpd is unknown but they are different from the 7-

hydroxy glucuronide conjugate). In **humans**, the major metabolic pathway is **direct glucuronidation to form the 10-N-glucuronide** which could not be detected in any of these species except for trace amount in dog urine. Some oxidation occurs in humans but to lesser degree than animals. [See attached table from sponsor].

Table 15 Metabolites of LY170053 (Olanzapine) in the Urine and Plasma of Several Animal Species(ADME Reports 19, 22, 30, 36, 51 and studies F1D-LC-HGAI)

Report #22



* position of ^{14}C

Compound	MOUSE		RAT		DOG		MONKEY	HUMAN	
	Urine	Plasma	Ur	Plasma	Urine	Plasma	Urine	Urine	Plasma
Olanzapine	✓	✓	✓	✓	✓	✓	–	✓	✓
2-CH_2OH-	✓	✓	✓[a]	✓	✓	✓	✓	✓	✓
2-CH_2OH-gluc	–	–	–	–	–	–	✓	–	–
2-COOH-	✓	..	✓	–	✓	–	✓	✓	–
2-COOH-gluc[b]	–	–	–	–	–	–	–	✓	..
N-oxide-	–	*	–	✓	✓	✓	✓	–	✓	✓
N-desmethyl-	✓	✓	✓	✓	✓	✓	–	✓	✓
2-CH_2OH, N-desmethyl-	✓	–	–	–	–	–	✓	–	–
2-COOH, N-desmethyl-	–	–	–	–	–	–	✓[a]	✓	–
2-CH_2OH, N-oxide-	–	–	–	–	–	–	✓	–	..
2-COOH, N-oxide-	–	–	–	–	–	–	✓	–	–
10-N-gluc-	–	–	–	–	✓	–	–	✓[a]	✓
4'-N-gluc-	–	–	–	–	–	–	–	✓	–
7-OH-	✓	–	–	✓	✓	✓	–	–	–
7-OH-gluc-	✓[a]		✓		✓				
7-OH-N-desmethyl-gluc	–	–	✓	–	–	–	–	–	–
7-OH-N-oxide-	–	..	–	–	✓[a]	–	–	–	–
GSH conj[c]	–	✓	–	–	–	..	–	–	–
NAC conj[d]	–	–	–	–	–	–	✓	–	–
Cysteine conj	–	–	–	–	✓	–	–	–	–
N-oxide-CYS[e]	–	–	–	–	✓	–	–	–	–

[a] major metabolite; [b] gluc = glucuronic acid, [c] glutathione conjugate also detected in rat bile; [d] N-acetylcysteine conjugate; [e] cysteine conjugate of N-oxide

Mouse

- Identification of olanzapine metabolites in mouse urine/Report# 19/Lilly Labs, IN/Nov 1993. Lot # not reported.

Six urinary metabolites of olanzapine were identified using HPLC/MS. Cold and ^{14}C-olanzapine were administered as a mixture at 20mg/kg single oral dose to 8m CD-1 mice. Urine samples were collected for 24hr after dosing. Metabolites identified in the aqueous phase included(% of urinary activity): olanzapine-2-carboxylic acid (7%), 7-hydroxy-olanzapine glucuronide (40%), 2-hydroxymethyl-N-desmethyl- olanzapine (2%), and 2-hydroxymethyl-olanzapine (15%). In the organic fraction, the following metabolites were identified: 2-hydroxymethyl-olanzapine, 7-hydroxy-olanzapine, N-desmethyl olanzapine, unchanged olanzapine, and 2 unknowns. [see figure below from sponsor].

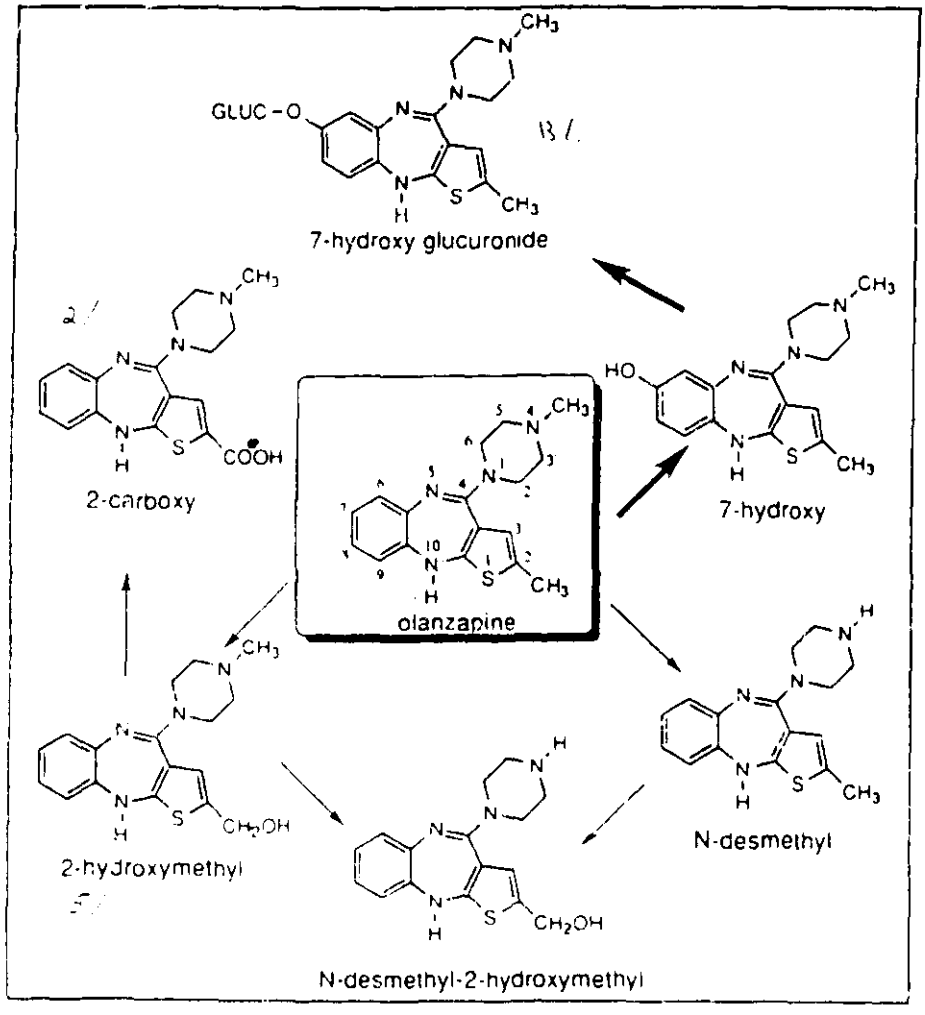


Figure 55.1. Major urinary metabolites of olanzapine in the mouse. Bold arrow indicates the major metabolic pathway.

Rat

- Metabolism of olanzapine in the rat/Report# 512/Lilly Labs Nuref 1995.

Olanzapine and 7 of its metabolites were identified in rat bile and olanzapine plus 8 metabolites were identified in the rat urine following 8mg/kg oral dose of ^{14}C-olanzapine to 3-4 rats. The analytical method was HPLC/MS. Urine and bile samples from reports 11&13 were used. Bile samples from 3 rats were collected after 12-24hr of dosing which represented 19% of administered radioactivity (report# 11). This sample contained high radiolabel per ml of bile. The following 7 metabolites were identified in bile in decr quantitative order: **glutathione adduct of olanzapine (34% of biliary radioactivity)**, N-acetylcysteine adduct (17% of bile radioactivity; tentatively i.d.), olanzapine-2-carboxylic acid (10% of biliary radioactivity), N-desmethyl-2-carboxy-olanzapine (5%), N-desmethyl-hydroxy olanzapine glucuronide (3.5%), 2-hydroxymethyl-olanzapine glucuronide (3.4%), olanzapine (2%), and N-desmethyl olanzapine (1%). These biliary metabolites plus olanzapine accounted for 75% of total bile radioactivity. Approximately 39% of the 8mg/kg radiolabelled dose was secreted into the bile within 72hr of dosing.

Metabolites identified in **urine** were, in decr quantitative order: **2-hydroxymethyl olanzapine**>N-desmethyl-hydroxy-olanzapine-glucuronide(tentative)>olanzapine>N-acetylcysteine adduct (tentative)>olanzapine-2-carboxylic acid>7-hydroxy-glucuronide>7-hydroxy-olanzapine>N-desmethyl-olanzapine>olanzapine 4-N-oxide. Urinary radioprofiles from one rat was analyzed on days 1, 7, 14, and 21 following oral dosing of 8mg/kg ^{14}C-olanzapine for 21days. HPLC analysis did not show any new metabolites therefore, indicating that the urinary excretion profile was relatively constant when steady state was reached. Approximately 35% of administered dose was eliminated in the urine within 72hr of dosing.

It was concluded that the metabolic pathway in rats include in decr quantitative order: thiol conjugation, 2-alkyl hydroxylation, aromatic ring hydroxylation, demethylation, and N-oxidation. [see figure below from sponsor].

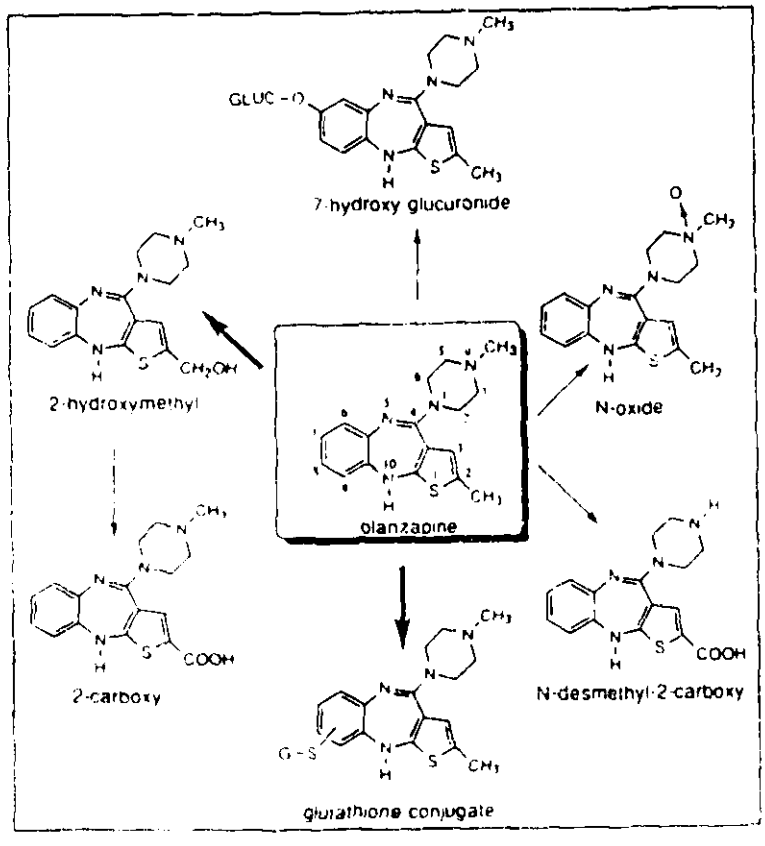


Figure 55.2 Major urinary and biliary metabolites of olanzapine in the rat. Bold arrows indicate the major metabolites in urine (2-hydroxymethyl olanzapine) and bile (glutathione conjugate of olanzapine)

- Analysis and PK of olanzapine and 2 metabolites in rat plasma using reverse HPLC with electrochemical detection/Report# 34/Lilly Labs, IN/Mar 1995.

HPLC (dl 1ng/ml) was used to quantitate plasma conc of olanzapine, N-desmethyl- and, 2-OHCH3-olanzapine. Male Fischer 344 rats were orally dosed with 8mg/kg ^{14}C-olanzapine and blood collected at 0.5, 1, 3, 6, 12, and 24hr postdose. Except for the N-desmethyl, radioactivity was detectable upto 24hr post dose.

Table 34.3. Plasma Concentration of LY170053 and Two Metabolites (ng/ml; mean ± SD) in Male Fischer 344 Rats Following the Administration of a Single, Oral Dose of ^{14}C–LY170053 at 8 mg/kg

Time (hr)	Total Plasma Radiocarbon (ng eq./ml) Mean ± SD	LY170053 (ng/ml) Mean ± SD	2–hydroxymethyl (ng/ml) Mean ± SD	N–desmethyl (ng/ml) Mean ± SD
0.5	1106 ± 260	352 ± 105	48.7 ± 12.1	31.1 ± 11.8
1	1530 ± 463	609 ± 149	130.6 ± 72.1	80.2 ± 51.1
3	1129 ± 243	286 ± 154	72.7 ± 15.2	37.6 (n = 2)
6	626 ± 133	152 ± 47.7	31.8 ± 7.20	51.5 (n = 2)
12	296 ± 28.9	33.8 ± 6.55	5.80 ± 2.11	9.01 ± 3.29
24	97.8 ± 15.4	4.44 ± 2.92	4.89 (n = 2)	BLQ
Mean C_{max} (ng or ng eq. /ml)	1,530	609	130.6	80.2
Cmax as % of total ^{14}C–Cmax	100	39.8	8.54	5.24
Mean T_{max} (hrs)	1	1	1	1
Mean $AUC_{(0-24\ hr)}$ (ng•hr/ml)	11,079	2,579	582	515
AUC as % of total ^{14}C–AUC	100	23.3	5.25	4.65
$t_{1/2}$ (hrs)	5.86 (1–24 hrs)	3.31 (1–24 hrs)	4.83 (1–24 hrs)	3.81 (1–12 hrs)
Coefficient of determination	0.9789	0.9862	0.3089	0.8494

BLQ = Below Limit of Quantitation (1 ng/ml)

Analysis and PK of olanzapine and 2 metabolites in rat plasma using reversed phase HPLC-EC detection/Report# 34/Lilly Labs, IN/Oct 1993.
Lot# for label cpd: V866ME267; Lot# for cold cpd: 552PP2F

A validated HPLC method was used to quantitate plasma olanzapine and its metabolites: 2-CH2OH and the N-desmethyl in rats. ^{14}C-olanzapine was orally administered to male Fischer rats at 8mg/kg. Blood was collected starting at 0.5hr and upto 72hr postdose (3rats/time point) for measurement of total radioactivity in plasma and blood and, plasma conc of olanzapine and the 2 metabolites. Plasma conc of olanzapine and its metabolites were detectable by 0.5hr of oral dosing (see table from

sponsor). Mean maximum conc of olanzapine was 609±149ng/ml at 1hr accounting for 40% of total plasma radioactivity at max conc. C_{max} of 2-OHCH3 was 131±72ng/ml at 1hr accounting for 8.5% of dose, and C_{max} for N-desmethyl was 80±51ng/ml also at 1hr and accounting for 5% of dose. These 3 cpds accounted for 54% of total plasma radioactivity and 33% of the AUC for total plasma radioactivity within 24hr postdose. Mean AUC_{0-24} (ng.hr/ml) for olanzapine was 2579 which was 23% of administered dose, for 2-OHCH3 582 which was 5%, and for N-desmethyl it was 515 accounting for 4.7% of administered dose. Half lives were similar among these cpds at 3-4.8hr. Plasma elimination half life ranged between 3-5hr for olanzapine and its metabolites and about 6hr for total radioactivity Olanzapine's conc and exposure were higher than the corresponding values for the 2 metabolites at all time points upto 24hr postdose. The 2-hydroxymethyl conc was generally higher than the conc of the N-desmethyl at all time points including 24hr period. Total radioactivity in plasma exceeded that of olanzapine and its metabolites upto the 24hr period.

Dog

- Identification of olanzapine metabolites in dog urine/Report# 30/Lilly Labs, IN/Jan 1995.

Using HPLC/MS, 10 metabolites of olanzapine plus unchanged drug were identified in dog urine 48hr after 5mg/kg oral dose of ^{14}C-olanzapine. Approximately 38% of dose was eliminated in urine within 6days and 47% in feces. About 32% of dose was excreted in urine within the 1st 48hr of dosing. The following are the metabolites listed in decr quantitative order (% of urinary activity and administered dose): **7-OH-4-N-oxide olanzapine (21% and 8%)**, 2-OH-CH3 olanzapine (9% and 3%), olanzapine 2-carboxylic acid (8% and 3%), olanzapine (6%), cysteine conjugate of olanzapine (2% and 1%), 4-N-oxide (3.4% and 1%), 7-OH olanzapine (3% and 1%), cysteine conjugate of N-oxide (5% and 2%), 7-OH olanzapine glucuronide (1% and <1%), and N-desmethyl olanzapine (0.3% and <1%). Detection of cysteine adducts indicates formation of glutathione adducts. These metabolites and olanzapine accounted for 60% of radioactivity in urine or 23% of administered dose. It was concluded that the major pathways of metabolism in dog urine are: **aromatic hydroxylation, 4-N-oxidation, and oxidation of the methyl gr of the thiophene ring.** [see figure from sponsor].

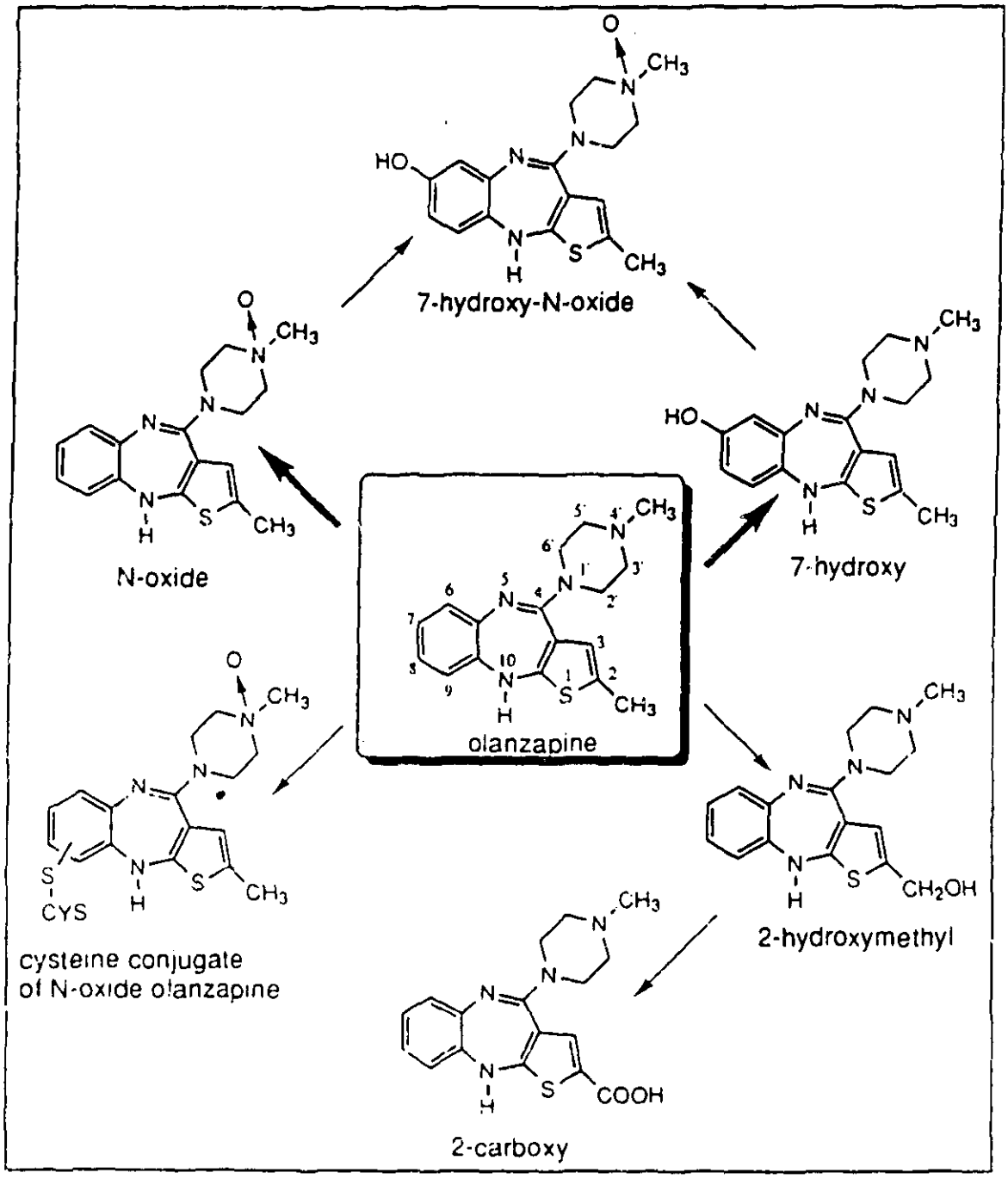


Figure 55.3. Major urinary metabolites of olanzapine in the dog. The pathways leading to the major metabolite (7–OH–N–oxide olanzapine) are indicated by bold arrows.

Report #30

Monkey

- metabolism of olanzapine in Rhesus monkeys/Report# 36/Lilly Labs, IN/Jan 1995.

Monkeys (2/sex) were orally (nasogastric) administered 5mg/kg of ^{14}C-olanzapine and urinary metabolites were analyzed by HPLC and identified by LC-MS/MS. Urine and feces were collected at 24hr intervals for 7days postdose. Approximately 55% of the administered dose was eliminated in urine within 7days with 48% cleared within the 1st 24hr. Eight metabolites were identified in urine accounting for approximately 83% of urine radioactivity or 40% of administered dose. The **major metabolite was N-desmethyl-2-carboxy olanzapine** at 36% of urinary radioactivity (17% of administered dose), followed by 4-N-oxide-2-OHCH$_3$ olanzapine at 12% (6% of dose) and 4-N-oxide-2-carboxy olanzapine at 9% (4% of dose)(this metabolite was tentatively i.d. since its retention time did not match any authentic standard). Metabolite 2-OH-methyl olanzapine glucuronide co-eluted with olanzapine 2-carboxylic acid both producing 8.7% of urinary radioactivity. The remaining 3 metabolites are in decreasing quantitative order: N-desmethyl-2-OHCH3-olanzapine (8%), 2-OH-CH$_3$ olanzapine (6%) and N-acetylcysteine adduct of olanzapine (3%)(tentatively identified). Based on these data, three main metabolic pathways accounted for urinary metabolism of olanzapine in monkeys: **oxidation of CH3 on the thiophene ring, oxidation at the 4-N of the methyl piperazine, and 4-N-demethylation** (see figure below from sponsor). There was no appreciable amounts of the parent drug in the urine samples indicating the extensive breakdown of olanzapine. This however, in contrast to findings in urine from dog, mouse, rat, and humans. These metabolites accounted for 83% of urinary activity or 40% of administered dose.

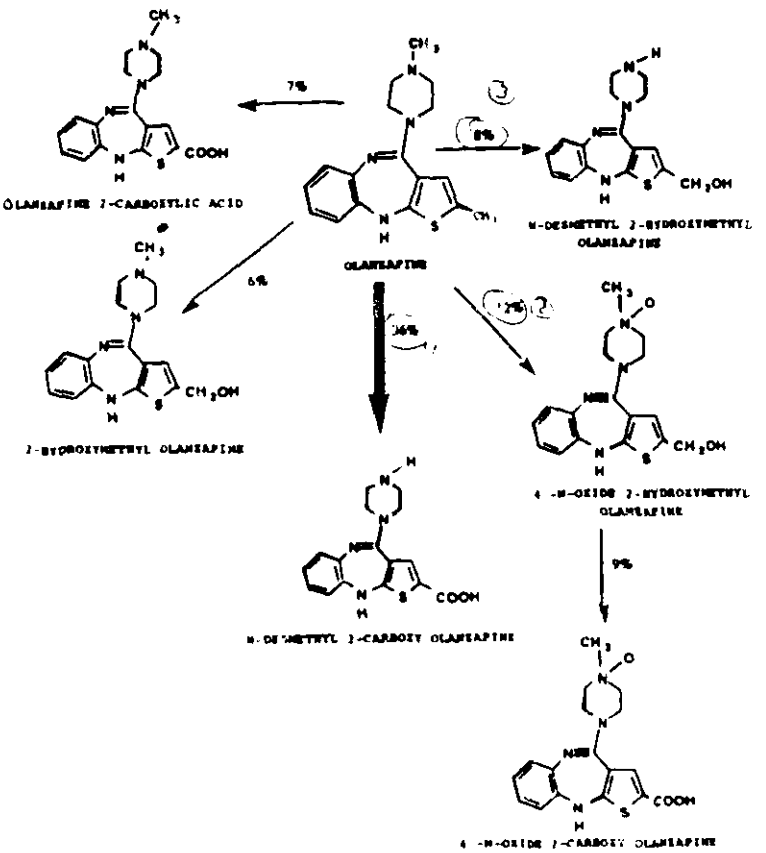


Figure 36 11 Proposed pathways for the metabolism of olanzapine in monkeys after oral administration of [^{14}C]-olanzapine. Recoveries of individual metabolites are expressed as percentage of radioactivity in urine

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METABOLITES/IN VITRO

Humans

Metabolism of olanzapine in human liver slices/Report# 32/BIbRA Toxicology International, UK/Feb 1995.

Human liver slices were obtained from a male donor age 6yr and 8mo. Slices were incubated (2/vial) under proper standard conditions. Three conc of ^{14}C- olanzapine were tested 50, 250, and 500uM (Lot# V86-6ME-267). A positive standard was used to test the liver slice viability for glucuronidation (LY280810). Mass spectroscopy indicated that the cpds formed in vitro were similar to the metabolites formed in vivo. Among phase I metabolites: N-desmethyl, 2-OHCH3-, 7-OH-, 4-N-oxide, and a hydroxylated cpd of which the attachment of the OH gr could not be verified. Phase II reactions included the N-10-glucuronide which was not detected in mouse, rat, or monkey urine, only trace amounts in dog urine, and the 4-N-quaternary glucuronide. No sulfate or GSH adducts were detected (see table and figure from sponsor).

Report #32

Table 32.3. Summary of Compounds Detected in Media from Human Liver Slice Incubations with ^{14}C-LY170053 at 3 Concentrations

Metabolites	Protonated Molecular Ion (m/z)	50 µM Incubation	250 µM Incubation	500 µM Incubation
N–desmethyl–LY170053 (LY170052)	299		√	√
2–hydroxymethyl–LY170053 (LY290411)	329	√	–	–
7–hydroxy LY170053	329	√	√	√
4'N–oxide LY170053 (LY170238)	329	√	√	√
?–hydroxylated LY170053	329	–	–	√
LY170053	313	√	√	√
10N–glucuronide of LY170053*	489	√	√	√
Quaternary glucuronide of LY170053	489	√	√	√
glucuronide of hydroxy–LY170053	505	–	–	√**
unknown	311	–	√	√
unknown	355	√	√	√

* = two N–glucuronides of LY170053 detected in each sample
** = not enough for CAD confirmation

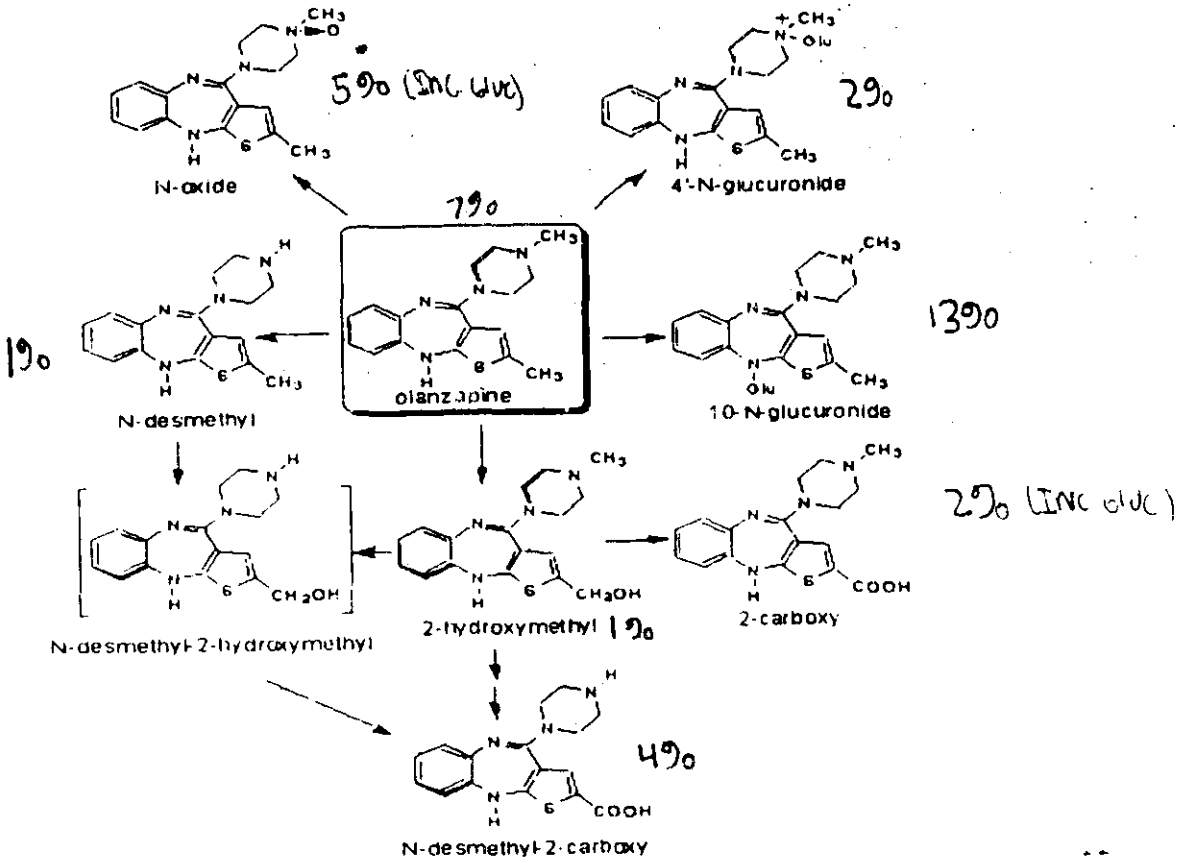


Figure 24 Proposed metabolic pathways of olanzapine in humans. The compound in brackets has not yet been identified. Glu stands for glucuronic acid.

- Analysis of olanzapine metabolites 2-CH2OH, N-oxide, and N-desmethyl following microsomal incubation/Report# 43/Lilly Labs, IN/Mar 1995.

Validated HPLC with radiochemical detection was used to detect olanzapine metabolites using microsomes (un-reported origin i.e. human or animal). The major metabolites detected were the 2-CH2OH, N-oxide, and N-desmethyl olanzapine.

EXCRETION

Mouse

- Mass balance studies in CD-1 mice following a single oral dose of ^{14}C-olanzapine at 15mg/kg/Report# 2 /Study# /Lilly Labs, Indiana/Jan 1995.

CD-1 mice (5/gr, 3 groups) were orally administered a single dose of ^{14}C-olanzapine at 15mg/kg and radioactivity was measured in feces and urine upto 120hr postdose. Major route of elimination in mice was feces with 64% of radioactivity eliminated over 120hr (mean of 3gr with 5mice/gr) most of which (73%) was eliminated within the 1st 24hr of dosing. Approximately 32% was eliminated in urine within 120hr and most of it (78%) excreted within the1st 24hr. Less than 1% of administered dose was found in the carcasse. Total recovery of radioactivty was 97%.

Rat

- PK, mass balance, and tissue distribution of ^{14}C-olanzapine in rats after 21d repeate oral dose/Report# 26/Hazleton Wisconsin, WI/July 1994/GLP.

Thirty six male Fischer 344 rats received 8mg/kg ^{14}C-olanzapine as a single daily dose for 21d, 4 rats were used for PK, 4 for mass balance, and 28 for tissue distribution/profile. Approximately 5-10min postdose, rats were stuporous, hypoactive, had rough hair coat, loose muscle tone, and the eyes had crust around them. Animals were normal by 6-7hr postdose. The bone marrow was creamy yellow-red in color rather than the usual bright red. For the PK study, blood was collected from the tail vein prior to dosing on day1 and upto 24hr and then every 24hr on days 2-20 and upto 168hr on day21. For the mass balance study, urine and feces were collected at 24hr intervals on days 1-20 and on day21 from 0-168hr postdose. For the distribution study, 4 rats/time point were killed at 24hr postdose on days 1, 7, and 14 and at 24, 72, 96, and 168hr after the last dose; blood and various tissues were collected and radioactivity analyzed by LSC.

PK: mean max conc on day1 from 0-24hr postdose was 1.34±0.106ug.Equiv/g reached at 2hr, AUC_{0-24} was 14±0.4ug.Equiv hr/g (AUC_{0-inf} 17±0.5ug.Equiv.hr/g: mean±s.d.), and plasma elimination half life was 9hr. The corresponding values after day21 were C_{max} 2±0.1ug.Equiv.hr/g reached at 2-6hr, $AUC_{2-168hr}$ 171±6ug.Equiv.hr/g (AUC_{2-inf}) 457±92ug.Equiv.hr/g), and plasma elimination half life was 34±3hr calculated from 2-24hr and 272±63hr calculated from 2-168hr. Steady state conc was reached around 408hr (d17) postdose with a mean of 1.3±0.03ug.Equiv/g.

Mass balance: most radioactivity was eliminated in feces (88% of dose) and some 30% in urine by 168hr after the last dose on d21. Carcass had 8% and CO_2 (breath) 0.4%, total clearance of radioactivity was 126% of dose. Most of radioactivity was eliminated in the 1st 24hr postdose: urine 25% and 66% feces with total of 118% of dose (include cage wash and wipe) days 21-28; cummulative radioactivity (0-168hr) in feces was 88% and in urine 30% of radioactive dose indicative of no sig accumulation Conc of radioactivity at 168hr days 21-28 in blood was 0.8ug.Equiv/g and 0.06ug.Equiv/g in plasma.

Tissue distribution: highest radioactive conc 24hr after day 1, 7, 14 was measured in the liver>thyroid>kidneys values ranged between 1.14-11ug.Equiv/g. On day 21 at 24, 72, 96, and 168hr postdose, highest conc was in the thyroid>kidneys>liver>spleen>adrenals, with moderately high radioactivity in testes, pituitary, and bone marrow (femoral). At 168hr on day 21 the conc of radioactivity in the thyroid remained reasonably high at 10ug.equiv/g, in kidneys 6.4, and 4ug.Equiv/g in liver, spleen 3.4ug.Equiv/g, and in the adrenals 1.84ug.Equiv/g; conc in all other tissues was <1.84ug.Equiv/g. Elimination half life in tissues calculated over 24-168hr postdose after day 21 ranged from 30hr (lg.intestine) to 242hr in thyroid. At 24hr after days 1, 7, 14, and 21, the total percent of administered radioactivity in carcass and tissues was 12, 2.5, 2, and 1.4% respectively. At 168hr post the last dose on day 21 only a total of 0.4% of administered dose was measured indicating no accumulation and almost complete clearance from the body.

- Billiary excretion of radioactivity following a single oral dose of ^{14}C-olanzapine to male Fischer rats/Report#11/Lilly Labs, IN/Mar 1995.

Bile-cannulated male Fischer 344 rats (n=4; 10wks old) were orally dosed either 8 or 16mg/kg of ^{14}C-olanzapine (Lot# V86-6ME-267; specific activity 26.2uCi/mg; radiopurity >99%) and cold olanzapine (lot# 552PP2F and Dista 58962). Bile was collected at 0-6, 6-12, 12-24, 24-36, and 36-48hr for the 16mg/kg dose and at 48-60 and 60-72hr for the 8mg/kg dose. Results showed large amount of administered radioactivity is eliminated in bile over 72hr (mean±s.d. 39±18% for LD and 32±20% for HD). Highest excretion of the drug into the bile and urine at 8mg/kg occurred within 24hr postdose (15±13% bile and 17±9% urine) and at 16mg/kg, maximum excretion into bile was within 6hr at 12±7% and for urine at 18±12% during 24-48hr. Total recovery ranged between 87-95% with a mean of 91±3.3% at 8mg/kg and a mean of 84±7% at 16mg/kg. Urinary elimination accounted for 35±14% of administered dose at 8mg/kg and 28±14% at 16mg/kg. Fecal excretion was small at 4.3±2% at 8mg/kg indicating that most of the radioactive dose was well absorbed and reached the feces via bile excretion. None of the HD rats defecated during the study, therefore, the GIT and contents were analyzed for radioactivity which was 3.5±0.9% (eliminating one rat value), and adding the carcass, radioactivity was 14%.

- Mass balance in Fischer rats following a single oral or i.v. dose of ^{14}C-olanzapine at 16mg/kg/Report# 10/Lilly Labs, IN/Jan 1995.

Male and female Fischer 344 rats (3/sex/route) were administered 16mg/kg ^{14}C-olanzapine by oral and i.v. routes (males only). Radioactivity in urine and feces was measured upto 120hr postdose. Following either route of administration, most of radioactivity was detected in feces and small amount in urine. After oral dose, total fecal excretion in males and females by 120hr was 66±2 and 61±7% respectively, and the corresponding urinary values were 24±2 and 29±3%. Most of the oral and i.v. urinary clearance occurred within 24hr and fecal elimination with 48hr or dosing in males and females (oral/urine: 20±2m and 17±5%f; for feces: 42±7m and 50±21%f (n=2 for the latter value), for the i.v.: urine: 18±1% and fecal: 46±11%). Total recovery of radioactivity after oral dose was 91% and for i.v. 89%. It was concluded that major route of elimination of olanzapine after a single oral or i.v. dose, is feces and no difference in elimination between males and females.

- PK, mass balance, and tissue distribution of ^{14}C-olanzapine in rats after a 21-d repeate oral dosing/Report# 26/Study# HWI 6180-117/Hazleton, Inc, WI/July 1994/GLP.
Lot# for radiolabel: V86-6ME-267; for cold cpd: 552PP2; purity of radiolabel >98.6%.

Male Fischer rats were administered 8mg/kg/d ^{14}C-olanzapine by gavage for 21d. Four rats each were used for PK (gr1), mass balance (gr2), and 28 rats for tissue distribution study (gr3). From gr1, blood was collected on day1 at 5min predose, and 2, 6, and 24hr postdose. Thereafter, blood was collected every 24hr on days 2 through 20 and on day21, samples were collected at 2, 6, 24, 48, 72, 96, and 168hr postdose. For the mass balance study, urine, feces, expired air, and volatile organics were collected at given times on days1-21 and upto 168hr after the last dose on day21. Four rats/time point were killed in gr3 at 24hr postdose on days 1, 7, and 14, and at 24, 72, 96, and 168hr postdose on day21. A number of tissues and matrices were collected for analyses by direct LSC or after combustion. Animals were fasted 16-18hr predosing the first dose. Clinical signs were: stupor observed 5-10min after each dose lasting 6-7hr, hypoactivity with loose muscle tone on day3, ungroomed rats, rough hair coat, and crust around eyes. Bone marrow from gr3 was creamy and yellow-red in color rather than the normal bright red color.

Results

PK:

PK parameters on day1 from 0-24hr postdose after a single dose were: mean max conc was 1.34±0.1 ugEquiv/g reached at 2hr (t_{max}), mean half life was 9±0.1hr, AUC_{0-24} 14±0.4 ugEquiv.hr/g and ranged between 13.9-14.7ugEquiv.hr/g, and AUC_{0-inf} ranged between 16.7-17.7 ugEquiv/g. Pk parameters on day21: mean max conc 2±0.08ugEquiv/g, t_{max} 2-6hr, half life 272±63hr, $AUC_{2-168hr}$ 171±6 ugEquiv.hr/g and ranged between 165-178 ugEquiv/g. Steady state conc of radioactivity seems to have been reached by 408hr postdose at a mean of 1.26ugEquiv/g. On day21, max conc of 2 ugEquiv/g was reached at 6hr postdose and by 168hr on day 21, conc of radioactivity was declined steadily to 0.72 ugEquiv/g.

Mass Balance:

within the 1st 24hr of dosing, 49±9% of radioactive dose was eliminated in feces, thereafter, a given amount was excreted every 24hr ranging between 59-73%. The mean radioactivity excreted by end of 20d was 66±7% of the dose. Percent of radioactive drug excreted in urine every 24hr ranged between 22±3 to 27±2% consequently, the daily radioactivity excreted in feces and urine ranged between 83-100%. Values for cage wash and wipe were 13-17% and 0.8-1% respectively. For expired CO2 the mean radioactivity eliminated was 0.3-0.5%, and that for the volatiles it was very small ranging from below detection to <0.01% of daily radioactive dose. For study day21 upto 168hr postdose, a total of 128% of the administered dose was measured in urine (30%), feces (88%), residual carcass (8%), expired CO2 (0.4%), and nondetectable in volatiles. Most of the radioactivity was eliminated in the 0-24hr interval on day21in urine, 25%, and feces 66%, from 48hr and on, radioactivity steadily declined reaching by 168hr on day21, 0.5% in feces and 0.2% in urine. Blood and plasma conc of radioactivity at 168hr postdose days 21-28 was 0.8% and 0.06% respectively, indicating that most of the radioactivity is bound to blood elements.

Tissue Distribution:

At 24hr after a single dose (day1), the highest radioactive conc (in ug equivalents of label per g tissue), excluding radioactivity taken up by the GI content and wash, was detected in the liver (3) followed by, in decr order: thyroid (1.7), kidneys (1), spleen (0.8), and testes (0.7). At 24hr postdose on days 7 and 14, radioactivity conc (ugEquiv/g), in decr order was measured in: liver (8&11), thyroid (6&9), kidneys (4&7), spleen (3&4), adrenals (1.6&2.3%), testes (1.5&2), bone marrow (1.3&2), and pituitary (1.3&1.8). At 24&72hr postdose on day21, conc of radioactivity in decr order was: thyroid (15&11), liver (12&8), kidneys (10&8), spleen (6&5), adrenals (3&2), bone marrow (2.6&2), lymph nodes (2&1.4), and pituitary (2.5&1.3). Tissues did not seem to reach steady state conc with time this

was evident by the relatively high radioactive conc remaining in tissues by 96 and 168hr postdose on day21 (ug Equivalents/g): the thyroid (12&10), kidneys (8&6) and liver (7&4), also conc was measured in spleen (5&3), adrenals (2&1.8), and bone marrow (1.7&1.4): conc was low or non detectable in some tissues such as the lens and retina. Elimination half lives calculated from 24-168hr after day21, were for blood 201hr and, plasma 52hr, the longest half life was in the thyroid at 242hr. Difference between blood and plasma indicated that radioactivity was taken up by blood elements (bound).

In summary, after oral dosing of 8mg/kg of radiolabeled olanzapine to rats for 21d, mean max conc in blood after 24hr postdose was 1.3ugEquiv/g with elimination half life of 9-9.2hr calculated from the 0-24hr interval. On day21, mean max conc of 2ugEquiv/g reached at 6hr postdose with $t_{1/2}$ of 31-38hr. Conc of radioactivity seemed to have reached steady state by 408hr postdose at 1.3ugEquiv/g. Each day, radioactivity eliminated in urine and feces accounted for: 83-100% and at 168hr post the last dose: only 0.4% of radioactivity was measured indicating no accumulation of the drug in tissues. Tissues with highest radioactive conc included the thyroid, liver, and kidneys. Steady state was not reached in tissues by day21 as indicated by the relatively high conc remaining in these tissues by 168hr post the last dose. Elimination half lives in tissues calculated from 24-168hr postdose on day21 ranged from 30 (in L.intestine) to 242hr (in thyroid).

Dog:

- Mass balance study in female dogs following oral administration of ^{14}C-olanzapine at 5mg/kg/Report# 17/Lilly Labs, IN/Oct 1993.
Lot# label/V866ME267; cold/552PP2.

Four female beagle dogs were administered a single oral gavage dose of 5mg/kg ^{14}C-olanzapine. Blood, urine, and feces were collected for radioactivity analysis. Blood was collected at 0, 0.5, 1, 3, 6, 12, 24, 48, 96, and 168hr postdose, plasma was prepared and radioactivity counted (Report# 18). Urine and feces were collected every 24hr upto 168hr postdose; dogs were fasted overnight prior to collection of any fluids. Radioactivity was eliminated in urine and feces with slightly less amount in urine (total at 168hr 38±2.6% of administered dose) than the amount excreted in feces (total at 168hr 46±5% of administered dose). Most of the urinary radioactivity was eliminated by the 1st 24hr (55%) whereas, the majority of radioactivity excreted in feces occurred during the 1st 48hr postdose (50%). Urinary metabolites were studied further; see Report# 30. Mean total recovery of radioactivity by 168hr was about 84±5% of administered dose. Radioactivity in feces remained detectable in the 4 dogs upto 4wks postdose. The sponsor monitored this radioactivity until it reached background however, this duration of time was not reported. After decline of radioactivity to normal background levels animals were returned to their colony and used for other studies.

Monkey

Mass balance and PK in male and female Rhesus monkeys given a single oral (nasogastric) dose of ^{14}C-olanzapine at 5mg/kg/Report# 28/Tox study# P00694/Lilly Labs, IN/July 1994.
Lot#s V86-6ME-267 (labeled); 522PP22F (unlabeled).

Rhesus monkeys (2/sex) were administered 5mg/kg of ^{14}C-olanzapine by nasogastric route. Urine and feces were collected over 168hr and PK of whole blood and plasma were also measured at specific times. Blood was sampled from each animal at 0.5, 1, 4, 8, 12, 24, 48, 96, 120, and 168hr postdose. Urine and feces were collected every 24hr period. The major route of excretion was urine with a total of 55% of radioactive dose measured in urine and 29% measured in feces. Most of the urinary excretion occurred by 24hr (48%) compared with feces at 48hr (14%). Total recovery was 83% of radioactive dose administered.

The table below presents PK parameters:

Plasma olanzapine	C_{max}	range 34-74ng/ml (mean±s.d. 60±18ng/ml)
	T_{max}	1hr
	$T_{1/2}$	range 2.3-4.9hr (3.4±1.2hr)
	AUC	range 349-814ng.hr/ml (mean±s.d. 537±208ng.hr/ml)
^{14}C-whole Blood	C_{max}	range 637-923ngEq/ml (mean±s.d. 753±130ngEq/ml)
	T_{max}	1hr
	$t_{1/2}$	range 3.8-7hr (mean±s.d. 5.3±1.3hr)
		Range 54-65hr (mean±s.d. 59±4.7hr)
	AUC_{0-t}	range 9865-15415ngEq.hr/ml (mean±s.d. 11547±2601ngEq.hr/ml)
	AUC_{0-inf}	range 10564-16784ngEq.hr/ml (mean±s.d 12558±2856ngEq/ml)
^{14}C-Plasma	C_{max}	range 621-930ngEq/ml (mean±s.d. 757±130ngEq/ml)
	T_{max}	range 0.5-4hr (mean±s.d. 1.5±1.7hr)
	$t_{1/2}$	range 4.4-6hr (mean±s.d. 5.3±0.7hr)
		range 75-135hr (mean±s.d. 99±27hr)
	AUC_{0-t}	range 13186-16682ngEq.hr/ml (mean±s.d. 14429±1572ngEq.hr/ml)
	AUC_{0-inf}	range 16722-19830ngEq.hr/ml (mean±s.d 18299±1395ngEq/ml)

There was no difference between sexes regarding route or degree of excretion. Most of total radioactivity was eliminated by 72hr of dosing (urine 98% and feces 93%). Plasma conc of olanzapine was below quantitation limit of 1ng/ml by 24hr of dosing in all monkeys. However, in 2/4 monkeys plasma conc was still detectable at 48 and 96hr postdose. Half life of olanzapine elimination was 3.4hr. Clearance of radioactivity from whole blood and plasma was biphasic with mean half lives of 5 and 59hr respectively.

In summary, the major route of elimination in monkey is urine which is similar to human elimination but in contrast to that in the mouse, rat, and dog where drug is eliminated mainly via feces. Mean plasma C_{max} of olanzapine was 8% of total radioactivity which is less than that found in the rat (40%) and dog (18%). Similar trend was found for AUC values between these 3 species where AUC accounted for 4% of the total plasma AUC in monkey and 27&14% in rats and dogs respectively (reports 14&18). Mean elimination half life in plasma was approximately 4hr similar to that in the rat (3hr) and dog (6-8hr) but dissimilar to humans (27hr). Elimination of total radioactivity from whole blood and plasma was biphasic with alpha phase mean value of 5.3hr and beta phase value of 59 and 99hr respectively (note however, that the s.d. for the latter value (27hr) was large, indicative of high variability). Terminal half lives in the rat and dog are 30 and 24hr respectively.

ENZYME INDUCTION-INHIBITION STUDIES:

- In vitro interaction of olanzapine with human cytochromes P450 CYP2C9, CYP2C19, CYP2D6, and CYP3A/Report#38/Lilly Labs, IN/Jan 1995.

The ability of olanzapine to inhibit the metabolism of marker catalytic activity of four P450 subfamily enzymes, was studied. Olanzapine inhibitory effect was compared in vitro to that of clozapine (a marketed antipsychotic), and other known specific enzyme inhibitors. In all cases, data were modeled using standard enzyme inhibition relationship. Three human liver samples were obtained from liver transplant unit at the Medical College in Wisconsin and a 4th sample obtained from Medical College of Virginia.

Microsomal fractions were prepared and the following inhibitors were tested:

Inhibitors	Enz Specificity	
ketoconazole	CYP3A	non-competitive inhibition
quinidine	CYP2D6	Competitive inhibition
phenytoin	CYP2C9	Competitive
omeprazole	CYP2C19	Competitive

Olanzapine was tested at various conc depending on the assay system. The results showed olanzapine to produce in all cases examined, K_i that was larger/higher than those seen with clozapine. This indicated that at equimolar plasma conc, co-administration of olanzapine with substrates for each of these enzymes results in less inhibition than that expected from co-administration of clozapine with these substrates.

		K_i (uM)
CYP3A:	olanzap/non-competitive	491±33
	clozap/non-competitive	99±7
	ketocon/non-competitive	0.11±0.01
CYP2D6:	olanzap/competitive	89±5
	colzap/competitive	19±2
	quinid/competitive	0.03±0
CYP2C9	olanzap/non-competitive	715±73
	clozap/competitive	31±2
	phenytoin/competitive	17±1
CYP2C19	olanzap/non-competitive	920±65
	clozap/competitive	69±3
	omepraz/competitive	4±0.4

The sponsor also modeled the results using olanzapine conc 100x higher than the anticipated therapeutic level (0.2uM). In all cases modeled, olanzapine percent inhibition of these P450 enz was <0.3% indicating very little in vivo inhibition of metabolism of substrates co-administered with olanzapine which are metabolized by these P450 enzymes.

- Identification of human enzymes responsible for the formation of major in vitro oxidative metabolites of olanzapine/Report# 39/Lilly Labs, IN/Aug 94 - Jan 95.

Olanzapine was incubated with human liver microsomes to determine oxidative metabolism. Formation of 2-OHCH3-olanz, N-O olanz, and N-desmethyl (NdM) olanz was assessed in 2 human liver microsomal samples and formation of 7-OH olanz was assessed in 1 human liver sample. The identification of the enzyme subfamilies responsible for metabolism of olanzapine was then conducted. Metabolites were analyzed by HPLC; conc of olanzapine tested to determine the formation of these 3 metabolites were 1,2,4,6,8,10,12,15,20,40,75,100,150,200 and 300uM. Slightly different conc (5-300uM) were used to estimate kinetics (Km, Vmax, intrinsic Cl(CLint)). The results were as follows:

- formation of 2-OHCH3 and NdM was biphasic indicating the involvement of at least 2 enz. The model estimated that the high affinity enz was responsible for 72&91% of 2-OHCH3 and 92&98% of NdM olanzapine formation in the 2 human samples tested when olanzapine conc

was 0.2uM (therapeutic conc). The rate of formation of N-O olanzapine was linear over the conc range tested, indicating one enz responsible for formation of this metabolite and not saturated by olanzapine conc upto 300uM; this enzyme was the FMO3 (flavin-containing monooxygenase). Similarly, for the 7-OH metabolite, a single enz was suggested but there was no authentic standard making the absolute rate of formation of 7-OH uncertain. The intrinsic CL was as follows for:

2-OHCH3	0.2ul/min/mg in both samples
NdM	1ul/min/mg in both samples
N-O	1.7&0.32ul/min/mg in the 2 samples respectively,
7-OH	could not be measured/see above.

The apparent K_m and V_{max} values were as follows for the 2 human liver samples:

	K_m (uM)	V_{max} (pmol/min/mg)
2-OHCH3	50±18 & 75±7	8±3 & 16±1
NdM	42±7 & 34±2	41±5 & 34±1
N-O	could not be calculated	

- Identification of the enz responsible for formation of these 4 metabolites was done by correlating the formation of a metabolite with the immunoquantified levels of specific enzymes and forming selective catalytic activities for these enzymes using a bank of 14 human microsomal liver preparations. The results identified the following enzymes responsible for the formation of: **2-OHCH3 is CYP2D6, for N-O is FMO3, and for NdM&7-OH is the CYP1A2.**

The CYP1A2 is an enzy that catalyzes the metabolism of many substrates. Therefore, its involvement in olanzapine metabolism is subject to drug-drug interactions with CYP1A2 substrates, inhibitors, and/or inducers. This interaction was evident in case of the related drug clozapine where its metabolism was inhibited in vivo when cpds metabolized by CYP1A2 were used concomitantly with clozapine (Jerling et al., 1994; Bertilsson et al., 1994). However, because olanzapine has mutiple pathways of metabolism (N-glucuronidation, FMO3), inhibition of one route may affect little the overall clearance of olanzapine.

- Hepatic microsomal enzyme induction for a chronic tox study in beagle dogs given daily oral doses of olanzapine for 1yr followed by 1mo reversibility phase/Report# 48/Tox study# D02093/Lilly Labs, IN/Feb 1995.

Microsomes were prepared from liver samples obtained from all dogs necropsied at termination of a 1-yr tox study and in all dogs necropsied after 1-mo reversibility/recovery period. These dogs were orally dosed olanzapine at 2, 5, 10mg/kg (4/sex/dose). The following cpds were used to identify the P450 subfamily enzy: 7-ethoxyresorufin O-deethylase (EROD) for CYP1A, benzphetamine N-demethylase (BND) for CYP2B, and erythromycin N-demethylase (END) for CYP3A. P450 content was also determined. The results at end of 1yr showed a non-sig 1.7x incr in CYP1A activity in MDm over the cont as indicated by the incr in EROD (4.2±1 vs. 2.5±0.3nmol/hr/mg in the cont). In females at end of 1yr, a non-sig incr in CYP2B activity was noted in LD&MDf (1.4x the cont) but a non-sig decr was recorded in CYP3A of HDf (41%; 92±12 vs. 156±18nmol/hr/mg cont/mean±s.e.). The only change at end of recovery phase was a sig ($p<0.05$) incr in CYP1A activity in HDf relative to the cont (1.5x higher or 46% incr over the cont); no change in males. In summary, olanzapine dosed orally to dogs for 1yr does not seem to affect enzyme activity or P450 content when liver microsomes analyzed at end of 1yr and end of 1mo recovery period. The above changes noted were not statistically sig and the sig incr in CYP1A noted in HDf did not occur at end of the 1yr but rather at end of recovery, and this change was not seen in males.

- Effect of olanzapine on hepatic GSH content in male rats/Report# 1/Study# R11183 and R01184/Lilly Labs, IN/Nov 1984/GLP.

Olanzapine caused a small decr in GSH in male rats dosed for 2 wk (#R02883) and in preliminary studies with isolated hepatocytes from normal rats, olanzapine at 10^{-4}M (30ug/ml) caused sig decr in GSH. Flumezapine, an analog of olanzapine (no 7-fluorine), caused a dose-dependent decr in GSH similar to that observed with olanzapine. In this study olanzapine potential to deplete GSH stores was tested in vivo after a single oral dose to male Fischer rats and flumezapine was used as a reference cpd. Animals were dosed 5 or 25mg/kg and killed at 1, 2, 4, or 24hr later for measurement of GSH. Neither cpd depleted GSH content at any time point. Olanzapine at the HD caused a small but sig incr at 4hr postdose. The drugs were absorbed as noted by the sedation observed after dosing. The lack of effect (depletion of GSH) of either cpd was explained by the sponsor as follows: conc reached in vivo were not sufficient to decr GSH and/or these 2 cpds or their metabolites did not interact with GSH in the rat liver. it was concluded that olanzapine dosed at 5 or 25mg/kg to rats did not decr hepatic GSH content.

Summary of ADME Studies

[The following summary includes data from previous reviews written by Drs. Hollenbeck, DeGeorge, and Freed as well as those in the present review by Dr. Atrakchi].

The pharmacokinetics of olanzapine was studied in CD-1 mice, Fisher 344 rats, Beagle dogs, and Rhesus monkeys after single and repeate administration by the oral and parenteral routes. A validated HPLC method with dl of 1ng/ml was used to quantitate plasma conc. Metabolites of olanzapine have been detected in plasma, urine, and bile using LC/MS-MS methods.

Absorption and Distribution:
Olanzapine was well absorbed following single oral doses to mice, rats, dogs, and monkeys. In the rat, absorption was greatest from the small intestine and colon. The absolute oral bioavailability of olanzapine was determined in the rat at 47% in contrast to absorption of radioactivity of 79%. These findings indicate good absorption and significant first pass effect/metabolism. Peak plasma concentrations were reached between 0.5hr in the mouse to 3hr in the dog (T_{max} in humans is 5hr) indicating rapid absorption. Plasma concentrations of olanzapine were much lower than total plasma radiocarbon in all species examined which indicated extensive metabolism. Concentrations of olanzapine were approximately 10x higher in portal than that in systemic circulation which reflected extensive 1st pass effect. Mean plasma $t_{1/2}$ ranged between 3hr in rodents and monkeys to 9hr in dogs; plasma elimination half life in humans was 27hr. Terminal plasma elimination $t_{1/2}$ of total radioactivity was 11hr in mice, 30hr in rats, 28hr in dogs, and 98hr in monkeys; the corresponding value in humans was 59hr.

To set exposure limits for safe-handling of olanzapine in the work place, rats were exposed via inhalation to single and multiple doses of olanzapine. Single dose inhalation studies showed linear kinetics between plasma levels and increasing exposure concentration to olanzapine aerosol that ranged between 6-250ug/L. In multiple dose studies, rats were exposed for 4hrs/d for 12days to 1.2, 6, and 30mg/m^3 olanzapine. Drug did not accumulate in plasma when measured on day10 under these experimental conditions. Mean plasma levels of olanzapine measured 15-20min postdose were 3, 40, and 253ng/ml for 1.2, 6, and 30mg/m^3 doses respectively. [see attached table from the sponsor for PK parameters in different species].

In multiple dose studies, there was no gender differences in plasma drug levels. Plasma levels increased with increasing dose and there seemed to be no drug accumulation. The incr in conc was generally linear at low doses and tended to be non-linear with incr in dose and duration. In 2wk oral tox study in rats, olanzapine was administered at 1, 2.5, and 4mg/kg. Plasma data best fit a single compartment model, exposure increased in more-than dose-proportionate manner on both days 1 and 15. Systemic exposure also increased with prolonged duration of dosing specially at the HD. Similar finding to those in the 2wk rat study were recorded in a 2wk study in mice dosed at 2, 5, 15, and 30mg/kg.

Olanzapine widely distributed to various tissues following administration. Maximum radioactivity in rats after a single oral dose was detected in the following tissues/organs: the Harderian gland>liver>lungs>kidneys>jejunum. Maximum radioactivity was reached between 2-6hr postdose. Moderate to high radioactivity was also detected in adrenals, bone marrow, duodenum, ileum, pituitary, spleen, and thyroid. Lowest levels were in the plasma/blood, eye, cerebellum, medulla, spinal cord, muscle, and white fat. In terms of percent of radioactive dose, the liver accounted for the highest value of 11% of total recovered radioactivity measured at 2hr postdose. Radioactivity was detected in the brain 2-6hr postdose and levels at both time points were higher than those in the blood. In a 21d tissue distribution study, the urinary profile of metabolites was not altered over the duration of the study.

Olanzapine was detected in milk and plasma samples obtained from lactating rats administered radioactive drug at 5mg/kg as a single oral dose. In another study, olanzapine was administered to pregnant rats on gd12 at 18mg/kg oral dose. Radioactivity was detected in all tissues by 1hr of dosing with max levels reached between 1-3hr. Highest activity was in maternal tissues: adrenals, bone marrow, GI, Harderian gland, kidney, liver, mammary glands, ovary, pancreas, salivary glands, spleen, urinary bladder, placenta, and yolk sac. By 24hr postdose, radioactivity was still detectable in all except maternal blood, fetal tissue, pancreas, and placenta. These studies clearly indicate placental transfer of the drug into the fetus.

Metabolism:

Olanzapine in all species tested (mouse, rat, dog, and monkey) was extensively metabolized as indicated by the higher plasma conc of total radioactivty over the parent drug. However, olanzapine was most extensively metabolized in the monkey and least metabolized in the rat. The degree of metabolism in mice, dogs, and humans lies between that of the monkey and the rat. In no one species the metabolic profile was similar to that of the humans i.e. direct glucuronidation to form the 10-N-glucuronide. This metabolite was found in trace amounts in dog urine. In vitro studies from liver slices and microsomes from human donors, the P450 enzyme subfamilies responsible for olanzapine metabolism were CYP2D6 (to form 2-OHCH3), CYP1A2 (to form N-desmethyl and 7-OH), and Flavin-containing monooxygenase (to form the N-oxide). Studies with liver microsomes from mice showed no effect in mice treated for 3mo on any enz activity tested. In rats treated for 6mo with 1mo recovery, generally the changes in enz activity were slight. There was a sig incr in CYP1A in male rats dosed 4 and 16mg/kg, also, total P450 content was reduced in males and females. In dogs treated at 2, 5, and 10mg/kg/d for 1yr, small and statistically insignificant increases in enzyme activities were observed in CYP1A (1.7x over the cont), CYP2B (1x cont), CYP3A (1.7x cont). The only sig incr noted at end of 4wk recovery period was in female dogs dosed 10mg/kg in CYP1A at 1.5x cont. There was no drug effect on P450 content. It can be concluded that the overall effect of olanzapine on enzyme activity is slight in animals tested for long periods upto 1yr. Because of the multiple metabolic pathways, olanzapine is not expected to interact or affect the metabolism of other drugs specially those that are metabolized by CYP1A2. Olanzapine had no effect on GSH content when tested in rats at 5 and 25mg/kg

Urine:
mice, the major urinary metabolites are the **7-OH glucuronide**, 2-OHCH3-, and 2-carboxy olanzapine accounting for 13, 5, and 2% respectively of 20mg/kd administered dose. Therefore, the main urinary metabolic pathways in the mouse are: **aromatic hydroxylation, 2-alkyl oxidation, and N-demethylation**. The major metabolites accounted for 70% of the urinary activity.
rats, the main urinary metabolite was the 2-OHCH3 olanzapine followed by N-desmethyl-hydroxy-olanzapine-glucuronide (tentative). In bile, a GSH adduct was identified (N-acetylcysteine adduct; tentative). Urinary radioprofiles after single or repeate dose seem to be relatively constant. The **metabolic pathways in rats in decr quantitative order are: thiol conjugation, 2-alkyl hydroxylation, aromatic ring hydroxylation, demethylation, and N-oxidation.**
dogs, the major urinary metabolite is 7-OH-N-oxide olanzapine (8% of administered dose) and the main metabolic pathways include: **aromatic hydroxylation, N-oxidation, and 2-alkyl oxidation.** Also in urine, cysteine adducts were tentatively identified and accounted for 1-2% of dose. Therefore, detection of these putative cysteine cpd suggests formation of GSH conjugates. The major metabolites including unchanged olanzapine accounted for 60% of urinary activity.
monkeys, the main urinary metabolite was N-desmethyl-2-carboxy-olanzapine accounted for 17% of dose or 36% of urinary activity. The **main urinary metabolic pathway in monkeys involved double oxidation reactions of the allyl carbon and the N-CH3 of the piperazine ring; there was no oxidation of the methyl thiophene ring seen in the other species.**

Plasma:
In addition to unchanged olanzapine, some of the urinary metabolites were also present in plasma of mice, rats, and dogs including the GSH conjugates detected in rat bile.

The metabolic profile of olanzapine in animals included aromatic hydroxylation, alkyl oxidation, N-dealkylation, N-oxidation, in addition to conjugation with glucuronide and GSH. Only in the dog, both aromatic and N-oxidation reactions were found (7-OH-N-oxide). The monkey differed from the rat, mouse, and dog, in that oxidation of the benzene ring was absent. The metabolism of olanzapine differs between humans and animals in 2 ways:

1. Direct glucuronidation is absent in animals (except for a trace amounts detected in dog urine); its the main pathway in humans forming the 10-N-glucuronide.

2. Absence of aromatic oxidation in any of the human biological fluids, however, much of this pathway was found in animals.

The monkey does not form the 10-N-glucuronide but seemed to have a similar oxidative metabolism as humans.

Bile:
Seven metabolites were identified in rat bile after oral administration of 8mg/kg of labelled olanzapine. The 7 metabolites and olanzapine represented 75% of radioactivity in bile and 39% of administered dose. The major metabolite was glutathione adduct of olanzapine that accounted for 34% of biliary radioactivity and N-acetylcysteine adduct at 17%; unchanged olanzapine accounted for 2% of biliary radioactivity.

Excretion:

Major route of elimination of olanzapine in rodents and dogs is by feces. Rats dosed a single i.v. of labelled olanzapine showed the same pattern of elimination as that after oral dosing. Monkeys similar to humans, mainly excrete olanzapine by urine. In rats as indicated above, most of fecal elimination came via the bile and enterohepatic recirculation.

Table 1 Selected Mean Plasma Pharmacokinetic Parameters Associated with an Oral Dose of ^{14}C–LY170053 to Animals and Humans

Parameter	Mouse	Rat	Dog	Monkey	Human
Dose (mg/kg, po)	15	8	5	5	0.17 - 0.18
Dose Form	Aq. Gavage	Aq. Gavage	Aq. Gavage	Aq. Gavage	Capsule
Gender	Male	Male	Female	Male	Male
Cmax (ng or ng eq./ml)					
LY170053	421	609	172	71.5	11
^{14}C	2,260	1,530	949	747.3	39
(LY170053 as % of total ^{14}C)	(19%)	(40%)	(18%)	(10%)	(28%)
Tmax (hr)					
LY170053	0.5	1	3.3	1	4.9
^{14}C	4	1	1	2.3	4.9
t-1/2 (hr)					
LY170053	3.2 (7–12)	3 (1–24)†	9.24 (3–48)	3.2 (1–12)	27
^{14}C	10.6 (7–48)	30 (24–72)	27.58 (24–96)	5.2 (4–12)	59
(range [hrs] in parentheses)				79.7 (48–168)	
AUC (0–t; ng x hr/ml)					
LY170053	1,522	2,352	1,923	581.7	269
14C	15,201	8,715	13,405	15,490	1,961
(LY170053 as % of total ^{14}C)	(10%)	(27%)	(14%)	(4%)	(14%)

* study number F1D–LC–HGAI **(Found in ITEM 6 Vol. 1.103 / Pg. 328)**

† numbers in parentheses are time-points used for calculating the t-1/2

Table 55.1 Metabolites of Olanzapine in Urine and Plasma of Several Species

Compound	MOUSE		RAT		DOG		MONKEY	HUMAN	
	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine	Urine	Plasma
Olanzapine	√	√	√	√	√	√	–	√	√
2-CH_2OH	√	√	√[a]	√	√	√	√	√	√
2-CH_2OH-gluc	–	–	–	–	–	–	√	–	–
2-COOH	√	–	√	–	√	–	√	√	–
2-COOH-gluc[b]	–	–	–	–	–	–	–	√	–
N-oxide	–	–	√	√	√	√	–	√	√
N-desmethyl	√	√	√	√	√	√	–	√	√
2-CH_2OH, N-desmethyl	√	–	–	–	–	–	√	–	–
2-COOH, N-desmethyl	–	–	–	–	–	–	√[a]	√	–
2-CH_2OH, N-oxide	–	–	–	–	–	–	√	–	–
2-COOH, N-oxide	–	–	–	–	–	–	√	–	–
10-N-gluc	–	–	–	–	√	–	–	√[a]	√
4′-N-gluc	–	–	–	–	–	–	–	√	–
7-OH	√	–	–	√	√	√	–	–	–
7-OH-gluc	√[a]	–	√	–	√	–	–	–	–
7-OH-N-des-methyl-gluc	–	–	√	–	–	–	–	–	–
7-OH-N-oxide	–	–	–	–	√[a]	–	–	–	–
GSH conj[c]	–	√	–	–	–	–	–	–	–
NAC conj[d]	–	–	–	–	–	–	√	–	–
Cysteine conj	–	–	–	–	√	–	–	–	–
N-oxide-CYS[e]	–	–	–	–	√	–	–	–	–

[a] major metabolite; [b] gluc, glucuronic acid; [c] glutathione conjugate also detected in rat bile; [d] N-acetylcysteine conjugate; [e] cysteine conjugate of N-oxide

Acute Toxicity
These studies were reviewed by Dr. Hollenbeck for more detail see Original Review dated Aug 20 1986 IND#

Species	Route	LD_{50} (mg/kg) M	F
Mouse	p.o.	211	208
Rat	p.o.	174	177
	i.p.	112	107
Dog	p.o	>100	>100
Rhesus Monkey	p.o.	>100	>100

Clinical signs noted in all of these species included hypoactivity, lethargy, coma, poor grooming, ptosis, tremors, ataxia, and clonic convulsions.

Subchronic Toxicity
Some of the following subchronic studies were reviewed previously in IND# 28,705 (the name of the reviewer is stated for each study):

Mouse:
1. 3-month tox and blood level study in B6C3F1 mice treated orally with olanzapine/report# 28/studies# M00487&M00587/Oct 1989/Reviewed by Dr. DeGeorge.
2. 3-month oral toxicity study in CD-1 mice/report# 32/study# M01090/Aug 1991/Reviewed by Dr. Atrakchi.

1. 3-month tox and blood level study in B6C3F1 mice treated orally with olanzapine/report# 28/Reviewed by Dr. DeGeorge.

Doses/No. Animals per dose: **5, 15, 45mg/kg/d**; for main study: 15/sex/dose; for PK study: 96/sex/dose treated for 1month and killed on day2 and wks 6&12.
Route: oral gavage.
Parameters studied: survival, clinical signs, B.wt, food intake, ophthalmology, hematology, clinical chemistry, urinalysis, organ wt, gross and histopath.

Results and Conclusions:
Survival: marked unscheduled deaths occurred in HD mice mainly in females. The sponsor stated that most of the deaths in the HD involved mice in th PK study. Survival rates were given only through the 2nd wk of study: males 98, 95, and 66% and in females 92, 86, and 31%. In the main study survival was ≤80% in HD for both sexes. The sponsor suggested that the incr mortality in the PK study was related to smaller mice (lower initial B.wt) which made them more sensitive to the drug. This high mortality in the PK study led to terminating the study early without an assessment of the cause of death. Note that in the main study, 4/6 deaths in the HD were not accidental.
Clinical Signs: no data provided. The sponsor reported no signs in LD, mice in MD were hypoactive for upto 20hr postdose and in HD, mice were catatonic for several hrs.
B.wt: mean terminal wt was reduced 3, 12, and 15% in m and not affected in f. Note that mean wt of cont was 7-8% higher than the drug grs. therefore, the decr in wt was <10%.
Hematology: **sig decr in WBC count with males being more sensitive than females.** The decr in males was **dose-dependent at 36, 65, and 70% with decr in lymphocytes and neutrophils.** Not only mean but also individual data at all dose grs, were lower than the normal range. In LDf, the decr

was small at <12% but in **HDf the WBC count was 53% less** than the cont. In contrast to the males, females showed a 2x incr in neutrophils.
Clinical Chemistry: BUN in HDm&f was 2x higher than the cont, ALT incr sig in HD (males 40% and 3x in females), and ALP was sig incr in MD&HDm (upto 36% of cont).
TK: samples were pooled from 4mice/sex/time point upto 2hr. Peak plasma levels reached **0.5-1hr** (T_{max}) postdose indicating rapid absorption. PK followed 2 compartment model with rapid phase shortly after peak level and a half life of <1hr, and a **slow elimination with half life ≥12hr**. Conc incr with dose with slight nonlinearity. Mean levels were as follows:

Day2

Dose	mean conc (ng/ml)	
	0.5hr	2hr
5	144m/95f	35m/52f
15	173m/172f	80m/174f
45	132m/861f	431m/517f

Day92 conc was not detectable at 5mg/kg. The 1hr conc for the 15 and 45mg/kg doses were (ng/ml): 175m/280f and 290m/324f respectively.
Organ wt and Gross Exam: no sig drug related finding.
Histopath: lymphoid depletion of spleen and thymus in MD&HDf. No other findings.

It was concluded that oral administration of olanzapine to mice at 45mg/kg caused death and at 5 and 15mg/kg sedation and hypoactivity were observed. Drug related effects included in males **dose-dependent decr in WBC count due to decr in lymphocytes**. Males were more sensitive than females, the decr in WBC was seen mainly in HDf. **Lymphoid depletion was seen in MD&HDf**. The drug seemed to be well absorbed as peak plasma levels reached by 0.5-1hr of dosing. Mean peak plasma levels ranged between 132 to 431ng/ml. The **NOEL is <5mg/kg due to hematology finding in males.**

2. 3-month toxicity study by oral gavage/study# M01090/Tox report# 32/Lilly Res. Labs-IN/1991/GLP/Reviewed by Dr. Atrakchi.

Lot#	58962/purity 100.2%
Species/wt/Age:	CD-1 mouse/initial mean wt±s.d. 24.7±1.8g males and 20.4±1.3g females/ 5-6wk initial age.
Dose/duration:	**3, 10, 30mg/kg/day** for 3months by oral gavage; control gr administered the vehicle 10% w/v aqueous acacia solution. Few drops of simethicone emulsion were added to drug and control suspensions to decrease foaming.
No./sex/dose:	10/sex/dose.

Parameters measured: clinical signs and survival (daily), B.wt (weekly), hematology (at 2mo; (5/sex/dose) and, end of study (surviving rats); orbital sinus puncture; mice were non-fasting at 2months and fasting at end of study), clinical chemistry (end of study; fasted mice), enzyme induction (by measuring the activity of hepatic p-nitroanisole O-demethylase (end of study 5/sex/dose), organ wt (kidneys, liver, heart, spleen, uterus, and testes), gross exam and histopath (all grs). Statistics by Dunnett and Bartlett tests.

Results:

Survival: 100% in MD&HDf and LD&MDm, only 70% in LDf (7/10) and 80% in HDm* (8/10); also 1 each m and f of control mice died. Deaths were accidental and occurred early in the study.

* one of these males was killed moribund and its the one with histopath findings in the spleen (see histopath section).

Clinical Signs: **hypoactivity** and sternal recumbancy noted in all drug grs during 1st wk of study, and remained in the two high doses till end of study. Other signs mainly noted in males included rough hair coat and soiled genital area.

B.wt: no change in mean wt or wt gain in males but a significant increase in mean wt at end of study and wt gain of all female drug grs (non-dose dependent)(table below from sponsor).

Dose (mg/kg/day)	Mean Weight at Start (g)	Number of Survivors	Mean Weight at Termination (g)	Mean Weight Gain (g)
		MALES		
0	24.6	9	35.4	10.8
3	24.4	10	35.0	10.6
10	25.5	10	35.3	9.7
30	24.4	8	34.0	9.7
		FEMALES		
0	20.4	9	28.1	7.6
3	20.4	7	32.1**	11.6**
10	20.4	10	30.1*	9.7*
30	20.2	10	30.0*	9.8*

*Significantly different from control, p≤.05, Dunnett's two-tailed "t".
**Significantly different from control, p≤.01, Dunnett's two-tailed "t".

Hematology: **after 2months**, the only effect was a **significant decrease in RBCs** (8.5%), **Hb** (6.5%), and **PCV** (6%) noted in **HDf** relative to the control values; this was not found in males and the values for Hb and PCV were comparable to those of the control at termination. The **WBC count was moderately reduced** in **HDm** after 2months (non significantly, 47% of control). **At termination, HDf** had a **significant decrease** (9%) in **RBC** relative to the control. The **WBC count was dose-dependently reduced in MD&HDm** expressed as reduced leukocytes (59&72%), lymphocytes (52&68%), and neutrophils (also noted in LD; 48, 71, and 80% in LD, MD, and HD respectively). In females at termination, the data were inconsistent since a significant increase in leukocytes was noted at MD but a significant decrease at HD, lymphocytes however, were significantly reduced in HDf relative to the control. Also, noted was a significant reduction in the # of monocytes in MD&HDm at termination.

Clinical Chemistry: non-dose dependent and scattered findings were observed. In HDm, there was a significant **increase in BUN** (58±21 vs. 27.6±8.8 control; $p<0.05$) and an increase in **total protein** levels, perhaps due to increase in Alb. BUN was also increased significantly in HDf (35.7±13.8 vs. 19.4±5.5 in control, $p<0.05$) and the **AST** level was significantly elevated in HDf (160±74 vs. 93±22.5 in control); $p<0.05$). No other findings were observed. There was a great deal of interanimal variation in clinical chemistry parameters.

Hepatic Enzyme Activity: no increase was measured in p-nitroanisole O-demethylase mean activity of any drug gr. indicating that LY 170053 did not induce enzymes in mice at doses upto 30mg/kg.

Organ wts. There was a high variability in the absolute and relative wt of the spleen in all male grs including the control. In females, some of the changes noted were related to the increase in mean wt of mice in drug grs; a significant increase was measured in the absolute liver wt of LD&MDf but not in HDf.

Gross Morphology: there were no drug-related gross findings in any gr. Esophageal rupture was observed which was considered secondary to gavage accidents that contributed to the deaths. Histopathology: main finding included **lymphoid depletion of the spleen** in all drug grs with severity ranging between marked (2/10LDf), moderate (3/10 each HDm&HDf), minimal (2/10LDm, 1/10LDf, 2/10 each MDm&MDf), slight (3/10 each control m&f, 2/10LDm, 3/10LDf, 3/10MDm, 4/10MDf, 6/10HDm, 7/10HDf) ; slight hemosiderosis noted in all grs including the controls. Also in the spleen, minimal to moderate **multifocal lymphoid necrosis** noted in HD mice (1-3 of 10 mice). **Mammary gland** moderate acinar hypertrophy in MDf (3/10) and HDf (5/10), moderate **ductal ectasia** MDf (1/10), HDf (4/10), cont. f (2/10), and slight **ductal epithelial hypertrophy** in MDf (6/10), HDf (6/10), and cont. f (3/10) (LDf had it in 1/10 mice).

Summary and Conclusions:
Oral administration of LY 170053 to male and female mice at 3, 10, or 30mg/kg for 3 months produced CNS clinical signs such as sedation and hypoactivity during 1st wk of study in all drug grs. These signs disappeared in LD but remained in MD&HD mice till end of study. Hematology findings noted after 2months and end of study included **significant decrease in RBC and WBC parameters in HD** mice. There were no gross findings and histopath was limited to lymphoid depletion and necrosis of the spleen, slight epithelial hypertrophy and moderate ductal ectasia of mammary gland in MD&HDf. It was concluded that **3mg/kg is the NOEL and 10mg/kg is a LOEL** due to slight histopath and hematology findings.

Comment:
Concurrent with the above study, a 2-week pilot toxicity study (#M15390) was conducted to determine MTD in mice; a summary was attached as Appendix J, to the 3-month study report. CD-1 mice (5/sex/dose) were orally administered LY 170053 at **45, 70, or 100mg/kg/d for 2wks**. Mice were 5-6wks of age at study initiation with mean wt (±s.d.) 27.3±2g m and 22±1.5g f.
Survival: All HDm and 4/5HDf died on day 3 of the study, 3/5MDm and 2/5MDf died by day4; all LD and cont mice survived till end of study.

Clinical Signs: 1st 3days: hypoactivity in LD, semicomatose in MD, and comatose in HD; these signs lasted several hr postdosing. Days 4-6 all surviving mice were semicomatose immediately after dosing then hypoactive for several hrs postdose. From day7-end all surviving mice were hypoactive after dosing.
B.wt(2x per wk): mean wt and wt gain were significantly decreased throughout the study in LD&MDm however, LD&MDf mean wt and wt gain were similar to the controls. Note HD animals died early.

Hematology: **significant dose-related decrease in lymphocytes and neutrophils in male and female** mice. These decreases led to depletion of total leukocyte count. Platelet count was slightly increased (non dose-dependently).

Clinical Chemistry: a trend toward increase in BUN and hepatic enzyme activities (ALP, AST, ALT) in both sexes from LD&HD. The enzyme changes were also elevated in the single surviving 100mg/kg dosed female mouse.

There were no organ wt, gross morphology, or histopath done except gross exam was done on the animals that died; no findings were observed.

It was concluded that a NOEL could not be established and the LOEL is **<45mg/kg** based on decrease in B.wt, hematology findings, and changes in enzyme activity.

Rat:

1. 2-wk oral pilot and dose-range finding study in rats/report# 12/study# R02883/Jan 1985/Reviewed by Dr. Hollenbeck.
2. 3-months oral tox study in rats/report# 15/study# R08583 & R08683/July 1985/Reviewed by Dr. Hollenbeck.

1. 2-wk oral pilot and dose-range finding study in rats/report# 12/Reviewed by Dr. Hollenbeck.

Doses/No. Animals per dose: **2, 6, 18, 54mg/kg/d**; 5 /sex/dose.
Route: oral gavage.
Parameters studied: survival, clinical signs, B.wt, food intake, EFU, hematology, clinical chemistry, enzyme nduction, Glutathione analysis, organ wt, gross and histopath.

Results and Conclusions:
Survival: all HD rats died. Deaths occurred between treatment days 3 and 10. All rats in other drug grs survived.
Clinical signs: HD rats were severly depressed that they were unable to feed or drink. Rats in other doses showed hypoactivity that was dose-dependent and lasted till end of study.
B.wt and Food intake: **mean wt and wt gain were sig reduced at doses ≥6mg/kg at end of study with sig reductions starting on day3. Mean food intake and EFU were also sig reduced in these grs throughout the study.** The percent loss in wt gain ranged between 27 to >100*% of the cont (* HD rats lost 14-20g). Food intake was similarly reduced in these animals with HD rats nearly not eating.
Hematology and Clinical Chemistry: no drug effect on any parameter.
Enzyme induction: was assessed by determining the activity of p-nitroanisole O-demethylase. Liver samples (2g each) at necropsy were obtained from each animal at each dose. Liver homogenate were prepared and enz activity was measured. No drug effect except for a slight but sig incr in males dosed 6mg/kg relative to the cont (mean±s.e. 38±6 vs. Cont 26±1.4nmol PNP produced/mg protein/hr).
Glutathione Analysis: both reduced (GSH) and oxidized (GSSG) concentrations were measured using a kinetic assay in which the catalytic amounts of GSH and GSSG and glutathione reductase cause the continued reduction of 5,5-dithiobis(2)-nitrobenzoic acid (DTNB), by NADPH. The cpd formed, 5-thio-2-nitrobenzoate was measured spectrophotometrically. Olanzapine had no effect on this parameter.
Organ wt, Gross, and Histopath: no drug related finding. The decreases in rel organ wt noted in the 2HD were probably related to the sig reduction in B.wt of these animals.

It was concluded that 54mg/kg is fatal to rats upon repeate dosing. Clinical signs were dose-dependent and included hypoactivity. Mean wt, wt gain, food intake and EFU were sig reduced throughout the study at doses ≥ 6mg/kg in both sexes. No other drug related finding was observed.

2. 3-month oral tox study in Fischer 344 rats/report# 15/Reviewed by Dr. Hollenbeck (Aug 1986).

Doses/No. Animals per dose: **2.4, 7.5, 22.5mg/kg/d**; 20/sex/dose.
Route: oral gavage.
Parameters studied: survival, clinical signs, B.wt, food intake, ophthalmology, hematology, clinical chemistry, urinalysis, organ wt, gross and histopath.

Results and Conclusions:
Survival: 1LDm, 1MDf, and 3HDf died during the study. Deaths occurred between days 18 and 93. The death of the HDf was considered drug related

Clinical Signs: severity incr with dose. Signs observed in all drug grs included sedation, lethargy, and lacrimation. Tolerance seemed to develop to the clinical signs with repeate dosing except some rats in the HD. Lethargy, lacrimation, salivation, red muzzle and chromodacryorrhea occurred within 15min of dosing early in treatment. During the 3rd wk HDm were very irritable and HDf were hyperactive prior to dosing, also postdose mydriasis noted in these animals. These effects were slightly less with time however, did not go away. Hyperirritability and now hypoactivity, mydriasis and red muzzle remained in HDm&f.

B.wt and Food intake: dose-dependent and sig decr in mean wt, wt gain, mean food intake, and mean efficiency of food utilization (see table below from sponsor).

TABLE 1. SUMMARY OF GROWTH, FOOD CONSUMPTION, AND EFFICIENCY OF FOOD UTILIZATION FOR RATS GIVEN DAILY ORAL DOSES OF COMPOUND LY170053 FOR 14 WEEKS. STUDY R08583.

Dose (mg/kg)	Mean Weight At Start (g)	Number of Survivors	Mean Weight At Termination (g)	Mean Weight Gain (g)	Mean Daily Food Consumption (g)	Mean E.F.U.[a]
			MALES			
0.0	113.7	20	322.2	208.6	15.6	13.8
2.5	109.1	19	291.5[c]	182.4[c]	14.4[c]	13.0[b]
7.5	110.3	20	218.3[c]	108.0[c]	12.2[c]	9.1[c]
22.5	112.0	20	173.0[c]	61.0[c]	10.7[c]	5.8[c]
			FEMALES			
0.0	89.0	20	181.7	92.7	10.4	9.1
2.5	89.2	20	176.3	87.2	9.9[b]	9.0
7.5	89.9	19	142.2[c]	52.3[c]	8.4[c]	6.3[c]
22.5	90.4	17	108.2[c]	17.8[c]	7.1[c]	2.5[c]

[a]E.F.U. = Efficiency of food utilization - grams of body weight gained per 100 grams of food consumed.
[b]Significantly different from control, p less than or equal to 0.05, Dunnett's two-tailed "t".
[c]Significantly different from control, p less than or equal to 0.01, Dunnett's two-tailed "t".

Ophthalmology: no sig drug related findings

Hematology: small but sig dose-dependent incr in erythrocyte parameters: Hb, PCV, MCV, and MCHC of females but not in males. **WBC count was sig reduced in HDm&f due to sig decr in lymphos**, but a sig (1.4x the cont) incr noted in neuts of this gr in both sexes.

Clinical chemistry: a sig incr in HDm&f in BUN (1.3x), T.bili (males only; 1.3x), ALP (1.5-1.8x; also MDf), ALT (males only, 1-1.5x). Creatinine level was sig reduced in HDm only (20% of the cont).

Urinalysis: no sig drug related findings

Organ wts: the **relative wts of the ovary and uterus were reduced dose-dependently** perhaps due to prolactin release induced by the drug.

Histopath: No drug related findings

Plasma levels: plasma levels ranged between 0.1-4ug/ml. Conc incr with dose, there seemed to be some accumulation as levels on day 30 were higher than those on day1 (table below from sponsor).

Sex	Dose mg/kg	Day 1 µ g/mi	∓ ± SE	Sex	Dose mg/kg	Day 30 µ g/ml	∓ ± SE
M	2.5	.09		M	2.5	*	
M	2.5	.14		M	2.5	*	
F	2.5	.16		F	2.5	*	
F	2.5	.11	0.13 ± 0.02	F	2.5	*	
M	7.5	.34		M	7.5	.74	
M	7.5	.58		M	7.5	.94	
M	7.5	.38		F	7.5	.95	
F	7.5	.44	0.44 ± 0.05	F	7.5	.78	0.85 ± 0.05
M	22.5	2.03		M	22.5	3.72	
M	22.5	2.57		M	22.5	3.88	
F	22.5	1.80		F	22.5	3.06	
F	22.5	1.68	2.02 ± 0.20	F	22.5	3.51	3.54 ± 0.18

*Large interference peak prevented determination.

It was concluded that oral administration of olanzapine for 3months to rats caused deaths in 3 of 20 HDf. Some degree of tolerance developed to clinical signs with repeate dosing however, sedation, lacrimation, hyperirritability, and hyperactivity persisted in HD and some MD. **Mean wt and wt gain were sig reduced in all drug grs.** Erythrocyte parameters were sig and dose-dependently increased in females but not in males (Hb, PCV, and MCV). **In males and females of HD, WBC count was sig reduced due to decr in lymphocytes. Mean relative wts of the ovaries and uteri were sig reduced in HDf but no histopath finding. The NOEL in this study is 7.5mg/kg.**

Dog

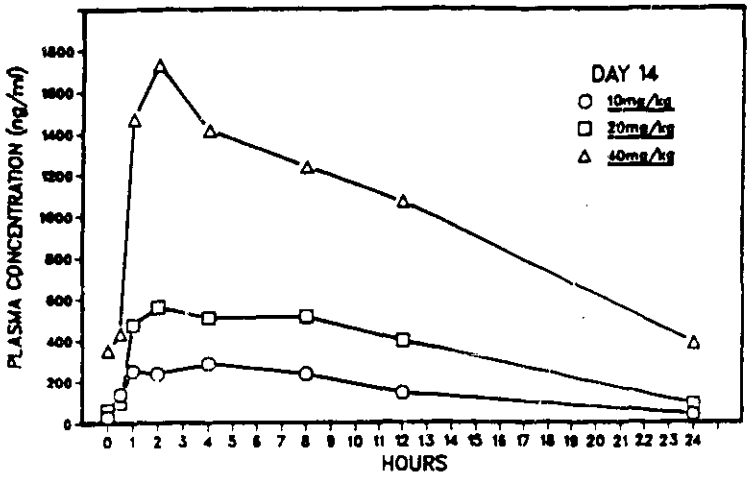
1. 2-wk pilot and dose-ranging study in Beagle dogs/report# 14/study# D00883/June 1985/Reviewed by Dr. Hollenbeck.
2. 3-months oral tox study in dogs/report# 16/study# D02283/Oct 1985/Reviewed by Dr. Hollenbeck.
3. Additional data for animal# 174433 given daily oral doses for 3-months/report# 23/study# D02283/Dec 1988/Reviewed by Dr. Atrakchi.

1. 2-week/report# 14/Reviewed by Dr. Hollenbeck: (Aug 1986):

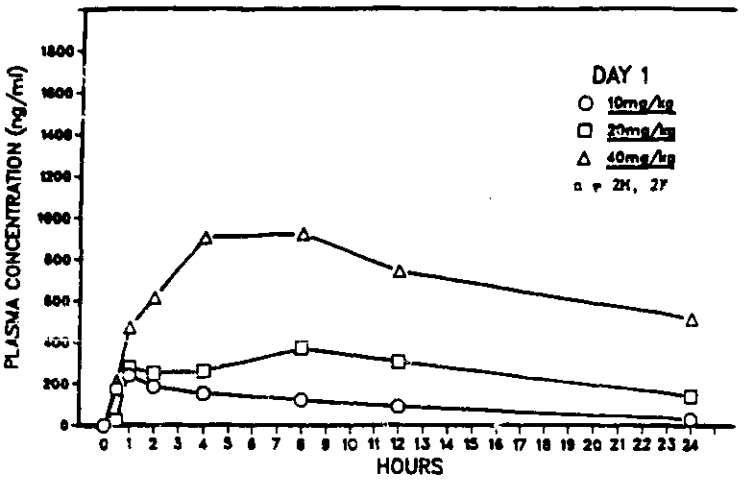
Doses/No. animals per dose: **10, 20, 40mg/kg/d**; 2/sex/dose; the cont received empty gelatin caps.
Route: oral capsules.
Parameters studied: survival, clinical signs, B.wt, Food intake (visual estimation), EKG, ophthalmology, clinical chemistry, hematology, bone marrow morphology and type of any abnormalities, enzyme induction, gross and histopathology, and blood levels.

Results and Conclusions:
Survival: all dogs survived.
Clinical signs: noted in all treated dogs: ataxia, hypoactivity, sedation, and miosis; severity and duration were dose-dependent. Also in HD, tremors and anorexia.
B.wt and Food intake: no effect on mean wt at wk1 or termination except for a 17% decr in mean wt of HDf at termination relative to the cont.. Food was reduced in MD&HD dogs based on visual determination; no data were provided.
Ophthalmology: slit lamp biomicroscopy and direct and indirect ophthalmoscopy were done. Lacrimal flow was measured by Schirmer tear test. **Dose-dependent and significant reduction in lacrimal flow noted 6hr post the last dose. Miosis noted in all treated dogs but the extent could not be correlated to dose.** All of these dogs had normal pupil reflexes, however, pupils of dogs in HD did not dilate completely. A dose-response effect of more complete dilation noted in the eyes of LD&MD dogs. The exact cause of miosis could not be explained by the sponsor, but suggested to be due to either a direct parasympathetic stimulation or indirectly to inflammation (uveitis/iridocyclitis) caused by histamine and prostaglandin release. Such inflammation can be revealed through histopathological exam of the iris and ciliary body both of which were not done in this study. Also, one dog had retinal dysplasia but the ophthalmologist dismissed any relation to treatment. **The arguments presented by the sponsor are not convincing to suggest an incidental and drug unrelated effect. Other studies in dogs as well as in other species should be considered to evaluate this effect on the eye.**
EKG: transient incr in HR noted in all dogs in all dose gr at 2hr postdose (mean±s.d. 205±39 in LD, 190±45 in MD, and 213±22BPM in HD vs 119±20BPM in cont), but was normal by 24hr.
Clinical Chemistry: no drug related findings
Hematology: **erythrocyte parameters were depressed at HD and there was a reduction in erythroid precursors in bone marrow of 2 HD dogs.**
Bone marrow: **2 HD dogs (1m and 1f) had decreased erythroid precursors with the female showing high myloid/erythroid ratio compared with the cont.**
Enzyme induction: hepatic p-nitroanisole O-demethylase activity was determined from liver samples at end of study. A 1.4-2x incr in mean enzyme activity was measured in all 3 female dose groups with each individual value in drug grs being higher than that in the cont. No effect in males.
Histopath: **lymphoid depletion of the thymus in all drug gr.** No other findings.

Blood levels: samples collected at 0 and upto 24hr on day 1 and 14 of the study, however, no tabulated data were provided, only the figure below. There seem to be some drug accumulation in MD&HD as seen with much higher plasma levels on day14 relative to those on day1 of the study. Peak plasma levels in HD reached 1700ng/ml on day14 vs. 900ng/ml on day1.



PLASMA CONCENTRATION IN BEAGLE DOGS GIVEN DAILY DOSES OF COMPOUND 170053 (STUDY D00883)



It was concluded that oral administration of olanzapine to male and female dogs for 2wks at 10, 20, 40mg/kg had no effect on survival but caused marked sedation and anorexia in HD of 40mg/kg. Erythrocyte parameters were depressed in HD and there was a reduction in erythroid precursors in bone marrow of 2 HD dogs (1m and 1f) with the female showing high myloid/erythroid ratio compared with the cont. Hepatic p-nitroanisole O-demethylase activity was incr 1.4-2x in all 3 female dose groups with each individual value in drug grs being higher than that in the cont; no effect in males. Histopath finding was limited to lymphoid depletion of the thymus in all drug gr. Olanzapine was rapidly absorbed and levels incr with dose. There seem to be some drug accumulation in MD&HD as seen with much higher plasma levels on day14 relative to those on day1 of the study. Peak plasma levels in HD reached 1700ng/ml on day14 vs. 900ng/ml on day1. **The NOEL is <10mg/kg/d** based on presence of lymphoid depletion of the thymus.

2. 3-month oral tox study in dogs/report# 16/Reviewed by Dr. Hollenbeck/(Aug 1986).

Doses/No animals per dose: **2, 5, 10mg/kg/d**; 4/sex/dose, the cont received empty gelatin caps.
Route: oral capsules
Parameters studied: survival, clinical signs, B.wt, food intake (visual estimate only), EKG, ophthalmology, clinical chemistry, hematology, bone marrow morphology and type of any abnormalities, gross and histopathology.

* Blood was collected for plasma levels but no conc were detected in any sample. The sponsor indicated that this was due to decomposition of the parent during storage or extraction method. It is the opinion of the reviewer that stability should have been tested throughout the study; the sponsor's explanation is poor and inadequate.

Results and Conclusions:
Survival: all dogs survived. **1HDm had immunologic response** early in the study and was removed from the study on day 37 thru day 67. When treatment restarted, **12days into dosing, this dog developed severe neutropenia and thrombocytopenia with markedly elevated erythrocyte sedimentation rate.** (see below *). Another HDm developed an infection and was removed from the study on day 59 thru 69.
Clinical Signs: severity incr with dose. Signs included miosis and hypoactivity in all treated dogs with tolerance developing mainly in LD, with repeate dosing. Ataxia accompanied these signs in HD.
B. wt. and Food intake: mean wt was reduced 4-17% in HDm&f at termination. No data or mention of food intake.
Ophthalmology: no drug related findings.
EKG: heart rate was sig incr in all 3 drug grs at end of study (day 89) at 2hr postdose, mean values were: 131, 147, and 143BPM in LD, MD, and HD respectively, and that of the cont was 107BPM.
Clinical Chemistry, Hematology, and urinalysis: no drug related findings. [except for the 2 above mentioned dogs with neutropenia and thrombocytopenia and leukocytosis].
Bone marrow: 1f each in MD&HD and 1HDm had slight incr in erythroid series. The HDm had an incr in eosinophils, the HDf had a decr in seg. neutrophils. These findings were not considered of tox sig.
Organ wt: testes relative wt of all HDm was sig decr (0.07g vs. 0.16g in cont), a finding that could be related to prolactin release. Note that final wt of dogs in this gr was also sig reduced relative to the cont.
Gross and Histopath: all 3 HD male had hypospermatogenesis, the sponsor could not conclude if this was a drug effect or stress related. No other findings.

* Immunologic study: 1HDm showed on day 34 of the study, neutropenia, thrombocytopenia, and bone marrow erythroid hypoplasia. The treatment was stopped on day37 and the dog was allowed to recover. The sponsor wanted to investigate the possibility of an immune-mediated mechanism by rechallenging this dog with olanzapine 3times: 2x at 10mg/kg and once at 2mg/kg. The peripheral hematologic findings were reproduced within 4-9days of each rechallenge. Antibody levels and immune complex were measured during the 1st rechallenge at 10mg/kg and the 3rd rechallenge at 2mg/kg. At the 2nd rechallenge of 10mg/kg drug-related incr in amount of surface immunoglobulin on isolated neutrophils was investigated. The results showed that the hematological findings i.e. neutropenia and thrombocytopenia in this dog were **not due to a drug effect on myloid component of the bone marrow but due to peripheral destruction. The mechanism of the latter was supported by an incr in soluble immune complex levels and incr in amount of ^{14}C-olanzapine bound to serum immunoglobulin.**

It was concluded that dogs treated with olanzapine at 2, 5, or 10mg/kg for 3months caused no deaths in any gr. Clinical signs were dose-dependent in seventy and included sedation, hypoactivity, and miosis. Slight decr in mean wt, no effect on urinalysis, opthalmology, or clinical chemistry. A marked incr in HR noted in all drug grs 2hr postdose at end of study; the sponsor contributed this to anticholinergic effect of the drug. The relative wt of testes of HD was sig reduced/atrophied compared with the cont. The only histopath finding was hypospermatogenesis in HDm; the sponsor could not conclude if this was a direct drug effect or non drug finding. There were no drug-related effect on hematology parameters except in one HDm. This dog had **neutropenia, thrombocytopenia, and bone erythroid hypoplasia** on day 34 of the study. Treatment was terminated on day 37 and a possible immunologically mediated mechanism was investigated by rechallenging this dog with 2 doses of olanzapine 3 times. **The results indicated that olanzapine effected the immune system and not the myloid component of bone marrow** causing the neutropenia and thrombocytopenia. **The NOEL is 5mg/kg.**

3. Additional data for animal# 174433 given daily oral doses for 3-months/ report# 23/Reviewed by Dr. Atrakchi.

In this study, the 1HD dog from the above 3mo dog study, was retained for 45months after rechallenge with olanzapine for observation and evaluation. This study described clinical signs, B.wt, ophthalmology, hematology, bone marrow, clinical chemistry, urinalysis, and histopath not reported in the previous report# 16.

Results and Conclusions:
Miosis and hypoactivity were observed after the rechallenge with 10mg/kg; some skin redness was also seen. No CNS or autonomic effects were seen during the rechallenge with 2mg/kg but the dog seemed thin for upto 5.5 mo postrechallenge. There were no ophthalmologic finding. This dog lost 0.7-1kg by the end of each rechallenge but gained back some wt during the off-treatment period. All findings were within normal for hematology, bone marrow, clinical chemistry, and urinalysis indicating no delayed effects. Also no gross or histopath findings.

Chronic Toxicity
Some of the following studies were reviewed previously in IND# 28,705 (the name of the reviewer is reported for each study).

Rat:
1. 6-months oral gavage toxicity study in Fisher 344 rats followed by 1-month reversibility period/report# 55/study# R03193, R22593, & R22693/May 1995/Reviewed by Dr. Atrakchi.
2. 1-year oral gavage toxicity study in Fisher 344 rats/report# 22/study# R18685 & R18785/July 1988/Reviewed by Dr. DeGeorge.

1. 6-months oral gavage toxicity study in Fisher 344 rats followed by 1-month reversibility period/report# 55/Studies# R03193, R22593, and R22693/Reviewed by Dr. Atrakchi.

Doses/No. animals per dose: Treatment phase (study# R03193): **0.25, 1, 4,16mg/kg/d**; 15/sex/dose, studies R22593 and R22693/TK studies: **1, 4, 8, 16mg/kg/d**; 21- and 24/sex/dose respectively; the cont received the vehicle: acacia 10% w/v in purified water.
Route: oral gavage.
Parameters studied: survival, clinical signs, B.wt, food intake, EFU, ophthalmology, enz induction, clinical chemistry, hematology, urinalysis, blood levels, organ wts, and gross and histopathology.

10 of the 15 rats were killed at end of 6mo; the 5 rats/sex/dose were kept for a recovery period of 1mo. In the accompanying TK studies, olanzapine plasma profiles were determined on day1 of dosing and after 2&6mo of dosing.

Results and Conclusions
Survival: no deaths in any gr.
Clinical signs: hypoactivity and sedation were observed in all doses with severity being dose-dependent but decreasing with time indicating tolerace development.
B.wt and Food intake: dose-dependent decr in mean wt, wt gain, food intake, and EFU in males and females doses 4&16mg/kg (see tables below provided by the sponsor). At the end of dosing, **wt gain was decr 25&59% in males and 10&48% in females of the 4&16mg/kg doses respectively.** Body wt gain and EFU of rats dosed 4 and 16mg/kg were greater than the cont during the recovery period. However, food intake of these grs remained slightly less than that of the cont during the recovery

period Mean wt of rats dosed 4mg/kg at the end of the 1mo recovery period was comparable to that of the cont whereas, mean wt of the 16mg/kg remained depressed and lower than the corresponding cont (30% m and 23% f). Food intake of the 4&16mg/kg females was comparable to that of the controls, while that of the males was still less than the wt of the controls.

Table G-2. Summary of Survival, Growth, Food Consumption, and Efficiency of Food Utilization for Rats Receiving Olanzapine (LY170053) by Gavage for 6 Months Followed by a 1-Month Reversibility Period. Study R03193. Treatment Period.

Dose (mg/kg/day)	Number of Survivors	Mean Body Weight At Start (g)	Final Mean Body Weight[a] (g)	Mean Body Weight Gain (g)	Mean Daily Food Consumption (g)	Mean EFU[b]
			Males			
0	15	116.1	407.1	291.1	17.9	9.0
0.25	15	116.7	409.2	292.5	18.3	8.8
1.0	15	114.1	399.1	285.0	18.0	8.8
4.0	15	116.4	334.3*	217.9*	16.9*	7.1*
16.0	15	116.9	236.8*	119.9*	14.7*	4.5*
			Females			
0	15	94.4	222.7	128.3	12.7	5.6
0.25	15	94.8	217.3	122.5	12.7	5.3*
1.0	15	95.4	217.3	121.9	12.7	5.3*
4.0	15	96.0	212.1*	116.1*	12.3	5.2*
16.0	15	94.6	161.1*	66.5*	11.4*	3.2*

[a]Test Day 180
[b]EFU = Efficiency of food utilization = grams of body weight gained per 100 g of food consumed.
*p≤.05 for Tukey's trend test, two-tailed.

Table G-3. Summary of Survival, Growth, Food Consumption, and Efficiency of Food Utilization for Rats Receiving Olanzapine (LY170053) by Gavage for 6 Months Followed by a 1-Month Reversibility Period. Study R03193. Reversibility Period.

Dose (mg/kg/day)	Number of Survivors	Mean Body Weight At Start[a] (g)	Mean Body Weight At Termination (g)	Mean Body Weight Gain (g)	Mean Daily Food Consumption (g)	Mean EFU[b]
			Males			
0	5	392.8	405.8	13.0	18.4	3.0
0.25	5	404.4	420.6	16.2	19.1	3.5
1.0	5	406.6	400.8	-5.3	17.5	-2.7
4.0	5	341.4*	375.8	34.4	16.8*	8.5
16.0	5	226.8*	282.6*	55.8*	15.5*	15.1*
			Females			
0	5	222.8	230.6	7.8	13.4	2.3
0.25	5	208.6	216.8	8.2	13.0	2.5
1.0	5	215.2	225.2	10.0	13.2	3.1
4.0	5	207.6*	220.8	13.2*	13.1	4.0*
16.0	5	158.4*	177.2*	18.8*	12.8	5.9*

[a]Test Day 183
[b]EFU = Efficiency of food utilization = grams of body weight gained per 100 g of food consumed.
*p≤.05 for Tukey's trend test, two-tailed

Ophthalmology: no drug related findings in any gr.
Hematology: parameters were measured using 10/sex/dose at end of 6mo and from 5/sex/dose at end of recovery period **Mean WBC count was decr (27%) in HDm. This was due to a slight decr in lymphocyte (29%) and neutrophil count (20%). This decline in mean total WBC was still present during the recovery period with the decr in neutrophil reaching statistical sig (27%)**, but the decr in lymphocyte was small and did not reach statistical sig (9%). During treatment, there was a small incr in Hb and PCV in males dosed 4 and 16mg/kg (6&9% and 5&7% respectively) without change in mean RBC count. Also in both sexes, a dose-dependent incr in 4&16mg/kg noted in MCV, MCHC(only in m), and MCH (these changes ranged between 3-12% in m and 1-2% in f). Reticulocytes were decr non dose-dependently in 4&16mg/kg dosed m (3-14%) and in HDf (12%). During recovery period, the only parameters of the erythrogram that did not recover included MCV (MD&HDm and HDf) and MCH (MD&HDm and HDf). At end of recovery period some changes in RBC parameters persisted in HD males and females but there were no differences in RBC count or Hb.
Clinical Chemistry: the following changes were reported: in HD males and females there was an incr in **BUN** (mean 13-18%) and decr in **glucose** (18-26%), **calcium** was decr dose-dependently in MD&HDm&f (4-7%), **inorg phosphate** unaffected in males but dose-dependently incr (sig only in HD) in females dosed 1, 4, and 16mg/kg (9-23%), **ALP** was incr dose-dependently in females (27-59% or 1.3-1.6x the cont) and in HDm (40% or 1.4x the cont), **CPK** was incr only in HDm (49% or 1.5x the cont). Levels of **AST** were decr dose-dependently in all 4 treated female grs (17-26%) and in the 2 high dosed male grs (23-28%). Also reduced was the level of **ALT** in HDm and females dosed 4&16mg/kg (22-27%). A small but sig and dose-dependent decr noted in **total proteins** of treated female grs (4-7%) and very small decr in HDm (1%). **Albumin** was unaffected in males but dose-dependently reduced in all 4 female grs (5-8%) and the A/G ratio was sig reduced in HDf but incr in HDm; the globulin was unaffected in females but reduced in HDm (7%). At recovery period, the incr in BUN was limited to HDf and a slight dose-dependent incr in inorganic phosphate noted in males and females of MD&HD, cholesterol was decr dose-dependently in MD&HDm&f, TG were decr in HDm&f, the small incr in ALP was now limited to HDm&f and a small incr noted in GGT of HDf. Also, total proteins, albumin, and globulin levels were slightly but sig reduced in HDm and only albumin was decr in HDf.
Urinalysis: slight incr in urinary pH of HDm remained elevated through the recovery period, but the slight incr in urine vol (26&29%) of 4&16mg/kg dosed females was reversed.
Enzyme Induction: at end of treatment, a dose-response incr (32 to 102%) noted in EROD in MD&HDm and HDf and a dose-response incr (17-25%) in BND noted in females dosed 4&16mg/kg whereas a dose-dependent decr noted in males dosed 1,4, and 16mg/kg (sig at MD&HD). Liver P450 content was reduced (8-9%) in MD&HDf; a small and nonsig decr noted in HDm. At end of recovery period, P450 content was reduced 12% in HDm and 16% in HDf.
TK: blood was collected between 0.5 and upto 48hr postdosing on day0 and months 2&6 of the study. There was no sex difference, conc on day0 in the 1 and 4mg/kg dose gr were below detection limit of 1ng/ml, but conc in rats dosed 8&16mg/kg incr with dose. At 2&6mo, conc incr non-linearly with dose and tended to be higher at all doses as duration of treatment continued, indicating some accumulation. Generally, the relationship between AUC, max conc, and dose was nonlinear specially at the higher doses (8&16mg/kg). **After 6mo of dosing, mean max conc in males and females combined were: 24, 241, 802, and 2076ng/ml** for 1, 4, 8, and 16mg/kg respectively, and the corresponding values for **mean AUC were 222, 1282, 6579, and 29109ng.hr/ml** (see attached table from sponsor).

attach to 6 month Rat Report # 55

Appendix L (Continued).

Table 31.2.

Some Pharmacokinetic Parameters (Mean ± SE) in Male and Female Rats Receiving Daily Oral Doses of LY170053 at 1, 4, 8 or 16 mg/kg for up to 6 Months (Toxicology studies R22593 and R22693)

Dose	Sex	Mean C_{max} (ng/ml)	Mean T_{max} (hrs)	Mean AUC¥ (ng x hr/ml)	Mean t1/2 (hrs)
DAY 0					
1	M	11.0 ± 5.7	0.5	-	-
	F	15.8 ± 0.9	0.5	-	-
	M+F	13.4 ± 2.8	0.5	-	-
4	M	65.9 ± 1.7	0.5	176.4	-
	F	85.1[a]	0.5	322.9	-
	M+F	73.6 ± 4.8 (n=5)	0.5	247.2	-
8	M	257 ± 39.0	0.5	1199.6	1.9*
	F	363.1 ± 38.5	3	1658.0	1.7*
	M+F	297.7 ± 35.8	3	1439.2	1.8*
16	M	1180 ± 100.6‡	0.5	5076.9	3.2*
	F	1067 ± 112.8‡	0.5	6234.1	4.3*
	M+F	1123 ± 72.2	0.5	5655.5	3.8*
MONTH 2					
1	M	7.7 ± 1.2	0.5	19	-
	F	24.6[a]	8.0	102.6	-
	M+F	10.7 ± 2.3	0.5	52.2	-
4	M	166.1 ± 29.8	0.5	782.4	2.7#
	F	180.7 ± 60.2	0.5	920.0	3.8#
	M+F	173.4 ± 30.2	0.5	851.2	3.2#
8	M	624.9 ± 155.9	0.5	5405.3	9.1#
	F	526.7 ± 122.3	0.5	5172.0	6.6#
	M+F	575.8 ± 91.3	0.5	5288.7	7.6#
16	M	1279.5± 235	8	19409.7	3.4¶
	F	2257 ± 600.4	5	22914.3	4.0†
	M+F	1754.2 ± 355.4	5	21191.2	4.1†
MONTH 6					
1	M	17.3 ± 5.8	0.5	205.3	-
	F	33.1[a]	0.5	247.4	0.9@
	M+F	23.6 ± 5.9	0.5	222.3	1.5@
4	M	257.5 ± 11.4	0.5	1474.2	3.1§
	F	225.3 ± 64.6	0.5	1085.3	2.8§
	M+F	241.4 ± 30.2	0.5	1282.5	2.9§
8	M	801.1 ± 63.9	0.5	6285.1	2.2§
	F	802.0 ± 112.2	0.5	6836.3	2.2§
	M+F	801.6 ± 57.7	0.5	6578.8	2.2§
16	M	2043.1 ± 162.9	3	27973.3	6.7¶
	F	2164.5 ± 90.4	5	30409.0	4.7¶
	M+F	2076.3 ± 130.0	0.5	29109.3	5.8¶

[a] n = 2
¥ = 0 - t
- = no value (insufficient data)
§ = 8 to 24 hours
# = 5 to 12 hours
* = 8 to 12 hours
¶ = 12 - 48 hours
‡ = values outside of standard curve
† = 5 to 24 hours
@ = 3 to 8 hours

Organ wts: many of the changes were secondary to the decr in mean wt. However, the following were directly related to the drug: **incr in relative wt of the adrenals in HDm and an incr in relative wt of the pituitary of HDf during recovery period.** Also the **absolute and rel wts of the ovaries** in females dosed 4&16mg/kg were **decr at end of treatment, uterine wt remained decr in HD at end of recovery period,** and ovarian wts incr in HDf. The sponsor indicated that the changes of the ovaries and uterus were secondary to the decr in B.wt and wt gain.
Gross and Histopath: treatment related effects noted in the **adrenals (males), mammary glands (m&f), and vagina and ovaries.** At end of treatment, adrenals of HDm, showed decreased vacuolation in cortical cells compared to that normally present in male rats. This change remained through the recovery period and at this time, it was seen in males dosed 4mg/kg as well as HDm. The following changes in mammary glands could be linked to incr prolactin level: male mammary gland tissue was changed from the normal lobuloalveolar to tubuloalveolar pattern in 4&16mg/kg grs and presence of secretions in mammary glands in females dosed16mg/kg. The incidence and prominence of mucoid metaplasia of the vaginal epithelium were incr in females dosed 4&16mg/kg, and ovarian follicular prominence was incr in HDf. All of these effects reversed during recovery period. In the ovary, thecal (stromal) prominence was seen in 1/10 and 4/10 females dosed 4&16mg/kg respectively, at end of treatment. This effect was absent at end of recovery and the sponsor indicated that it was related to the decr in wt gain in these grs. Uterine hypoplasia was observed in 7/10 and 10/10 females dosed 4&16mg/kg respectively, at end of treatment and, in 2/5 HDf at end of recovery period. Note that except for the small size, the uterus appeared normal indicating that the decr in wt of this organ was secondary to the decr in B.wt in this gr.

Summary and Conclusion:
Oral administration of olanzapine to rats for 6mo at 0.25, 1, 4, 8, 16mg/kg caused no deaths. Dose-dependent hypoactivity that decr in severity with time indicating tolerance. Mean wt, wt gain, food intake, and EFU were sig and dose-dependently reduced in males and females doses 4&16mg/kg. At the end of dosing, wt gain was decr 25&59% in males and 10&48% in females of the 4&16mg/kg doses respectively. Body wt gain and EFU of rats dosed 4 and 16mg/kg were greater than the cont during the recovery period. However, food intake of these grs remained slightly less than that of the cont during the recovery period. Mean wt of rats dosed 4mg/kg at the end of the 1mo recovery period was comparable to that of the cont whereas, mean wt of the 16mg/kg remained depressed and lower than the corresponding cont (30% m and 23% f). Food intake of the 4&16mg/kg females was comparable to that of the controls, while that of the males was still less than the wt of the controls. There were no sig drug related finding in ophthalmology and the changes in clinical chemistry parameters were non-dose dependent and random. Urine pH of HDm was incr and remained elevated through the recovery period, but the slight incr in urine vol (26&29%) of 4&16mg/kg dosed females was reversed. A dose-response incr (32 to 102%) noted in EROD in MD&HDm and in HDf and a dose-response incr (17-25%) in BND noted in females whereas a decr noted in HDm. Liver P450 content was reduced (8-9%) in MD&HDf but the decr in males was not statistically sig in any gr. At end of recovery period, P450 content was reduced 12% in HDm and 16% in HDf. Olanzapine was detected in blood and there was no sex difference. Conc on day0 in the 1 and 4mg/kg dose gr were below detection limit of 1ng/ml, but conc in rats dosed 8&16mg/kg incr with dose. At 2&6mo, conc incr non-linearly with dose and tended to be higher at all doses as duration of treatment continued indicating some accumulation. Generally, the relationship between AUC, max conc, and dose was nonlinear specially at the higher doses (8&16mg/kg). After 6mo of dosing, **mean max conc in males and females combined were: 24, 241, 802, and 2076ng/ml for 1, 4, 8, and 16mg/kg respectively, and the corresponding values for mean AUC were 222, 1282, 6579, and 29109ng.hr/ml.** Many of the changes in organ wts were secondary to the decr in mean wt. However, the following were directly related to the drug: incr in **relative wt of the adrenals** in HDm and an incr in **relative wt of the pituitary** of HDf during recovery period. Also the **absolute and rel wts of the ovaries** in females dosed 4&16mg/kg were decr at end of treatment, **uterine wt** remained decr in HD at end of recovery period, and ovarian wts incr in HDf. Treatment related effects in histopath were noted in the **adrenals**

(males), mammary glands (m&f), and vagina and ovaries. At end of treatment, adrenals of HDm, showed decreased vacuolation in cortical cells compared to that normally present in male rats. This change remained through the recovery period and at this time, was also seen in males dosed 4mg/kg. The changes in mammary glands could possibly be linked to incr prolactin level and included: male mammary gland tissue was changed from the normal lobuloalveolar to tubuloalveolar pattern in 4&16mg/kg grs and presence of secretions in mammary glands in females dosed16mg/kg. The incidence and prominence of mucoid metaplasia of the vaginal epithelium were incr in females dosed 4&16mg/kg, and ovarian follicular prominence was incr in HDf. All of these effects reversed during recovery period. In the ovary, thecal prominence was seen in 1/10 and 4/10 females dosed 4&16mg/kg respectively, at end of treatment. This effect was absent at end of recovery and the sponsor indicated that it was related to the decr in wt gain in these grs. Uterine hypoplasia was observed in 7/10 and 10/10 females dosed 4&16mg/kg respectively, at end of treatment and, in 2/5 HDf at end of recovery period. Note that except for the small size, the uterus appeared normal indicating that the decr in wt of this organ was secondary to the decr in B.wt in this gr. **The NOEL in this study is 1mg/kg.**

2. 1-year oral gavage toxicity study in Fisher 344 rats/report# 22/Reviewed by Dr. DeGeorge.

Doses/No. animals per dose: **1, 4, 16mg/kg/d**; 20/sex/dose, in a parallel study 8/sex cont and 20/sex/dose rats were dosed the same doses and used to measure plasma levels were killed on days 1, 29,176, and 364; the cont gr received the vehicle (10% w/v acacia sol).
Route: oral gavage.
Parameters studied: survival, clinical signs, B.wt, food intake, ophthalmology, clinical chemistry, hematology, urinalysis, blood levels, organ wts, and gross and histopathology.

Results and Conclusions:
Survival: total of 5 animals died, 2LDm, 1HDm, and 2HDf. They were suggested to be accidental and non-drug related.
Clinical signs: [data were not provided for review]. Hypoactivity and sedation were observed in all doses with severity being dose-dependent. These signs were absent in the LD after 4wks. HD rats after the 7th wk appeared hyperactive prior to dosing and this effect remained till end of study. Slight chromorhinorrhea and chromodacryorrhea were observed in HD on the 3rd day but absent by the 6th day. All other signs occurred at a similar frequency throughout the cont and drug grs.
B.wt and Food intake: **dose-related decr in mean wt gain for males (max decr 74%) and females (max decr 66% of cont), with decr wt throughout the study period. Mean food intake and EFU were dose-dependently reduced throughout the study.**
Ophthalmology: no sig findings.
Hematology: consistent incr in Ht, PCV, MCV, and MCH in both sexes at the 6 and 12mo measurments; RBC count was unaltered. **WBC count was reduced >25% in HD rats without sig alteration in cell distribution. There were 5/20 HDm with WBC count lower than the normal range.** The sponsor indicated the effect on RBC parameters was due to hemoconcentration but there were no supporting data indicating dehydration (such as clinical signs or incr water intake).
Clinical Chemistry: findings mainly in HD noted at 6 and 12mo: decr glucose (20%), decr Ca (>10%), and incr ALP (100%).
Urinalysis: no sig findings.

TK: conc incr linearly with dose, no evidence of accumulation, and no sex difference. The 2hr mean±s.e. conc range between day 1 and day 364 was (ug/ml):

LD	0.02±0.01 to 0.20±0.01
MD	0.13±0.01 to 0.64±0.07
HD	2.25±0.17 to2.81±0.09

n=10 for all 3 grs.

Organ wts: **in HD rats incr adrenal wt (absol 50% and rel 3x the cont) and decr in ovary and uterine wt >50% rel wt.** Other changes were correlated with the reduction in B.wt.
Gross and Histopath: no gross findings. **The only histopath finding was an incr in bone marrow hypocellularity in mD&HD rats. This incr was dose-dependent with >70% of HD rats showing this effect.**

It was concluded that oral dosing of olanzapine to rats at 1, 4, 16mg/kg for 1yr caused sedation and hypoactivity with severity being dose-dependent. Mean wt gain, food intake, and EFU were sig reduced in a dose-dependent manner. Plasma levels incr with dose and there seemed to be no sig drug accumulation. A sig decr noted in WBC count in HD with 5/20 rats having values lower than the normal range. Histopath showed incr in bone marrow hypocellularity in MD&HD. In HD rats, the wts of the adrenals was sig incr and in HDf, the wts of the ovaries and uterine were reduced. As indicated by Dr. DeGeorge, a **NOEL could not be established.**

Dog:

1. 6-months oral toxicity study in Beagle dogs to compare olanzapine and compound 170222/report# 56/study# D07290/May 1995/Reviewed by Dr. Atrakchi.
2. 1-year oral toxicity study in Beagle dogs/report# 18/study# D06184/June 1986/Reviewed by Dr. Hollenbeck.
3. Additional data for animal# 189083 from the 1-year toxicity study in dogs/report# 24/study# D06184/Reviewed by Dr. Atrakchi.
4. 1-year oral toxicity study in Beagle dogs followed by 1-month reversibility period/report# 54/study# D02093/May 1995/Reviewed by Dr. Atrakchi.

1. 6-months oral toxicity study in Beagle dogs to compare olanzapine and compound 170222/report# 56/study# D07290/May 1995/Reviewed by Dr. Atrakchi.

This study was conducted to compare the effects of repeate dosing of olanzapine to dogs for 6mo to that of cpd 170222. Both cpds are similar in structure except, olanzapine has a methyl gr at the 2 position of the thieno ring and cpd 170222 has an ethyl gr at that site.

Doses/No. animals per dose: **4 and 8mg/kg/d**; 4/sex/dose; the cont received empty gelatin caps./dogs were 6-12month's old.
Route: oral capsules.
Parameters studied: survival, clinical signs, B.wt, food intake (visual estimate only), ophthalmology, clinical chemistry, hematology, urinalysis, immunology, bone marrow cell culture (CFU-GM and CFU-MK), and gross and histopathology.

Results and Conclusions:
Survival: all dogs survived till end of study except for 1HDf dosed olanzapine. This dog was killed moribund on day 28 due to bacterial pneumonia.

Clinical signs: hypoactivity and miosis observed in all treated dogs. Miosis occurred 2-4hr postdose and persisted throughout the day. It was observed more consistently 24hr postdose in HD cpd 170222 but less frequently in olanzapine dogs and LD 170222 (4/8 and 7/8 dogs of LD&HD 170222 had miosis at end of study). Hypoactivity also occurred 2-4hr postdose and lasted for 24hr. Other signs included panting, hyperactivity, tremors, ataxia, vocalization, and incr salivation. These signs were inconsistent and occurred in one or both doses of one or both drugs.
B. wt. and Food intake: no statistically sig difference in any gr but mean percent wt gains were slightly less in HDm and in LD&HDf of olanzapine and HDm&f of 170222. No effect on food intake.
Ophthalmology: findings included **dose-dependent miosis, hyperreactive pupillary light response, and reduced response to mydriatic drug** (tropicamide 1%). The response was more intense in both drugs at HD. The miosis was more severe and noted in more dogs taking 170222 than those on olanzapine. At 3mo, miosis lasted longer in 170222 whereas at this time, olanzapine-treated dogs did not have pupil constriction remaining from the previous day's dosing. At end of study, miosis was observed in both dose grs of olanzapine but the finding remained more severe and occurred in more dogs dosed cpd 170222.
Hematology: In vitro models of hematopoiesis were used to investigate the possible inhibitory effects of serum from olanzapine-dogs on marrow granulocyte-macrophage (CFU-GM) and megakaryocyte (CFU-MK) progenitor cells. The inhibitory effect maybe due to humoral or chemical factors which result from production of antibodies or accumulation of parent or metabolites. With immune-mediated mechanism of cytopenia, the humoral factor might not only destroy the mature circulating blood cell, but also react with marrow precursor cells of the affected cell line.

Olanzapine dogs: cytopenias were first observed at about 6mo of treatment. **Two HDf were affected. one had hemolytic anemia** characterized by decr RBCs and erythroid hyperplasia of bone marrow, the 2nd female had **neutropenia, thrombocytopenia, and myeloid hyperplasia of bone marrow.** Extramedullary hematopoiesis was seen in smears of livers and spleens at necropsy. However, serum from this dog did not inhibit the cloning activity of CFU-GM or CFU-MK progenitor cells in bone marrow cell culture system (i.e. no bone marrow toxicity). Results of platelet-associated IgG assay on day 188 were equivocal but results of neutrophil-associated IgG assay on day 184 were negative. These findings suggested that olanzapine-induced cytopenia are due to effect of the drug on peripheral blood neutrophils and platelets rather than on marrow progenitor cells of these affected cell lines.

170222 dogs: cytpenias were seen in 2HD after 2-5mo and in 1LD after 6mo. One of the HD dogs had sustained marked neutropenia, thrombocytopenia, and moderate hemolytic anemia (days 66-122). Bone marrow exam (2x at 3mo, 1x at 5mo, and 3x at 6mo) showed myeloid hyperplasia and adequate megakaryocytes. Smears from the liver and spleen at necropsy showed extramedullary hematopoiesis. The indirect PAIgG assay was positive on day 76 but equivocal on day 84. The indirect NAIgG was positive on day 62 but equivocal on day 184. Direct Coombs test was negative on days 76&84. The 2nd dog had only neutropenia without anemia or thrombocytopenia. The neutropenia was marked and lasted till end of study. Bone marrow exam showed myeloid hyperplasia, smears of liver were negative whereas those of the spleen showed extramedullary hematopoiesis. The direct PAIgG was negative on day 136 and the indirect assay was negative on day 76 but equivocal on day 184. Results of NAIgG on day 170 were equivocal. The neutropenia for LD dog was moderate to severe with marrow cytology normal at necropsy. Impression smears of liver and spleen at necropsy were unremarkable. The indirect PAIgG on day 184 and indirect NAIgG on day 188 were equivocal.
Clinical Chemistry: both sexes dosed the HD of both test articles had changes in clinical chemistry pararneters. Males dosed olanzapine showed sig incr in mean tot bilirubin (21-33%), albumin (9-14%) and, A/G ratio (24-35%). Females dosed the HD 170222 had sig incr in ALT(37%), GGT (25%), cholesterol (41% on day 62 of dosing to 56% on day157), and tot proteins (17%).
Urinalysis: no drug related findings.
Organ wts: **mean absolute and relative wts (to B.wt and brain wt) of the ovaries were sig decr in all 4 grs dosed with the 2 test articles.** Ovary wts decr 24% in LDf of olanzapine gr and ca. 50% in

HDf of olanzapine and both doses of 170222. Mean liver wt in HDm of both test articles was sig incr (12-41%) relative to cont dogs. Relative mean kidney wt was sig incr (36-39%) in HDf of olanzapine gr. and sig incr noted in mean relative adrenal wt in HDm (both relative to B.wt and brain wt).

Histopath: see below discussion by the sponsor. Treatment related findings included increased incidence and magnitude of extramedullary hematopoiesis in cytopenic dogs, incr hematopoietic activity in bone marrow of cytopenic dogs, and hypospermatogenesis. The incidence and the extent of the hematopoietic findings were higher in male dogs dosed 170222 than those dosed olanzapine.

The principal treatment-related histopathological alterations seen in dogs given olanzapine or 170222 were extramedullary hemotopoiesis in the spleen and liver and increased hematopoietic activity in the bone marrow. Extramedullary hematopoiesis, characterized by randomly distributed foci of erythrocytic and/or myeloid progenitor cells accompanied by megakaryocytes, was present in the red pulp of the spleen in many treated dogs, and a few control dogs. One male dog (257024) that had been treated with 8 mg/kg 170222 also had foci of extramedullary hematopoiesis within hepatic sinusoids. The extent and degree of changes were similar in paraffin and methacrylate embedded sections. Four of the five dogs with documented circulating cytopenia (240602, 240692, 256364, and 257024) had the most prominent extramedullary hematopoiesis. No obvious differences in the extent or degree of extramedullary hematopoiesis were evident between control and treated dogs that did not have concomitant cytopenia.

4/5 dogs

Increased hematopoietic activity in the bone marrow was characterized by proliferation and relative increased cellularity of one or more of the hematopoietic progenitor cell populations. In one case (257063) only erythrocytic precursor cell populations were increased and was designated as erythrocytic proliferation. Unless otherwise specified, the increase was of mixed cellularity. These alterations were present in treated and control dogs. However, the degree of hematopoietic proliferation was greater in treated dogs, especially in those dogs that had been treated with 8 mg/kg of either olanzapine or 170222 and had concomitant cytopenia. This difference was due to changes in cytopenic dogs, as no obvious differences in the extent or degree of increased hematopoietic activity were evident between control and treated dogs that did not have concomitant cytopenia. More male dogs were affected that had been treated with 170222 than with olanzapine.

One female dog (240712) that had been treated with 8 mg/kg olanzapine was killed moribund during the course of the study. This dog had brown lung lesions at necropsy. Microscopically there was a severe diffuse pyogranulomatous pneumonia with numerous colonies of filamentous bacteria. This particular microorganism stained Gram positive and was partially acid-fast using the Fite's acid-fast stain, thereby indicating classification as a *Nocardia spp.* The other morphologic alterations present in this dog, such as myeloid proliferation in the bone marrow, were judged to be secondary to the severe inflammatory process in the lung and not related to treatment. One male dog (255432) that had been treated with 8 mg/kg olanzapine for the complete study duration had a focal, red lesion in the lung at necropsy. This lesion was characterized microscopically as a focally-extensive acute suppurative pneumonia. Neither of these instances could be attributed directly to treatment with olanzapine.

Hypospermatogenesis was seen in low numbers (1 or 2 of 4) in male dogs treated with either 4 or 8 mg/kg of olanzapine or 170222. The degree of change was greater at 8 mg/kg, however, there was no difference in effect between the two compounds.

Minimal to moderate necrosis of lymphoid cells was seen in treated and control male and female dogs. The degree of lymphoid necrosis was not apparently influenced by treatment. However, the incidence of these findings, especially in the spleen, tended to be more prevalent in dogs treated with 170222.

Summary and Conclusions:

Olanzapine and cpd 170222 are similar in structure with only a CH3 gr present in the 2 position of the thieno ring for olanzapine and a C_2H_5 for 170222 at that site. The effects of these 2 cpds were examined in dogs for 6mo at doses 4 and 8mg/kg. The findings in general, showed wide similarity of the effects of the 2 cpds. At doses that were equal on a per wt and equimolar basis, the effects of 170222 were either comparable or slightly greater than those produced by olanzapine. The 2 cpds caused a decr in mean wt gain and the main effect was on the hematopoietic system. Clinical signs included miosis and hypoactivity with severity being dose-dependent, tolerance seemed to develop with time. **Both cpds caused dose-dependent miosis, hyperreactive pupillary light response, and reduced response to mydriatic drug; the response was more intense at HD. Miosis was more severe** and noted in more dogs taking 170222 than those on olanzapine. At end of study, **miosis was observed in both dose grs of olanzapine** but the finding remained more severe and occurred in more dogs dosed 170222. The sponsor indicated that eye effects seemed to be neural since no structural damage was observed. However, the exact mechanism (sympathetic ve parasympathetic), and site (peripheral or CNS) could not be determined in this study.

Cytopenias in dogs treated with olanzapine were first observed at about 6mo of treatment. **Two HDf were affected, one had hemolytic anemia characterized by decr RBCs and erythroid hyperplasia of bone marrow, the 2nd female had neutropenia, thrombocytopenia, and myeloid hyperplasia of bone marrow.** Extramedullary hematopoiesis was seen in smears of livers and spleens at necropsy. However, serum from this dog did not inhibit the cloning activity of CFU-GM or CFU-MK progenitor cells in bone marrow cell culture system (*i.e. no bone marrow toxicity*). *Results of platelet-*associated IgG assay were equivocal but results of neutrophil-associated IgG assay were negative. These findings **suggested that olanzapine-induced cytopenia are due to effect of the drug on peripheral blood neutrophils and platelets rather than on marrow progenitor cells of these affected cell lines.**

Dogs dosed 170222 had cytpenias in 2HD after 2-5mo and in 1LD after 6mo. One of the HD dogs had **sustained marked neutropenia, thrombocytopenia, and moderate hemolytic anemia** (days 66-122). Bone marrow exam showed myeloid hyperplasia and adequate megakaryocytes. Smears from the liver and spleen at necropsy showed extramedullary hematopoiesis. The indirect PAIgG assay was positive on day 76 but equivocal on day 184. The indirect NAIgG was positive on day 62 but equivocal on day 184. Direct Coombs test was negative on days 76&84. The **2nd dog had only neutropenia** without anemia or thrombocytopenia. The neutropenia was marked and lasted till end of study. Bone marrow exam showed myeloid hyperplasia, smears of liver were negative whereas those of the spleen showed extramedullary hematopoiesis. The direct PAIgG was negative on day 136 and the indirect assay was negative on day 76 but equivocal on day 184. Results of NAIgG on day 170 were equivocal. The neutropenia for LD dog was moderate to severe with marrow cytology normal at necropsy. Impression smears of liver and spleen at necropsy were unremarkable. The indirect PAIgG on day 184 and indirect NAIgG on day 188 were equivocal. Both cpds affected clinical chemistry parameters in both sexes dosed the HD. Males dosed olanzapine showed sig incr in mean tot bilirubin, albumin and, the A/G ratio. Females dosed the HD 170222 had sig incr in ALT, GGT, cholesterol, and tot proteins. The incr in cholesterol has biological significance due to its early onset, persistence, and magnitude. There was no drug related findings on urinalysis. The mean absolute and relative wts (to B.wt and brain wt) of the **ovaries** were sig decr in all 4 grs dosed with the 2 test articles. Ovary wts decr 24% in LDf of olanzapine gr and ca. 50% in HDf of olanzapine and both doses of 170222. Mean **liver** wt in HDm of both test articles was sig incr (12-41%) relative to cont dogs. Relative mean **kidney** wt was sig incr (36-39%) in HDf of olanzapine gr. and sig incr noted in mean relative **adrenal** wt in HDm (both relative to B.wt and brain wt). Histopath findings included **increased incidence and magnitude of extramedullary hematopoiesis in cytopenic dogs, incr hematopoietic activity in bone marrow of cytopenic dogs, and hypospermatogenesis.** The incidence and the extent of the hematopoietic findings were higher in male dogs dosed 170222 than those dosed olanzapine.

2. 1-yr dog tox study/report# 18/Reviewed by Dr. Hollenbeck (Review Aug 1986).

Doses/No. animals per dose: 2, 5, 10mg/kg/d; 4/sex/dose; the cont received empty gelatin caps.
Route: oral capsules.
Parameters studied: survival, clinical signs, B.wt, food intake (visual estimate only), EKG, ophthalmology, clinical chemistry, hematology, bone marrow morphology and type of any abnormalities, immunology, blood levels, and gross and histopathology.

Results and Conclusions:
Survival: all dogs survived till end of study.
Clinical signs: hypoactivity and miosis observed in all treated dogs. Onset was 1-2hr postdose and lasted 4-6hr and sometimes all day. These dogs were normal by the next day. In the low dose dogs, these 2 parameters were absent after the 1st two doses. During month10, 1MD and 7HD dogs had intermittent tremors and restlessness (manifested as incr movement in cage, lifting of legs, and scratching the floor of the cage). Additionally, all HD dogs were ataxic 1-2hr post the 1st dose only.
B. wt. and Food intake: no effect except for the 1HD dog that lost wt continuously and refused to eat.
Ophthalmology: the only drug related finding was bilateral miosis. This effect occurred in 2MD and 3HD at 6months and end of study and in additional 3HD at end of study.
EKG: Lead II recorded from each dog prestudy and on day2, months 1,3,6,9, and end of study at 0 and 2hr postdose. Only random increases in HR noted in treated dogs and they were non dose-dependent.
Hematology, Bone marrow, Urinalysis, and Clinical Chemistry: no drug related finding except in1HD dog. This dog had hemolytic anemia with reticulocytosis*.

* this HD dog showed the following changes: 2 hemolytic anemia episodes with moderate reticulocytosis, sluggish bone marrow response, after the 1st hemolytic episode, sustained monocytosis, neutrophilia with left shift, leukocytosis, incr RBC sedimentation rate, early intermittent incr in ALT, incr in total serum immunoglobulin level, and mild-moderate intermittent bilirubinuria. The 1st hemolytic episode was characterized by long induction period of 5mo, severe anemia, and sluggish bone marrow erythrogenic response. The 2nd episode had a relatively shorter induction period (6wks), moderate severity, relatively rapid erythrogenic recovery by the bone marrow. These differences in the properties of the 2 hemolytic episodes suggested an immune mediated mechanism but contrary to the sponsor's suggestion, the reviewer does not find a correlation of these hemolytic findings to the cummulative drug levels since there was no difference in blood levels measured at 6 and 12mo (see attached table from sponsor)

Organ wts: dose-dependent decr in absolute and relative wt of the ovaries. No other changes.
Plasma levels: samples collected from all dogs at fixed times between 0-24hr of dosing on day1, months 1,3,6,9, and end of study. Several samples could not be analyzed due to interfering chromatographic peak. Plasma levels incr with dose with peak levels reached at 2-3hr at the low and mid doses and, 3-4hr in HD. Levels were slightly higher at end of study than values measured early on (see attached table by the sponsor). Exposure was proportional to dose. Half life ranged between 13-24hr in LD and 6-10hr in the MD&HD. Peak plasma levels at LD ranged between 37-208ng/ml, at MD 16-337ng/ml, and at HD 191-580ng/ml. The mean peak plasma levels for these doses ranged between 50±5 to 114±32ng/ml for LD, 151±24 to245±22ng/ml MD, and 325±26 to 456±46ng/ml HD. Mean $AUC_{ng.hr/ml}$ ranged between 636±43 to 912±77 LD, 1461±182 to 2164±218 MD, and 3895±244 to 5133±421 HD.
Gross and Histopath: no drug related finding.

1 yr. dog tox./Report #18

Attach to chronic tox. section

Table 6

Mean Plasma Levels of LY170053 in Dogs Given LY170053 Orally for One Year. Study 006184.

	Dose mg/kg	Day	Hours after Dose 0 (ng/ml)	0.5 (ng/ml)	1 (ng/ml)	2 (ng/ml)	4 (ng/ml)	7 (ng/ml)	12 (ng/ml)	24 (ng/ml)	AUC (ng-hr/ml)	Peak Time (hr.)	Peak Conc (ng/ml)	Half-life (hr.)
Mean	2	1	--	25.0	55.7	58.5	50.7	34.7	21.8	16.8	691.0	2	64.0	15.1
SEM			--	3.9	10.7	6.5	3.9	2.2	1.2	1.2	41.9	0	6.5	1.3
Mean	5	1	--	85.1	140.9	171.8	137.9	100.6	52.5	22.4	1460.7	3	181.4	7.3
SEM			--	4.3	41.7	16.0	27.5	17.4	9.9	3.4	284.6	0	29.6	0.2
Mean	10	1	--	98.2	246.5	393.5	349.0	287.5	149.7	69.4	4646.1	3	413.0	9.3
SEM			--	14.0	49.8	47.8	62.2	40.1	19.8	9.2	443.2	1	46.4	1.4
Mean	2	187	21.5	20.3	36.7	47.2	40.2	28.5	22.2	19.9	636.4	2	49.5	24.1
SEM			2.9	3.4	7.2	5.6	1.8	1.6	2.7	2.4	43.0	0	4.9	5.4
Mean	5	187	20.7	33.2	62.7	126.8	120.1	89.7	49.1	18.3	1460.7	2	150.9	10.4
SEM			1.6	10.6	27.4	29.8	17.5	12.6	8.3	1.9	181.7	0	28.9	2.5
Mean	10	187	38.3	41.9	228.2	320.0	292.8	254.9	143.5	41.9	3895.3	3	324.9	6.9
SEM			1.9	4.8	30.9	25.5	24.9	23.6	11.4	4.2	243.7	0	26.0	0.4
Mean	2	356	12.6	31.6	68.5	70.0	59.8	45.5	35.3	15.1	912.3	3	113.7	12.7
SEM			1.4	8.7	43.5	26.1	13.6	7.2	7.3	1.4	77.0	1	32.1	2.3
Mean	5	356	17.4	42.2	192.7	222.0	214.1	134.7	58.9	22.7	2163.6	2	245.4	6.0
SEM			1.7	6.4	17.5	30.3	20.6	15.7	8.7	4.2	217.6	0	21.9	0.4
Mean	10	356	43.3	96.7	257.8	422.4	412.3	332.3	189.4	47.9	5132.9	4	456.2	6.1
SEM			4.6	34.6	60.1	46.5	41.2	24.9	26.0	4.9	420.7	1	46.3	0.3

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It was concluded that dogs tolerated oral doses of olanzapine at 2 and 5mg/kg administered daily for 1yr. Clinical signs incr in severity with dose and included sedation, hypoactivity, and miosis. All dogs survived. Drug related effects included the findings in the 1HD dog that exhibited hemolytic anemia, reticulocytosis, and sluggish bone marrow erythrogenic responses (see above for detail). The effects in this dog suggested involvement of the immune system. The **NOEL in this study is 5mg/kg.**

3. Additional data for animal# 189083 from the 1-year toxicity study in dogs/report# 24/Reviewed by Dr. Atrakchi.

This is the dog from the above study (report# 18) that was administered the HD of 10mg/kg olanzapine for 1yr and developed hemolytic anemia and reticulocytosis. This dog was not killed at the end of the 1yr study, but retained for further assessment of its response to treatment (about 2yrs and 3mo). This report provides data not presented in the previous 1yr study (report 18) to include: clinical signs, physical and ophthalmologic exam, B.wt, hematology, clinical chemistry, urinalysis, organ wt, gross, and histopath.

Results and Conclusions:
This dog was not rechallenged for 29mo (the retaining period). There were no drug related findings on any of the measured parameters. Histopath findings were those of aging animals and included: incr fat in bone marrow, thymic hypoplasia, and slight hepatic congestion. The latter could have been caused by euthanasia as indicated by the sponsor. Therefore, these changes were nonspecific and considered unrelated to the drug and no long term effect or pathology noted on bone marrow.

4. 1-year oral toxicity study in Beagle dogs followed by 1-month reversibility period/report# 54/Reviewed by Dr. Atrakchi.

Doses/No. animals per dose: 2,5, 10mg/kg/d; 4/sex/dose (treatment phase); 4/sex/cont and 10mg/kg gr for reversibility phase. The cont received empty gelatin caps.
Route: oral capsules.
Parameters studied: survival, clinical signs, B.wt, food intake, EKG, ophthalmology, clinical chemistry, hematology, in vitro bone marrow cell culture, enzyme induction, TK, and gross and histopathology.

Results and Conclusions:
Survival: all dogs survived till end of study. **Treatment related neutropenia occurred in 4HD dogs.** Two f and 1m developed neutropenia with or without thrombocytopenia after 6-8wks of treatment. These 3 dogs were re-challenged with escalating doses at 2,4,8, and 10mg/kg, 2wks or longer at each dose. All 3 dogs again developed neutropenia, one dog after dosing with 2mg/kg, the other 2 dogs after receiving most of the doses; these dogs were removed from the study. Bone marrow biopsies revealed adequate no. of proliferative cells in these neutropenic dogs excluding bone marrow toxicity. The 4th dog was a male that developed neutropenia after 10-11mo of treatment. However, the neutropenia was not severe enough to warrent stopping treatment; neutrophil count seemed to improve with continued dosing (see hematology for more detail). A single LDf **developed hemolytic anemia after 10mo of dosing which progressed to myelofibrosis.** Also a MDm at termination developed anemia and bone marrow changes similar to those noted in the LDf. At necropsy, this MDm had hepatic amyloidosis. From serum chemistry analyses, it seemed that this dog had chronic inflammatory condition unrelated to drug treatment.
Clinical signs: hypoactivity, lethargy, and miosis observed in all treated dogs. The severity was dose-related. Dogs in mD&HD also developed tremors, hindlimb stiffness and weakness, and head pressing. HD dogs were ataxic during the 1st 3mo. **In MD&HD dogs, miosis was accompanied by conjunctivitis, decr tear production, ocular discharges, and blepharospasm.** Blepharospasm and

conjunctivits persisted through the recovery phase. The only signs during recovery phase were squinting and red and dry eyes.

B. wt. and Food intake: males and females of HD had markedly lower mean B.wt than the cont after days 300 and 335 respectively. Also mean wt gain was reduced in HD, at end of study, HDm&f weighed 1 and 2kg less than the corresponding cont dogs. Animal wts were comparable during the reversibility period. There was no apparent change in food intake in any gr. Supplemental diet was provided to 6HD dogs and 1 each male and female in the cont to maintain wt at different times of the study.

Ophthalmology: exams were done on all dogs pretreatment, 6mo, end of study, and on survivors at end of recovery phase. The exam was done 1-2hr postdosing; external exams and Schrimer tear test were done on dogs with signs of ophthalmic effects. Pupil size and pupillary light reflexes (PLR) were evaluated and eye lids, nictitating membranes, conjunctiva, cornea, sclera, and iris were also examined using focal light source. The fundus of each eye was evaluated by binocular indirect ophthalmoscopy. Findings included **miosis, altered PLR, and reduced tear production.** The latter was observed in 1/8, 2/8, and 4/16 for 2,5,10mg/kg doses respectively. Severity was dose-dependent. HD dogs also showed **incomplete mydriasis after using dilating agents** (Tropicamide 1%) and the more severe the miosis in this gr the greater incr reactivity of the pupil response and occurrence of blepharospasm in some dogs which was consistant with iris muscle spasm. Other findings included inflammation (conjunctivits) and discharge which according to the sponsor, were related to decr in tear production. The latter was not reversible by the end of dosing. The mechanism underlying miosis is unknown at this time.

EKG/Lead II: done shortly prior to dosing and 3hr postdosing on days1, 29, 186, and 361, and during the recovery phase days 371&393. Heat rate was assessed as well. HD dogs showed 24-30% incr in HR 3hr postdosing on days1&29, and end of study. This effect was absent during the recovery phase. There was no effect on EKG parameters in any gr.

Hematology: samples collected predose and at different intervals upto treatment day363 and recovery day393. In addition to the standard parameters, fibrinogen, Coomb's test, and bone marrow samples were done on selected dogs. Except as noted below, there were no sig drug related finding.

4 HD dogs (2m, 2F) showed **reversible neutropenia without a morphologic evidence of bone marrow toxicity, 3 of these dogs also had drug related thrombocytopenia.** Bone marrow was hypercellular with adequate proliferative pool cells but apparent decr in mature granulocytic cells specially seg neutrophils. The neutropenia occurred early in 3 dogs (wks6-8/early onset)(lasted 12-26days) and reversed quickly after drug withdrwal. In the 4th dog, neutropenia was less severe and reversed while the dog was still taking the drug, but it was delayed in onset (at wk 36) and lasted 50wks. In one of the early onset dogs, neutropenia was reinstated quickly upon rechallenge with 2mg/kg (1/5 of the 10mg/kg dose), in the other 2 dogs, the reinduction took longer at 6.5 to 9wks and required increasing doses of 2, 4, 8, and 10mg/kg per fortnight. Note that severe neutropenia meant 200/ul and thrombocytopenia of 75000/ul. Also, **there seemed to be no correlation between plasma levels and the hematology findings** as levels were comparable between neutropenic and noncytopenic dogs of the HD gr except in 1HD dog where plasma conc 24hr postdose was 262ng/ml (about 7-10x the values measured 24hr after dosing). In vitro culture of granulocytic precursors (CFU-GM Colony-Forming Units-Granulocyte) and platelet (CFU-MK) precursors from bone marrow of the 3HD neutropenic dogs and thrombocytopenic dogs showed adequate growth. Assays were conducted at various times during the initial neutropenic phase and rechallenge. For the dogs that were also thrombocytopenic, Colony-Forming Units-Megakaryocyte (CFU-MK) were done. Olanzapine tested at conc upto 1000ng/ml had no inhibitory effect on CFU-GM derived from untreated dogs. The sponsor concluded that olanzapine-induced neutropenia is likely caused by destruction of circulating neutrophils with possible effect on neutrophil maturation/storage compartment in bone marrow.

Clinical Chemistry: in addition to standard parameters, serum iron, total iron binding capacity, and fecal occult blood were determined on selected dogs. Results included small incr in total bilirubin in MD&HD dogs between months 4&11 and inconsistent and small changes in ALP and/or ALT in 2HDf and 1MDf

(<2x the upper limit of the normal range)
Urinalysis: no drug related finding.
Enzyme Induction: the activity of 7-ethoxyresorufin O-deethylase (EROD), benzphetamine N-demethylase (BND), and erythromycin N-demethylase (END) were determined in liver samples in addition to P450 content. A very small incr in EROD activity was observed in HDf at end of recovery period but no such effect noted at end of the study. No other findings.
TK: plasma levels were measured at different intervals between 1-24hr on day1, and months 3,6, and 12 of study. There were no sex differences, half life was about 6hr, max conc and AUC were proportional to dose and relatively linear, and exposure remained relatively constant over the study period (see attached table from sponsor). Mean max conc was 59, 178, and 284ng/ml for 2,5, and 10mg/kg respectively. Max conc was reached at 6hr indicating slow absorption. There was no drug detected in HD dogs 72hr and 1mo after the last dose, during the recovery period.

Dose (mg/kg)	Range of Conc (ng/ml)	
	Day1*	1yr
2	3-62	5-82
5	4-99	13-297
10	13-260	21-490

* Values were below detection limit of 1ng/ml at 1hr of measurement.

Appendix J (Continued).

Table 23.2.
Some Pharmacokinetic Parameters (Mean ± SD) in Male and Female Dogs Receiving Daily Oral Doses of LY170053 at 2, 5, or 10 mg/kg for One Year (D02093)

	Dose (mg/kg)	Sex	Mean C_{max} (ng/ml)	Mean T_{max} (hrs)	Mean AUC^{V} (ng x hr/ml)	Mean $t_{1/2}$ (hrs)
Day 0	2	M	57.1±8.66	7.0±0.0	515.6±78.8	4.5±1.4
		F	50.5±11.4	5.5±1.7	336.4±64.4	-
		M+F ave.	53.8	6.3	426.0	-
	5	M	121.7±20.6	6.3±1.5	1059.3±222.7	4.3±0.8
		F	184.5±61.2	4.3±2.1	1693.5±625.5	4.1±1.1
		M+F ave.	153.1	5.3	1376.4	4.2
	10	M	202.0±48.5	6.9±2.5	2391.0±329.1	11.8±11.4
		F	266.9±116.2	5.0±4.4	2686.4±382.6	6.2±2.5
		M+F ave.	234.5	6.0	2538.7	9.0
Month 3	2	M	60.5±35.4	8.5±4.7	530.5±146.1	5.8±1.0
		F	41.7 ± 6.2	8.0±0.0	355.5±32.4	4.6±0.7
		M+F ave.	51.1	8.3	443	5.2
	5	M	115.4±18.3	5.5±3.0	1305.2±168.1	5.2±0.3
		F	186.5±44.0	5.0±2.0	1756.9±535.2	5.9±0.9
		M+F ave.	151.0	5.3	1531.1	5.6
	10	M	236.4±74.2	5.7±2.1	2757.0±911.3	5.8±0.7
		F	334.5±63.3	4.7±1.6	2971.1±474.9	5.5±0.9
		M+F ave.	285.5	5.2	2864.0	5.7
Month 6	2	M	75.5±9.8	2.5±3.0	717.2±236.1	5.1±0.8
		F	57.8±22.9	8.8±3.9	644.7±153.0	4.4±1.0
		M+F ave.	66.7	5.7	681.0	4.8
	5	M	167.0±35.8	6.3±1.5	1606.3±453.2	5.3±0.4
		F	238.3±81.1	4.3±2.1	2238.1±332.9	5.1±0.6
		M+F ave.	202.7	5.3	1922.2	5.2
	10	M	217.7±59.0	7.3±2.4	2276.3±405.5	5.4 ± 0.7
		F	379.8±101.8	4.2±2.5	3491.9± 809.9	5.4 ± 0.4
		M+F ave.	298.8	5.8	2884.1	5.4
Month 12	2	M	65.9±25.0	8.3±4.8	721.6±210.9	5.9±1.3
		F	63.7±20.3	5.0±1.7	670.8±156.4	6.2±0.6
		M+F ave.	64.8	6.7	696.2	6.1
	5	M	154.3±21.9	6.3±1.5	1701.0±225.5	6.2±0.8
		F	255.5±102.8	3.0±1.2	2608.8±851.4	6.2±1.0
		M+F ave.	204.9	4.7	2154.9	6.2
	10	M	281.1±79.6	7.0±0.0	3149.9±813.5	5.5±0.7
		F	349.3±106.1	3.7±2.6	3641.1±754.0	6.3±1.2
		M+F ave.	315.2	5.4	3395.5	5.9

V = 0 - t

Organ Wt.: there were no sig drug related changes.
Gross and Histopath: drug-related **delayed estrous was observed in half MDf and all HDf as** indicated by immature uteri and absence of luteal remnants in the ovaries. This finding was reversible in the recovery phase with the return of the cycle. Other findings included: (1) myelofibrosis in 1LD which was removed from the study (see below), (2) early myelofibrosis with moderate extramedullary hematopoiesis in liver and spleen and tri-lineage expansion of bone marrow in 1MDm, (3) hepatic amyloidosis with hepatocellular atrophy that led to sinusoidal congestion and hepatomegaly in 1HD dog, and (4) slight and nonspecific vacuolar hepatocellular change in another HD dog.

The 1LDf and 1MDm had hemolytic anemia, bone marrow hypercellularity, and marrow fibroplasia, these findings are consistent with beagle dog myelofibrosis **as indicated by the sponsor. The hemolytic anemia had properties of an autoimmune reaction with agglutination of RBC in the** cold and a positive Coomb's test. The anemia was persistent despite discontinuation of treatment, administration of transfusion, and steroid therapy. Bone marrow changes in this LD dog, included hypercellularity and myelofibrosis proceeding through reticulin sclerosis and fibrosis. This condition **was seen in the breeding colony from which these dogs were obtained however, a drug-related** effect can not be ruled out. Two reports from JA. Bell and S. Moncrieff the former is a Staff Vet at Marshall farms from which these dogs were obtained. Dr. Bell indicated that Marshall farms had identified a cohort of pregnant or lactating females with regenerative anemia caused by myelofibrosis of unknown origin, similar to what is reported here. However, these and other female beagles were eliminated from the breeding program. Dr. Bell indicated that **Marshall farms has never seen a case of myelofibrosis in nulliparous females or males and concluded that the finding in Lilly's study differed from the Marshall farm dogs.** Dr. Moncrieff reviewed the medical record for the affected dogs and concluded that the findings are **compatible with idiopathic anemia which is suspected to be of immune-mediated mechanism.** He also concluded that since the hematologic changes are similar to those previously described in beagles and occurred in the LD gr, the anemia and myelofibrosis could be drug unrelated (both reports are attached). **It is the opinion of the reviewer that these hematological findings are drug related since hematological findings of similar and different nature have been reported in other species dosed with olanzapine.**

The hepatic amyloidosis noted in 1HD dog was contributed to inflammation based on serum chemistry and hematology findings for this dog. Note that a specific site or the nature of such inflammation could not be identified, the sponsor indicated that such findings might have been masked by the profound lethargy and sedation in this animal. The serum chemistry effects included an incr in ALP which according to the sponsor, is consistent with compression of the hepatic cords by amyloid deposition and consistent with other amyloidosis reported for dogs and humans (Levine 1962, Loeven 1994, Thornburg & Moody 1981). There was no signs of hepatic tox since ALT levels were only slightly elevated. A NOEL could not be established for this study.

Attachment F-1.

MARSHALL
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September 7, 1994

Dr. Lori Palley
CLinical Veterinarian,
Lilly Research Laboratories

Dear Dr. Palley:

This letter is to confirm our telephone conversation regarding the female beagle, 2124289, that developed myelofibrosis while on study at Eli Lilly.

Several years ago, we discovered a cohort of pregnant or lactating female beagles with non-regenerative anemia at Marshall Farms. On investigation, this was found to be caused by myelofibrosis of unknown origin. It appeared that there was a familial tendency. The pedigrees of affected animals were carefully studied. Sires of common families and affected females were eliminated from the breeding program. As a result, the prevalence of this disease at Marshall Farms has now dropped to near zero. The sire of beagle 2124289 was removed from stud service in 1992. Of the twelve daughters of this sire kept in the breeding colony, three developed periparturient anemia, probably due to myelofibrosis.

Marshall Farms has never seen or had reported a case of myelofibrosis in nulliparous females or male dogs. All affected animals were either pregnant or nursing a litter, and most had had two or three litters before the disease was expressed. In this respect, the dog in your study differs from the anemic dogs at Marshall Farms.

I hope this information is sufficient for your purposes. Let me know if I can be of more help.

Yours truly,

Judith A. Bell

Judith A. Bell, DVM, PHD
Staff Veterinarian

Attachment F-2.

Report to Lilly Research Laboratories concerning study D02093

On September 6th 1994 I examined Beagle dog number 259611 which was in the low dose group of study D02093. I also reviewed radiographs, the medical record, from 07-21-94 to 09-04-94 and hematologic data from 07-20-94 to 09-02-94.

Abnormalities identified on physical examination of a female intact beagle identified as dog 259611 were pale mucous membranes, cranial organomegaly (liver or spleen), and a grade I/VI systolic murmur. Abnormalities observed on lateral abdominal and thoracic radiographs were splenomegaly. Hematologic data showed a severe non-regenerative anemia which was first identified on 07-21-94 and had become more severe over the next 6 weeks. The anemia was unresponsive to immunosuppressive therapy with prednisone and cyclophosphamide at appropriate doses. Erythroid hyperplasia and myelofibrosis was reported on evaluation of bone marrow histopathology.

This history, physical examination findings, hematological data, and bone marrow findings are compatible with the idiopathic anemia and myelofibrosis which is described in my paper which will be published shortly in the Journal of the American Veterinary Medical Association (Treatment of 5 cases of nonregenerative anemia with human intravenous gamma globulin. *JAVMA in press*). This syndrome of anemia and myelofibrosis is also described in a paper in *Toxicologic Pathology* (A review of myelofibrosis in dogs W.J. Reagan 21:164-169, 1993). The myelofibrosis in these dogs is suspected to be due to immune-mediated mechanisms. Since beagle 259611 had clinical and hematologic changes similar to those previously described in beagles, and since the dog was in the low dose group, the anemia and myelofibrosis observed may be a spontaneous occurrence unrelated to the study compound.

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11/2/94

Summary and Conclusion:

Oral administration of olanzapine to beagle dogs for 1yr at 2, 5, 10mg/kg caused no deaths. Clinical signs are those observed previously and included miosis, hypoactivity, lethargy. In MD&HD dogs, miosis was accompanied by conjunctivitis, decr tear production/dry eyes, ocular discharges, and blepharospasm. Blepharospasm and conjunctivits persisted through the recovery phase. The only signs during recovery phase were squinting and red and dry eyes. Mean wt and wt gain were sig reduced in HD dogs. Ophthalmology findings included **miosis, altered PLR, and reduced tear production.** The latter was observed in 1/8, 2/8, and 4/16 for 2,5,10mg/kg doses respectively. Severity was dose-dependent. HD dogs also showed incomplete mydriasis after using dilating agents (Tropicamide 1%) and the more severe miosis in this gr led to incr reactivity of the pupil response and to blepharospasm in some dogs which was consistant with iris muscle spasm. Other findings included inflammation (conjunctivits) and discharge which according to the sponsor, was related to decr in tear production. The latter was not reversible by the end of dosing. The mechanism underlying miosis is unknown at this time. Heart rate in HD was incr 24-30% at 3hr postdose on days 1&29 and end of study; no changes in EKG. **The main findings were those of hemolytic anemia and myelofibrosis in 1LD and 1MD dogs, neutropenia and thrombocytopenia in 4HD dogs, hepatic amyloidosis with hepatocellular atrophy that led to hepatomegaly in 1HD dog, and slight and nonspecific vacuolar hepatocellular change in another HD dog.** The hematological findings of hemolytic anemia and myelofibrosis are thought to be due to an immunologically-mediated mechanism induced by olanzapine and not drug unrelated. Neutropenia and thrombocytopenia found in 4HD dogs was similar to those noted previously in the 3mo dog study and in rodent tox studies. The neutropenia in this study similar to the 3mo study, recovered when treatment was stopped and dogs became neutropenic again when re-challenged. These dogs had no bone marrow toxicity as indicated by adequate number of immature neutrophil precursors in marrow cytology as well as no effect on the cloning activity of granulocytic or platelet precursors. The hepatic amyloidosis noted in 1HD dog was contributed to inflammation based on serum chemistry and hematology findings in this dog. The serum chemistry effects included an incr in ALP which according to the sponsor, is consistent with compression of the hepatic cords by amyloid deposition and consistent with other amyloidosis reported for dogs and humans. Other drug related finding was lack of estrous in MD&HDf which might have been due to hormonal changes since olanzapine was shown to affect prolactin levels. Normal estrous returned during the recovery phase. Mean max conc were 59, 178, and 284ng/ml for 2,5, and 10ng/kg respectively. Max conc was reached at 6hr indicating slow absorption. There was no correlation between plasma levels and neutropenia. A NOEL could not be established for this study.

Summary and Conclusions for Subchronic and Chronic Tox Studies

The potential toxicity of olanzapine was examined in rodents and dogs dosed repeatedly at durations that ranged from 2wks to 1yr. The doses tested in mice were 3 to 45mg/kg/d, doses in rats were 0.25 to 54mg/kg/d and those in dogs were 2 to 40mg/kg/d. Common clinical signs in rodents and dogs included hypoactivity, lethargy, and miosis (except in mice). Other signs included catatonia in mice that lasted for several hrs postdose, in rats incr lacrimation, and some animals of high doses showed hyperirritability and mydriasis, dogs showed restlessness, tremors, and head pressing. The main drug related findings included **hematology, ophthalmology, organ wt changes, and histopath of uterus, mammary glands, and ovaries.**

Olanzapine affected the hematopoietic system in mice, rats, and dogs of both sexes, the mechanism seemed to be via an immunological effect and not bone marrow site. Male B6C3F1 mice dosed 5, 15, 45mg/kg/d for 3mo showed 36, 65, and 70% decr in lymphocytes and neutrophils relative to the cont with individual data in all drug grs being lower than the normal range. WBC count was also reduced in female mice mainly in high dosed females at 53% less than the corresponding cont values. CD1 male mice showed dose-dependent reduction in WBC count at end of 3mo dosing with 3, 10, and 30mg/kg/d at 52-68% decr in lymphocyte and 48-80% decr in neutrophils. CD1 females dosed 30mg/kg showed a sig decr in lymphocytes at end of study. These females only at 2mo, had sig decr in RBC count, Hb, and PCV. In a 2wk tox study in CD1 mice, dose-dependent decr in lymphocytes and neutrophils with total depletion of leukocytes, was measured in males and females dosed at ≥45mg/kg/d. Olanzapine had no effect on any hematology parameter in rats dosed for 2wks at 2, 6, 18, and 54mg/kg/d. However, a sig decr in lymphocyte count was measured in rats dosed 22.5mg/kg/d for 3mo and a dose-dependent incr in Hb, MCV, & MCHC values noted in females dosed 2.5, 7.5, and 22.5mg/kg/d. Male rats dosed 16mg/kg/d for 6mo, showed a 27% decr in WBC count due to a decr in lymphocytes (29%) and neutrophil (20% of the cont). This decline in WBC persisted during a 1mo recovery period. Reticulocyte count was also reduced in males dosed 4&16mg/kg (3-14%) and females dosed 16mg/kg (12%). Dose-dependent incr noted in male and female rats dosed 4&16mg/kg in MCV, MCHC (only in males), and MCH. In a 1yr tox study, the WBC count was reduced in male and female rats dosod 16mg/kg/d but without a sig change in cell type distribution. There were 5 of 20 male rats in this gr with WBC values lower than the normal range. In this 1yr study, the mean levels of Ht, PCV, MCV, and MCH were consistently elevated in both sexes measured at 6 and 12mo without an effect on RBC count. Histopath finding included dose-dependent bone marrow hypocellularity in rats dosed 4&16mg/kg/d for 1yr with >70% of these rats showing this pathology. In dogs, erythrocyte parameters and erythroid precursors of bone marrow were depressed in males and females dosed 40mg/kg/d for 2wks. These dogs and those dosed 10 and 20mg/kg/d had lymphoid depletion of the thymus. In a 3mo study, 1 male dog dosed 10mg/kg/d developed severe neutropenia, thrombocytopenia, and bone marrow erythroid hypoplasia on day34 of treatment. Treatment was stopped and the dog recovered. This dog was re-challenged twice with 10mg/kg and a 3rd time with 2mg/kg olanzapine; the hematologic findings were reproduced within 4-9days of each re-challenge. Immunological investigation showed incr in soluble immune complex levels and in the amount of ^{14}C-olanzapine bound to serum immunoglobulin. These results suggested that olanzapine-induced neutropenia and thrombocytopenia were immune-mediated and not a drug effect on the myloid component of the bone marrow. In a 6mo study, the effects of olanzapine were compared to those of cpd 170222, an analog that differs from olanzapine by having an ethyl instead of a methyl gr at position 2 of the thieno ring. Cytopenias occurred in dogs dosed with either cpds. In 2 female dogs dosed 8mg/kg olanzapine cytopenia was observed at 6mo of dosing, one dog showed hemolytic anemia with decr RBCs and erythroid hyperplasia of bone marrow, the 2nd dog had neutropenia, thrombocytopenia, and myeloid hyperplasia of bone marrow. Liver and spleen smears showed extramedullary hematopoiesis but without apparent bone marrow toxicity as indicated by the absence of inhibition of cloning activity of CFU-GM or CFU-MK progenitor cells in bone marrow. The results from platelet-associated and neutrophil-associated IgG assays were equivocal and negative respectively. These results suggested

that olanzapine-induced cytopenia is due to an effect of the drug on peripheral blood rather than a bone marrow toxicity. The findings in dogs dosed cpd 170222 were similar to those of olanzapine but slightly more severe. Histopathology for both cpds showed extramedullary hematopoiesis in liver and spleen and incr hematopoietic activity in bone marrow. In a 1yr study, one dog dosed 10mg/kg/d showed 2 episodes of hemolytic anemia with reticulocytosis and sluggish bone marrow response. Following the 1st episode, there was persistent monocytosis, leukocytosis, incr RBC sedimentation rate, incr in total serum immunoglobulins, and mild-moderate bilirubinuria. The 1st episode had a long induction period of 5mo whereas the 2nd had a short one at 6wks with relatively rapid erythrogenic recovery of bone marrow. The sponsor concluded that based on these differences in the properties of the 2 episodes, olanzapine-induced hemolytic effects are immune-mediated. In a 2nd 1yr dog study, olanzapine effects were re-examined using the same doses of 2, 5, and 10mg/kg/d. Similar to the other studies, drug-related hemolytic findings (neutropenia in this case) were observed in 4 dogs dosed 10mg/kg/d. Two females and 1m developed neutropenia with or without thrombocytopenia after 6-8wks of treatment. Upon rechallenge with escalating doses of olanzapine, all 3 dogs again developed neutropenia; bone marrow tox was excluded. Another dog dosed 10mg/kg developed neutropenia after 10-11mo, but treatment continued and neutrophil count improved with time. A female dosed 2mg/kg developed hemolytic anemia after 10mo of dosing which progressed to myelofibrosis. A male dog dosed 5mg/kg also developed anemia and bone marrow changes at end of study and later was diagnosed with hepatic amyeloidosis but serum chemistry analyses revealed chronic inflammation that was unrelated to the drug. In all 4 dogs, there seemed to be no correlation between plasma levels and the hematological findings except in 1 dog where blood levels were 7-10x the values measured 24hr postdose of unaffected dogs. Immunological tests were done and the sponsor concluded that olanzapine-induced neutropenia is likely caused by destruction of peripheral neutrophils with possible effect on neutrophil maturation/storage compartment in bone marrow. Histopath exam of the female dog dosed 2mg/kg and male dog dosed 5mg/kg that had hemolytic anemia, revealed bone marrow hypercellularity and marrow fibroplasia. The sponsor indicated that these 2 conditions are consistent with beagle dog myelofibrosis. The anemia was persistent despite termination of dosing, administration of transfusions, and steroid therapy and had properties of an autoimmune reaction with agglutination of RBC in Coombs test. The sponsor consulted 2 pathologists one of which Dr. Bell, was associated with Marshall farms where these dogs were purchased. Dr. Bell indicated that Marshall farms had previously identified a cohort of pregnant or lactating dogs with regenerative anemia caused by myelofibrosis of unknown origin, similar to what is reported here. These animals were eliminated from the breeding program. Dr. Bell stated in his report that Marshall farms had never seen a case of myelofibrosis in nonpregnant dogs or males and concluded that the finding in Lilly's study is different from the Marshall farm dogs. On the other hand, Dr. Moncrief concluded after reviewing the medical records for the affected dogs in Lilly's study, that these cases are similar to idiopathic anemia which is suspected to be of immune-mediated mechanism. He also concluded that anemia and myelofibrosis are unrelated to drug treatment since it occurred in low dose and have been previously described in beagle dogs. It is the opinion of the reviewer that olanzapine-induced hematological findings are drug related since they have identified in more than one species and in both sexes.

The ophthalmological findings were seen in dogs treated for 2wks, 6mo and 1yr at doses between 2-40mg/kg/d. In the 2wk study, miosis occurred in all drug grs but could not be correlated with dose. There was dose-dependent and sig reduction in lacrimal flow 6hr postdose. These dogs had normal pupil reflexes but pupils of dogs dosed 40mg/kg did not dilate completely in response to application of dilating agents. The mechansim of miosis in this study could not be deduced. No effect on ophthalmology was noted in a 3mo tox study in dogs dosed 2, 5, or 10mg/kg. In a 6mo tox study, dose-dependent miosis hyperreactivity to pupillary light response, and reduced response to mydriatic drug were seen in dogs dosed 4&8mg/kg/d. Similar to the 6mo study, dogs dosed 2,5, 10mg/kg for 1yr showed dose-dependent miosis, altered pupillary light reflex, and reduced tear production. In HD dogs blepharospasm was also noted. Other findings included conjunctivitis and discharge; tear

production was reduced and was irreversible by end of study. The doses used in the 1yr were the same doses used in the 3mo study where no ophthalmological findings were observed. The sponsor related the ophthalmological results to the anticholinergic effect of the drug.

In a 3mo oral gavage mouse study, histopath exam showed lymphoid depletion of the spleen and moderate multifocal lymphoid necrosis in all drug grs (3, 10, 30mg/kg/d) in addition, non dose-dependent mammary gland acinar hypertrophy, ductal ectasia, and ductal epithelial hypertrophy were seen in these 3 drug grs. Rats orally dosed for 3mo at 2.5, 7.5, and 22.5mg/kg/d had dose-dependent reduction in relative wts of the ovaries and uteri; without histopath findings. Dogs orally dosed at 10, 20, 40mg/kg/d for 2wks had lymphoid depletion of the thymus in all drug grs without histopath findings. The relative wt of the testes was sig reduced in rats dosed 10mg/kg/d for 3mo and histopath exam showed hypospermatogenesis. The decr in testes wt in this study might have been secondary to wt loss in this gr. The absolute and relative wt of the ovaries were reduced in female rats dosed 4&16mg/kg/d for 6mo and uterine wt remained depressed in rats dosed 16mg/kg through the 1mo recovery period. Also in this study, the relative wt of the adrenals in male rats dosed 16mg/kg/d was incr and histopath showed decr in vacuolation of cortical cells that persisted through the1mo recovery period at which time the vacuolation was also observed in males dosed 4mg/kg/d. Histopath exam showed mammary gland changes in males and females in this 6mo study. In males dosed 4&16mg/kg/d tissue morphology was changed from the normal lobuloalveolar to tubuloalveolar pattern and secretions were present in female rats dosed 16mg/kg/d. The incidence and prominance of mucoid metaplasia of vaginal epithelium were incr in females dosed 4&16mg/kg/d and ovarian follicular prominance was also incr in females dosed 16mg/kg/d. These mammary gland changes reversed during the recovery period. Uterine hypoplasia was observed in females dosed 4&16mg/kg/d at end of study and in females dosed 16mg/kg/d at end of recovery. There was thecal prominance in the ovaries of females dosed 4&16mg/kg/d. The findings in the ovaries and uteri were considered secondary to reduced wt in these animals. In a 1yr oral study in rats, the absolute and relative wt of the adrenals were incr in rats (m+f) dosed 16mg/kg/d and the relative wts of the ovaries and uteri were decr in females of this dose; there was no histopath findings. Dogs treated for 6mo showed a sig decr in absol and rel wts of the ovaries in animals dosed 4&8mg/kg/d. A sig incr noted in the rel wt of the adrenals in male dogs dosed 8mg/kg/d; no histopath findings. Similarly, in a 1yr dog study, the absol and rel wt of the ovaries was dose-dependently reduced (doses 2, 5, 10mg/kg/d); no histopath findings. In a repeate 1yr dog at the same doses, in contrast to the 1st study, there were no marked changes in any organ wt. However, there was a reversible dose-related delay in estrous in half of the dogs dosed 5mg/kg and all dogs dosed 10mg/kg; no histopath.

Plasma levels in mice, rats, and dogs incr with increasing dose, the incr was non-linear as the dose increased. Some indication of drug accumulation was noted as plasma levels measured later in the study were higher than those measured earlier (say day30 vs. Day1). Olanzapine in all of the subchronic and chronic studies was administered orally (gavage in rodent and capsule in dogs). In all species there was no sex difference (except in mice dosed 45mg/kg/d for 3mo). In mice mean plasma levels ranged between 35-431ng/ml in males and 52-861ng/ml in females at dosed 5, 15, and 45mg/kg/d. Peak level were reached 0.5-1hr postdose and PK followed 2 compartment model with rapid phase half life of <1hr and the slow phase half life of ≥12hr. In rats dosed for 3mo, mean plasma levels ranged between 0.1-4ug/ml with means between 0.13 to 2ug/ml at 2.5, 7.5 and 22.5mg/kg doses. Mean max conc in rats dosed for 6mo at 1, 4, 8, and 16mg/kg/d were 24, 241, 802, and 2076ng/ml respectively, the corresponding values for AUC were 222, 1282, 6579, and 29109ng.hr/ml. Mean Tmax reached between 0.5-8hr and, elimination half life ranged between 1-48hr. Mean max conc in dogs dosed for 1yr at 2, 5, and 10mg/kg were 114, 245, and 456ng/ml respectively, and the corresponding AUC values were 912, 2164, and 5133ng.hr/ml. Mean Tmax was 2-3hr and mean elimination half life ranged between 6-24hr. Some degree of acummulation was noted with time and high doses. Dogs dosed for 14days, peak plasma levels at 40mg/kg/d reached 1.7ug/ml on day 14 and 0.9ug/ml on day1 indicating some accumulation.

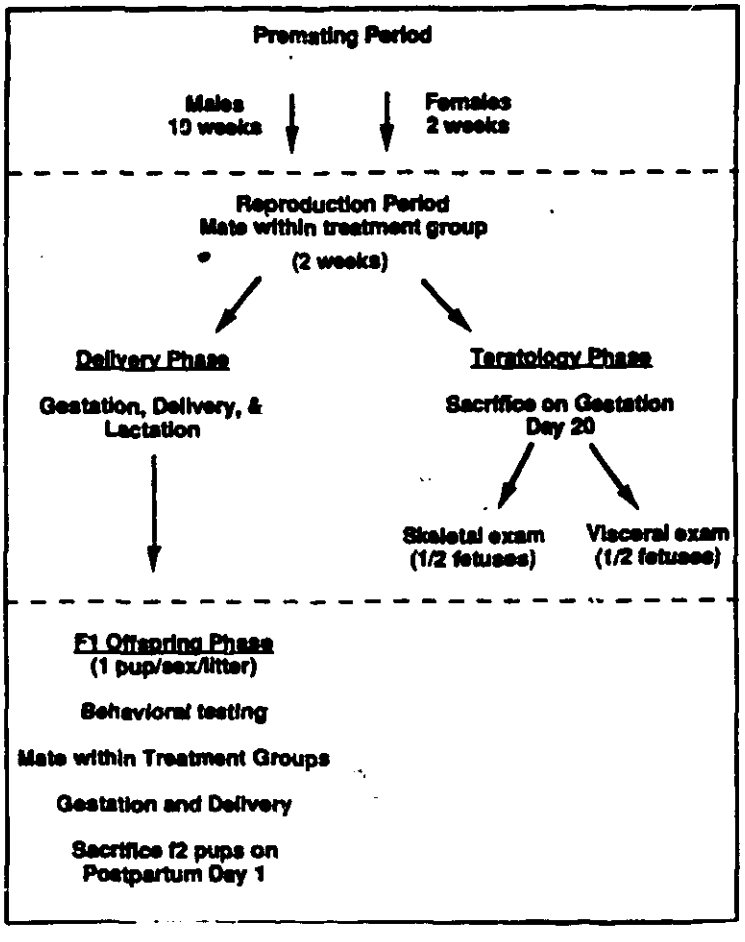
REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

- Fertility, perinatal, and postnatal study of olanzapine given orally to rats with behavioral and reproductive assessment of F1 generation/Report# 44/Study# R01192, R01292, R01392, R01492/Lilly labs, IN/1992/GLP. [Combined Segment I and III study]
Lot# 58962; purity 100%

Strain/age and/or wt:	CD-SD/5wks F0m and 10wks F0f/161±2g males (study# R01192); 225±1 and 212±1g females studies R01229&1392 respectively.
Dose/route/duration/rat # per dose:	0.25, 1.1, 5mg/kg/d/oral/F0m 18wks (10wks prior to mating & throughout 2 mating periods); F0f (study#R01292/Delivery gr) 11wks (2wks prior to mating and throughout mating, gestation, and lactation; F0f (study#R01392/Fertility gr) 7wks (2wks prior to mating and throughout mating and gestation). F1 generation no treatment/F0 generation 20/sex/gr; F1 generation 20,20,18, and 11 offspring/sex in 0, 0.25, 1.1, and 5mg/kg/d respectively.

See protocol design below from the sponsor

Figure 1. Design of Definitive Fertility Study of Olanzapine



The drug was prepared as suspension in 10% w/v aqueous acacia solution.
The basis for dose selection: previous tox studies with CD and F344 rats. Male fertility study using

F344 rats (# R11483): fertility not affected at 2.5 and upto 22.5mg/kg only mating activity was depressed at 22.5mg/kg. In a female fertility study (#R15185): fertility and no. of liveborn pups were reduced at 10mg/kg and a small reduction in fertility observed at 3mg/kg dose. Therefore, 5mg/kg was chosen in the present study as the HD to produce mild effects on fertility and other parameters. The 0.25mg/kg was selected because it had little effect on prolactin plasma levels in F344 rats (#R38090).

Results:

Survival: all animals in F0 and F1 generations survived.

Clinical Signs: were minimal noted mainly in HD rats of F0 generation and included ptosis in 19/20m and 20/40f and, hypoactivity in 17/20m and 40/40f. These signs occurred during the 1st wk of dosing and were absent on the next day prior to dosing. Two females of HD each had a single subcutaneous nodule that was diagnosed later as mammary gland adenoma, observed on days 43 and 58. One of these females delivered a litter and killed on ppd 21, the other female rat was not pregnant and was killed on postmating day25. The sponsor indicated that mammary gland adenomas are common and occur spontanteoulsy in adult females.

B.wt, Food Intake, and Efficiency of Food Utilization (EFU) - **F0/Males: a sig decr in wt gain** of HDm during the last 3wks of the 10wk premating period and **mean wt was also reduced** (10%) in these rats at end of study. This decr in wt was accompanied by a **decr in EFU** starting on day21 and through the study period. None of these parameters were affected at the 2 other olanzapine doses. Food consumption was unaffected in males.

F0/Females: HDf (both that delivered and those used in the teratology study), **mean wt and wt gain incr sig** during **premating period** (these incr also noted in MDf of teratology gr). **Food intake was sig incr in MD&HDf of the delivery gr and in all 3 drug gr of the teratology study.** However, during **gestation and postpartum periods mean B.wt and food intake of HDf in the delivery gr were reduced 7-10%.** The changes in **EFU corresponded to those of food intake** in HD: the mean EFU was incr sig during premating period days 1-7 in females from both studies and decr sig during gestation period days 0-6. In MDf of the teratology study the decr in EFU continued during gd 7-13.

Estrous cycle- F0 delivery gr: **prolonged** diestrous was observed in all HDf (20/20) and in 9/20 MDf during the 2wk premating period.

Mating Performance & Fertility: - F0: **mating index (MI) was reduced** (55 vs. 100% cont) in HDf in the delivery gr (MI values were 20, 20, 19, and 11 for cont, LD, MD, and HD respectively). In these females, **precoital interval was increased** (5.7days in HDf vs. 2.7days in cont). The MI was also decr (70 vs. 100% cont) in HDf of the teratology gr (MI values were 20, 20, 19, and 14 for cont, LD, MD, and HD respectively). Also, the precoital interval was prolonged in those pairs (6.3days in HDf vs. 2.7days in cont). **Fertility was unaffected by treatment in any gr.** Note that 3 of 20 HDm did not mate with either of the females with which they were cohabited (in the delivery gr). In the teratology study, 6/20 HDm did not mate with the females they cohabituated with.

Reproductive Parameters F0/females of the delivery group: there was **no drug effect on gestation length, litter size, or live birth indices.** Mean litter sizes were: 15, 16.3, 16.1, and 15.5 pups in cont, LD, MD, and HD respectively. Live birth indices were 100, 100, 99, and 99% in cont, LD, MD, and HD respectively. **F1 progeny of F0 delivery gr: there was no drug effect on total no. of liveborn** (299, 324, 287, and 167 in cont, LD, MD, and HD respectively), **B.wt, or sex ratio.** The low no. of fetuses in HD was due to lower no. of mated females (9/20 vs.20/20 in cont , 20/20 in LD, and 19/20 in MD), and not due to decr fertility or smaller litter size. At ppd21, survival was 100, 99, 99, and 99% in cont, LD, MD, and HD respectively. Also drug treatment had no effect on incisor eruption on ppd 10-12 or on eye openning on ppd 15-17.

F1 Observations and Necropsy/F0 delivery gr: in pups that were dead or died during lactation, no drug related findings were found upon external exam of 0, 2, 3, and 5 pups from cont, LD, MD, or HD gr respectively. Also, there was no effect on gross or internal exam of 39, 40, 36, and 22 weanlings of these grs.

Reproductive Parameters F0/females of the teratology group: there was no drug effect on number of corpora lutea, number of implantations, postimplantation loss, and live fetuses per litter. An incr was observed in MDf as follows:

Parameter	mean±s.d. Drug	cont	Percent (mean±s.d.) Drug	cont
Early resorptions	1.25±1.18	0.56±0.86	8± 7.5	3.6±5.7
Late resorptions/litt	0.06±0.25	0	0.42±1.7	0
Total resorptions/litt	1.3±1.1	0.6±1.0	8.5±7	3.6±5.7
Sum and percent of litters with resorptions	11/69%	7/39%	NA	NA
No. and percent of nonlive implants/litt	1.4±1.2	0.6±1.0		
	9±7%	4±5.7%	NA	NA
Litters with nonlive implants/sum&%	11(69%)	7(39%)	NA	NA

none of the above values reached statistical sig. Also there was no effect on number of live fetuses per litter in this gr of females.

Fetal Parameters/F0 Teratology Study: number of fetuses examined was 247, 260, 227, and 183 for cont, LD, MD, HD respectively. There was no drug effect on fetal wt or on the number of fetuses with malformations (# fetuses with malformations: 3, 4, 3, and 1 from cont, LD, MD, HD respectively). There was however, slight growth retardation in fetuses from HDf as indicated by higher number of fetuses with incomplete ossification and/or wavy ribs with incidences slightly higher than the historical values.

F1 B.wt, Food Intake, and EFU: there was no drug effect on mean wt or wt gain of males or females during the growth period except as noted. 4/11 HDm on ppd36 weighed 100g less than other males in this gr. Note that these males were 10-13days younger than the other males because of delay in mating of parental rats which could explain the smaller wt (i.e the decr in wt was drug unrelated). Mean wt and wt gain of F1 females during gestation was incr in the LD&MD grs which could explain the larger litter sizes delivered by these females. Food intake was unaffected in males but increased intake noted in MDf on ppd36 and LDf on gd0-6. EFU was sig incr in F1 HDm during the growth period; no effect on EFU for F1 females.

Postweaning Behavioral Effects/F1: **Activity testing**: rats were monitored at age 30, 60, and 140-160days. There was no drug effect on photocell counts determined during 1hr sessions or on rate of habituation. Activity was reduced in males age 30 in LD&MD grs and females age 60d in MD&HD gr relative to the cont. However, these rats were re-tested at age 140-160d and activity was comparable to that of the cont. **Auditory Startle and Passive Avoidance Responses:** no drug related findings on either parameter (rats tested at 19 and 55days of age for the auditory startle response and at 60days of age for the passive avoidance).

Mating Performance and Fertility of F1: there were no drug related effects on mating or fertility indices as mating was observed in 18/20, 19/20, 18/18, and 9/11 pairs in cont, LD, MD, HD respectively. Also the precoital period was unaffected by treatment with 17, 17, 17, and 8 pregnancies in these respective groups.

Reproductive parameters F1: there were no drug effect on any parameter including gestation period, litter size, or live birth indices. Mean litter sizes were 14, 16, 15.5, and 15 in cont, LD, MD, and HD respectively, and the corresponding values for live birth indices were 100, 100, 99, and 98% respectively.

Progeny Measurements of F1 Generation: total number of liveborn from F1 were 224, 254, 245, and 118 in cont, LD, MD, HD respectively. There was no drug effect on mean wt or survival through ppd1. There was an incr in number of live females but not males, per litter of HD relative to the cont.

Progeny Observations and Exam of F1 Generation: no drug related findings
Histopathology: no drug related effects. Spontaneous lesions included uterine dilation, prostatic inflammation, and mineralization; also testes were small in 1MDm.

Summary and Conclusion:
This study examined fertility, perinatal, and postnatal reproductive and developmental parameters (Segment I & III) in rats orally administered olanzapine at 0.25, 1.1, or 5mg/kg dose. The study conduct followed the ICH guidelines. Olanzapine at 5mg/kg caused hypoactivity and ptosis, and changes in mean wt, wt gain, and food intake of F0 parental rats throughout the drug period. Also at this dose, estrous cycle was prolonged, copulation was delayed, and decr mating indices were observed. Though fertility was unaffected in LD & MD, 3/20 males in HD failed to mate with either female which they cohibituated. At 1.1mg/kg dose, olanzapine effects were less severe on B.wt, food intake, and estrous cycle and without an effect on mating indices. There were no drug related effects at the LD of 0.25mg/kg therefore, this dose of **0.25mg/kg is the NOEL for F0 parental toxicity and reprodctive toxicity.** Developmental toxicity was seen as a transient decrease in activity in F1 pups and skeletal retardation (incomplete ossification and/or wavy ribs) in fetuses from HDf. There were no drug related findings on growth, development, or reproductive parameters of F1 generation. The **NOEL for developmental tox in F1 is 1.1mg/kg (due to some skeletal retardation in HD) and, that for reproductive tox for F1 is 5mg/kg.**

- Developmental tox study of olanzapine administered orally to New Zealand white rabbits/Report# 45/Study# B02693/Lilly Labs, IN/Oct-Nov 1993/GLP.
Lot# 029JD3, purity 99%.

Strain/age and/or wt: New Zealand white/5m/3.2±0.3g
Dose/route/duration/rat # per dose: 0, 2, 8, 30mg/kg/d/oral/duration gd6-18/20 females per gr.

The drug was suspended in 10% w/v acacia solution; simethicone emulsion was added to prevent or reduce foaming. All standard maternal and fetal parameters were assessed following ICH guidelines to include maternal survival, clinical signs, B.wt, food intake, weight of ovaries and uteri; for the fetus: live/dead, late and early resorptions, live fetuses were weighed individually and examined for external, visceral, and skeletal anomalies; gender of live fetuses was determined internally. Proper statistics was applied to all parameters.

Results:
Maternal Survival and Clinical Signs: number of rabbits that completed the study was: 20, 20, 19, and 19 corresponding to 0, 2, 8, and 30mg/kg olanzapine doses respectively. The corresponding number of pregnant rabbits examined on gd28 was: 17, 16, 16, and 18 respectively. There was no drug related deaths in any gr. Clinical signs occurred after dosing and were limited to **HD animals,** included: **hypoactivity**(20/20), **peripheral vasodilation**(15/20), **partially closed eyelids**(20/20), **ataxia**(20/20), **increased respiration**(2/20), and **nasal discharge**(2/20). **One rabbit each in MD and HD aborted late in gestation.** Postmortem findings included pulmonary congestion with inflammation or pneumonia suggestive of trauma during dosing. The sponsor also indicated that Pasteurella multocida is bacteria frequently found in the respiratory tract of rabbits and is responsible for reproductive tract disease such as mertitis and abortions. Therefore, the sponsor concluded that these 2 abortions in MD&HD rabbits were drug unrelated. It is unclear if this bacteria was found in these rabbits that aborted. Two other abortions were found in one animal each in cont and MD that were considered incidental and unrelated to olanzapine. These abortions were undected in these animals during the in-life phase and were identified as bloody discharges (red material in the trays, positive with Hemastix) and empty implantation sites in utero on gd28.
B.wt and Food Intake: mean wt was **decr 3.7% in HD on gd19** relative to the cont. **Mean wt gain**

was decr dose-dependently in MD&HD for the period gd6-13 (HD lost 6.7±3g relative to cont that gained 13±2g during this period), and during gd13-19 in HD only(i.e. mean wt gain was depressed in HD throughout gestation as seen below).

	wt.gain(g)	wt.gain(g/day)	corrected wt.gain(g)
Cont	446±29	16±1	112±35
HD	321±34	11±1	-1±41

values are means±s.e.; n=16-18; duration 0-28days; p<0.04-0.001; corrected wt.gain is that calculated by subtracting uterine wt from total B.wt gain.

Mean food intake (g/day) was sig reduced in HD during gd6-13, 13-19, and 19-28 (15-25% of cont). Similarly, food intake calculated as g/day/kg B.wt was also reduced (p<0.001) in HD during gd6-13, 13-19, and 19-28 (11-25% of cont).

Maternal Reproductive Parameters: there were no drug effect on number of corpora lutea, no. of implantations/dam, preimplantation loss, or late resorptions per litter. An incr in early resorptions was recorded in all groups with statistical significance in MD&HD. Mean±s.d. and percent values for the following parameters were:

Parameter	Cont	LD	MD	HD
Early Resorptions	0.2±0.4 (3±7%)	0.6±1 (8±15%)	0.7±0.8 (10±11%)	0.8±1 (13±20%)
Total Resorp. per litt.	0.4±0.5 (6±9%)	0.8±1 (10±14%)	0.8±0.9 (10±11%)	1±1* (16±20%)*
Litt with Resorptions Sum(%)	6(35%)	9(56%)	9(56%)	10(56%)

* not statistically significant.

The number of litters with nonlive implants was also incr in MD&HD (not sig) relative to the cont (7, 9, 11, and 10 in cont, LD, MD, and HD respectively). The above info were calculated using all litters including the 2 dams in cont and MD with undetected abortions. However, when these parameters were re-calculated without these 2 dams and using litters with at least one live fetus, there was no difference in the incidence of live fetuses per litter. Therefore, the sponsor concluded that there was no drug effect on fetal viability. This may be true for the MD but not for the HD group.

Fetal Parameters: the number of fetuses examined was 98, 125, 87, and 114 from cont, LD, MD, and HD respectively. Fetal wt was reduced sig in HD relative to the cont wt (7% of the cont (for both sexes); more in female fetuses at 7% than male fetuses at 4.7% of cont). Though not statistically sig, mean no. of fetal runts/litter was higher in HD relative to that in the cont (mean±s.d. for HD: 0.33±0.6(4±7%) vs. 0.06±0.3(0.7±3%) in cont). Also nosignificant, number of fetuses per litter with malformations was incr in MD&HD with mean±s.d. of 0.14±0.4 and 0.11±0.32 respectively vs. 0.06±0.3 in cont the corresponding percent were 5±14% and 1.5±5% for MD&HD respectively, vs. 1±4% in cont. However, there was no effect on number of litters with fetuses having malformations.

There was no drug effect on sex ratio. The number of affected implants per litter was incr nonsig in MD(1.4±2) and HD(1.1±1) relative to the cont(0.8±1.5) with the corresponding percent of 17±20 HD, 26±34 MD, and 12±25 in cont. The number of litters with affected implants was 7, 10, 11, and 10 in cont, LD, MD, and HD respectively. There was no drug effect on fetal morphology in any gr.

Summary and Conclusion: oral administration of olanzapine at 2, 8, and 30mg/kg/d to pregnant rabbits during organogenesis caused no teratogenicity or maternal deaths. Maternal clinical signs were observed in HD and included hypoactivity, peripheral vasodilation, partially closed eyelids, ataxia, increased respiration, and nasal discharge. Two dams one each in MD&HD aborted late in gestation. The sponsor indicated that these abortions were unrelated to the drug but possibly to inflammation or pneumonia or due to Pasteurella multocida which is frequently found in the respiratory tract of rabbits and is responsible for reproductive tract disease such as mertitis and abortions. Two other abortions were found one each in cont and MD that were also considered incidental and unrelated to olanzapine. These latter abortions were undetected in these animals during the in-life phase and were identified as bloody discharges and empty implantation sites in utero on gd28. Though the explanations given by the sponsor maybe adequate, a drug effect can not be dismissed. Mean wt of dams in HD was decr 3.7% on gd19 relative to the cont as well as mean wt gain throughout gestation; mean wt gain was also reduced in MD. Food intake was also reduced in HD dams. There were no drug effect on number of corpora lutea, no. of implantations/dam, preimplantation loss, or late resorptions per litter. An incr in early resorptions was recorded in all groups with statistical significance in MD&HD and the number of litters with nonlive implants was also incr in MD&HD (not sig) relative to the cont. The sponsor indicated that these data were obtained using all litters including the 2 dams in cont and MD with undetected abortions but when the calculations were made without the 2 dams and data from litters with at least one live fetus were applied, there was no difference in the incidence of live fetuses per litter therefore, the drug had no effect on fetal viability. Although this may be true for the MD gr the results remain for HD group. Fetal wt was reduced sig in HD relative to the cont wt (7% of the cont). Though not statistically sig, mean no. of fetal runts/litter was higher in HD relative to that in the cont and the number of fetuses per litter with malformations was incr in MD&HD. However, there was no effect on number of litters with fetuses having malformations. There was no drug effect on sex ratio. The number of affected implants per litter was incr nonsig in MD and HD relative to the cont. There was no drug effect on fetal morphology in any gr. **It is concluded that NOEL for fetal developmental tox in the rabbit is 8mg/kg and maternal tox NOEL is 2mg/kg. These doses represent approximately 8 and 2x the maximum recommended human dose on a mg/m^2 basis respectively (based on clinical dose of 20mg/d and 60kg wt).**

Summary and Conclusions for Reproductive and Developmental Tox:

The following studies have been submitted and reviewed:

1. 8-wk male fertility study in F344 rats/Segment I/report#13 (Reviewed by R. Hollenbeck/Aug 1986).
2. Teratology study in F344 female rats/Segment II/report# 19 (Reviewed by R. Hollenbeck/Oct 1986).
3. Teratology in New Zealand white rabbits/Segment II/report#20 (Reviewed by R. Hollenbeck Oct 1986).
4. 10-wk fertility study in female F344 rats/Segment I/report# 21 (Reviewed by J. DeGeorge/Feb 1991).
5. Teratology Special Study: effect of olanzapine on ovulation and fertilization of eggs from CD rats/report# 27 (Reviewed by J. DeGeorge/Feb 1991).
6. Fertility, perinatal, and postnatal study of olanzapine given orally to rats with behavioral and

reproductive assessmerit of F1 generation/report# 44 (Reviewed by A. Atrakchi/Mar 1996).

7. Developmental tox study of olanzapine administered orally to New Zealand white rabbits report# 45 (Reviewed by A. Atrakchi/Mar 1996).

The studies reviewed by Drs. Hollenbeck and DeGeorge are summarized below, for more detail refer to the reviews in the original IND:

- 8-wk male fertility study in F344 rats/Segment I/report#13 (Reviewed by R. Hollenbeck)

Male rats were orally dosed with olanzapine at 2.5, 7.5, and 22.5mg/kg for 10wks prior to mating and through the 1st 7days of mating. Untreated females were allowed to deliver and rear their pups through ppd21. Olanzapine treatment had no effect on male fertility at any dose and there was no effect on mean live litter size. Mating activity was reduced when none of the HDm mated while on treatment. Normal mating activity level was regained when treatment was discontinued (8/10 mated). **The NOEL for male fertility is therefore, 22.5mg/kg.**

Teratology study in F344 female rats/Segment II/report# 19 (Reviewed by R. Hollenbeck)

Female rats were orally dosed with olanzapine at 1, 4, and 18mg/kg during gd6-15 and killed on gd20 for evaluation of repro. parameters and fetal morphology (external, visceral, and skeletal exam). There were no deaths in any gr and fertility was unaffected. Clinical signs were observed in HD and included hypoactivity, ptosis, lethargy, chromodacryorrhea, chromorrhinorea, and lacrimation. At this dose, mean wt gain and food intake were sig reduced starting on gd6 through gd20. High dose embryo/fetal tox was observed as incr resorptions (% of live fetuses reduced due to 4 female rats that completely resorbed their litt), depressed fetal wt (12% of cont), and increased incidence of male fetal runts, and skeletal variations. At 4mg/kg clinical signs included hypoactivity and ptosis with decr wt and food intake. Fetal wts were also reduced in 4mg/kg dose gr. There was no drug effect on number of corpora lutea, number of implantations, and number of live or dead fetuses. **The NOEL for maternal and fetal tox is 1mg/kg and NOEL for teratogenicity is 18mg/kg.**

- Teratology in New Zealand white rabbits/Segment II/report#20 (Reviewed by R. Hollenbeck)

Female New Zealand white rabbits were orally dosed with olanzapine at 2, 8, and 30mg/kg during organogenesis gd 6-18 and killed on gd28 for evaluation of repro parameters and fetal morphology (external, visceral, and skeletal). Clinical signs in HD dams included hypoactivity, ataxia, partially closed eyelids, peripheral vasodialation, and decr mean wt gain and food intake (13% for wt gain and 18% of the cont for food intake). Mean wt gain and food intake were also reduced sig in MD dams (63% of cont for wt gain and 16% decr over the cont for food intake). Fertility and prenatal survival was unaffected by drug treatment. However, there were 2 abortions in HD on gds 24 and 27. One dam aborted 6 grossly normal fetuses with 6 implantation discs in cage, the 2nd dam aborted 2 grossly normal fetuses, one dead and one partially cannibalized with 2 late resorption specimens in cage. One of these dams had sig reduced food intake between gd13-27 and the other dam lost wt. The sponsor indicated that decr food intake and wt loss can cause abortion (Matsuzawa et al., 1981) therefore, these abortions were drug unrelated and secondary to maternal toxicity. Embryo/fetal tox was seen as reduced fetal wt in HD (13% of the cont). **The NOEL for maternal tox is 2mg/kg and for embryo/fetal tox is 8mg/kg; NOEL for teratology is 30mg/kg in the rabbit.**

- 10-wk fertility study in female F344 rats/Segment I/report# 21 (Reviewed by J. DeGeorge)

Female CD rats were orally dosed with olanzapine at 1, 3, and 10mg/kg for 2wks prior to mating and throughout lactation ppd21; males were not treated. All rats were allowed to deliver. Clinical signs were dose related regarding incidence and severity; the following occurred when treatment started: hypoactivity, lethargy, ptosis, chromodacryorrhea, and lacrimation, they were absent by d50. These signs were absent in lower doses immediately prior to dosing. Other signs ocurred on days22-50 and observed only in HD: ptosis and swelling of ears and paws. Mean wt gain was decr in MD&HD in a dose-related manner (max decr was 20%) accompanied by decr in food intake. These 2 parameters were unaffected during pp period. Fertility index was decr dose dependently (5% in LD, 12% MD, and 30% HD) but mating index was unaffected. In all doses, there was some acyclic periods and gestation period was prolonged in HD (22.3 vs. 21.4d; $p<0.05$). F1 generation findings included: liveborn litter size was reduced 16% in HD, pp survival was reduced in HD with 18% decr in survival on ppd1, 12% more decr on postculling by day14, and there were sig more male pups than females (48, 44, 51, and 62% male rats in cont, LD, MD, and HD respectively). There was no effect on pup wt and no malformations. **The NOEL for female fertility is 1mg/kg, and NOEL for teratology is 10mg/kg.**

- Teratology Special Study: effect of olanzapine on ovulation and fertilization of eggs from CD rats/report# 27 (Reviewed by J. DeGeorge)

This study was done to determine the cause of the reduced fertility observed in the above study, whether its due to decr ovulation caused by drug-induced incr in prolactin, or, from reduced implantation or other effects. Female CD rats were orally dosed with olanzapine at 0, 3, and 10mg/kg for 2wks prior to mating, during mating, and to post mating day 1; males were untreated. Females were killed on day1 after mating, oviducts removed and eggs and embryos collected. There were no deaths; hypoactivity and ptosis were observed in both dose gr. There was a statistically in-significant incr in precoital interval (mean 2.2d cont, 4.4d LD, and 5d in HD), and in number of females failing to mate (all mated in cont, 1/10 did not in LD, and 2/10 did not mate in HD). In females that mated, there was a 21% decr in number of ovulated eggs/rat in HD. However, the sponsor indicated that this decr in mean number of eggs was caused by a single female producing small number of eggs. The number of eggs ovulated ranged in the cont between 6-17 and that in HD between 3-15 (2females did not mate in HD so these ovulated eggs are from a totla of 8females whereas all 10 cont females successfully mated). The number of 2-cell embryos was unaffected. Dr. DeGeorge indicated that the rats in the cont gr in this study had low fertility and based on necropsy data on males from the breeder stock, there was an abnormally high incidence of hyposermatogenesis. This complicated interpretation of data from the present study. The present reviewer however, is unable to identify the decr in fertility of the cont gr mentioned by Dr. DeGeorge therefore, the decreased fertility of females seem to be due to decr in ovulated eggs in the HD gr. Dr DeGeorge stated that Segment I study was inadequate since it did not follow the standard FDA guidelines: no sacrifice of subset of mothers prior to term (no data on repro parameters re. live/dead embryos, corpora lutea...), mating period was much longer than recommended in the guidelines, and there was no assessment of repro parameters of F1 generation.

Based on the above studies reviewed by Drs. Atrakchi, DeGeorge, and Hollenbeck, the following is summary and conclusion for the Reproductive and Developmental toxicity(ies) of olanzapine:

Rats and rabbits were used in standard tests to evaluate the reproductive and developmental toxicity potential of olanzapine. The doses tested ranged between 0.25-22.5mg/kg in the rat and in the rabbit, between 2-30mg/kg. These doses represent in the rat 0.13-11x and in the rabbit 2-30x the max recommended human dose on a mg/m^2 basis.

In a combined Segment I&III study in rats, the main drug related findings were as follows:

- all F0&F1 animals survived.
- mean wt, wt gain, food intake, and EFU were reduced (7-10% of cont) in F0 males and females at given times during gestation and postpartum periods for females and pre-mating period in males; these findings occurred in HD of 5mg/kg and somtimes in MD of 1.1mg/kg. Note that food intake was sig incr when drug was administered during premating period in female rats dosed 0.25, 1.1, and 5mg/kg.
- prolonged diestrous in females dosed 1.1 and 5mg/kg
- mating index reduced and precoital period incr at 5mg/kg, fertility was unaffected upto 5mg/kg.
- an incr in no. of early resorptions, total number of resorptions/litter, and sum of litters with resorptions in females dosed 1.1mg/kg without an effect on number of live fetuses per litter; none of these findings reached statistical sig.
- slight growth retardation in F0 fetuses from females dosed 5mg/kg seen as an incr in number of fetuses with incomplete skeletal ossifications and/or wavy ribs.
- in F1 postweaning pups, activity was reduced in 30d old males and in 60d old females dosed between 0.25-5mg/kg however, activity was comparable to the cont when these animals were re-tested at ages 140-160days. There was no drug effect on auditory startle responses.

The NOEL for F0 parental toxicity and reproductive toxicity is 0.25mg/kg. The NOEL for developmental tox in F1 generation is 1.1mg/kg and for reproductive tox of F1 is 5mg/kg.

In a male rat fertility study, the **NOEL for male fertility was 22.5mg/kg**; note that mating index was reduced at this dose (10/10 males did not mate) but activity was normal when treatment was discontinued. In a female 10wk fertility study, fertility index was reduced dose-dependently but the mating index was unaffected (5, 12, and 30% at 1, 3, and 10mg/kg respectively, relative to the cont). Some rats in all 3 dose groups had acyclic periods and at 10mg/kg, gestation period was prolonged. **The NOEL for female fertility was 1mg/kg.** In a follow-up study, the underlying cause for female fertility was investigated further. Female rats were orally dosed with olanzapine at 3 or 10mg/kg for 2wks pre-mating, during mating, and to postmating day1. Oviducts removed and eggs and embryos were collected. There was a non-significant incr in precoital interval and in number of females failing to mate. In females that mated, there was a 21% decrease in ovulated eggs/rat at 10mg/kg gr. In a female rat teratology study, mean wt gain and food intake at 18mg/kg was reduced and clinical signs were those observed in other tox studies including ptosis, hypoactivity, lethargy, chromorrhinorea, and chromodacryorrhea. At 18mg/kg, embryo/fetal resorptions were incr, fetal wt decr, and incidence of male fetal runts and skeletal variations was incr. **The NOEL for maternal and fetal tox was 1mg/kg and that for teratogenicity was 18mg/kg.**

Rabbits treated during organogenesis at doses up to 30mg/kg, showed clinical signs similar to those observed in rats such as hypoactivity, ataxia, and partially closed eye-lids. Mean wt gain and food intake were reduced at 8 and 30mg/kg groups. There were 2 late abortions in 30mg/kg gr one dam was not eating and the 2nd lost wt, the sponsor indicated that decr food intake and wt loss can induce abortions therefore, these abortions were not drug related. Mean fetal wt was reduced at 30mg/kg dose gr. **The NOEL for maternal tox was 2mg/kg, that for embryotox was 8mg/kg, and the NOEL for teratology was 30mg/kg.** In a Segment II study in rabbits, olanzapine caused late abortions in one rabbit each in 8 and 30mg/kg dose gr. The sponsor contributed these abortions to dosing accident in one case and to Pasteurella multocida which is frequently present in the rabbit respiratory tract and is responsible for reproductive tract illnesses such as abortions and mertitis. It is unclear if this organism was infact detected in the respiratory tract of the aborted rabbit; if such an organism was not identified, then a drug effect can not be ruled out. Mean wt gain was reduced throughout gestation in 30mg/kg dose gr so did food intake. An incr was observed in early resorptions at all drug gr (2, 8, 30mg/kg) reaching statistical sig in the MD&HD grs. Also incr but nonsig in all 3 drug grs was, total resorptions per litter, litters with resorptions, and no. of litters with nonlive implants (at 8 and 30mg/kg gr). The sponsor indicated that the calculations for these findings were done using all litters including

those from 2dams one each in cont and mid dose that had undetected abortions. However, when calculations were made without the litters from these 2dams and with litters with at least one live fetus, there were no differences in these parameters. Mean fetal wt was sig reduced at 30mg/kg, no. of fetal runts/litter and no. of fetuses/litter with malformations were incr in HD and MD&HD respectively. The **NOEL for fetal developmental tox was 8mg/kg and for maternal tox 2mg/kg.**

Labelling:

Pregnancy Category C; Reproduction studies performed in rats at doses 2.5x the maximum recommended human dose on a mg/m2 and in rabbits at 30x the maximum recommended human dose on a mg/m2 basis did not show evidence of teratogenicity.

Olanzapine administered to the rat at doses that are 11x the maximum recommended human dose on a mg/m2 basis decreased male fertility and at doses equal to or >0.5x decreased female fertility. Precoital period was increased and mating index was reduced in female rats dosed at 2.5x the maximum recommended human dose on a mg/m2 basis. Diestrous and prolonged gestation periods were noted at doses that are ≥0.6x the maximum recommended human dose on a mg/m2 basis. Maternal toxicity as reflected by reduced weight gain and food intake, occurred in rats at doses ≥0.5x the maximum recommended human doses on a mg/m2 basis. Early resorptions and sum and percent of litters with nonlive implants occurred in rats dosed at 0.5x the maximum recommended human dose on a mg/m2 basis and developmental retardation noted at doses 2.5x the maximum recommended human dose on a mg/m2 basis.

In rabbits dosed at ≥8x the maximum recommended human dose on a mg/m2 basis, maternal toxicity was observed as decreased food intake and weight gain. Fetal toxicity was observed in females administered doses 30x the maximum recommended human dose on a mg/m2 basis and noted as a decreased fetal wt , increased number of fetal runts/litter, and increase in number of fetuses per litter with malformations. Olanzapine has not been studied in pregnant women.

MUTAGENICITY

- The effect of olanzapine on the induction of forward mutation at the TK locus of L5178Y Mouse lymphoma (MLP) cells/Report# 9/Study# 840221MLA1995/Lilly Labs, IN/Jan 1985/GLP.
Lot# 56786

A preliminary cytotoxicity assay was conducted in +/- S9 at 8 olanzapine conc of 0.1, 1, 10, 50, 100, 250, 500, and 1000ug/ml. One hundred percent cell lethality noted at 250ug/ml in -S9 and at 500ug/ml in +S9; suspension growth was 30% at 100ug/ml in -S9 and 1% at 250ug/ml in +S9 (see table from sponsor). The sloubility of test sub was verified by spectrometry (relative absorbance); note that using the naked eye would have sufficed. The test sub precipitated at 500ug/ml. Conc used in the main assay were: 10, 20, 40, 60, 80, 100, 120, and 140ug/ml in -S9 and 100, 120, 140, 160, 180, 200, 220, and 240ug/ml in +S9. The positive controls used were EMS in -S9 and 3MC in +S9 and they produced the expected positive response; DMSO was the negative-vehicle control. The criteria for a positive mutagenic response was a conc-response and at least a 2x incr over the negative control in mutation index in 2 consecutive conc. The results indicated no positive mutagenic response at any conc tested (see table from the sponsor). However, from the table, survivability in -S9 was 90% at 140ug/ml which is unacceptable since cytotoxicity of the high conc should be equal to or greater than 80% but not more than 90% (OECD and ICH guidelines). It is the reviewer's opinion that higher conc should have been tested; the results from this assay will be evaluated in view of those from the other mutation assays conducted for olanzapine.

The sponsor repeated the MLP forward mutation assay (Report 17; Sep 1985) because in the above assay (report# 9) cytotoxicity in -S9 at the highest conc was not observed. The following conc of olanzapine were tested in +/-S9: 75, 100, 125, 150, 175, 200, 225, and 250ug/ml. Marked cytotoxicity (suspension growth and % cloning efficinecy) was observed at ≥150ug/ml in -S9 and at 225ug/ml in +S9. The results indicated that olanzapine did not incr the mutation frequency (mutation index) of the MLP/TK locus compared with the negative controls. The positive controls produced the anticipated response (see tables from the sponsor).

Based on the above 2 assays of MLP/TK , **olanzapine is not mutagenic under these experimental conditions.**

Olanzapine N20-592
Report #1

TABLE 1. PRELIMINARY TOXICITY TESTING OF LY170053 IN L5178Y CELLS. STUDY 840221MLA1995.

Treatment	Concentration (µg/ml)	Day 1 Cell Counts (x106/ml)	Day 2 Cell Counts (x106/ml)	Percent Suspension Growth[a]
NON-ACTIVATED TEST				
LY170053	1000	-[b]	-	-
	500	-[b]	-	-
	250	-[b]	-	-
	100	0.540	1.080	30
	50	1.043	1.350	71
	10	1.643	1.305	109
	1	1.875	1.290	123
	0.1	1.305	1.298	86
DMSO	(1%)	1.695	1.163	100
ACTIVATED TEST				
LY170053	1000	-[b]	-	-
	500	-[b]	-	-
	250	0.01[illegible]	0.053	1
	100	1.133	1.418	129
	50	1.335	1.215	131
	10	1.208	1.613	157
	1	1.095	1.223	108
	0.1	0.870	1.395	98
DMSO	(1%)	0.885	1.403	100

[a]Calculated as indicated in Appendix C.
[b]Chemical toxicity, no surviving cells.

Report #9 olanzapine NDA 20-592

TABLE 5. A SUMMARY OF RESULTS FOR THE MOUSE LYMPHOMA FORWARD MUTATION ASSAY WITH LY170053. STUDY 840221MLA1995.[a]

Treatment	Concentration (µg/ml)	Percent Total Survival[b]	Mutation Frequency[c]		Mutation Index[d]
NON-ACTIVATED TEST					
LY170053	140	90	1.7		0.7
	120	75	2.4		1.0
	100	84	2.2		0.9
	80	94	2.1		0.9
	60	96	2.1		0.9
	40	87	2.0		0.8
	20	75	2.3		1.0
	10	94	2.6		1.1
DMSO[e]	(1%)	100	2.2		
DMSO[e]	(1%)	100	2.9	2.4[g]	1.0
DMSO[e]	(1%)	100	2.0		
EMS[f]	620	48	41.5		17.3
ACTIVATED TEST					
LY170053	240	34	2.2		0.7
	220	61	2.4		0.7
	200	60	2.1		0.6
	180	92	2.2		0.7
	160	90	2.4		0.7
	140	92	2.6		0.8
	120	120	2.7		0.8
	100	117	4.0		1.2
DMSO[e]	(1%)	100	2.6		
DMSO[e]	(1%)	100	3.7	3.3[g]	1.0
DMSO[e]	(1%)	100	3.5		
3MC[f]	2	57	26.4		8.0

[a]Consult Appendix C for calculations.
[b](Suspension growth) x (cloning efficiency).
[c]$TK^{-/-}$ mutants per 1 x 10^5 colony forming cells.
[d](Mutation frequency of treated culture)/(control mutation frequency).
[e]Solvent control.
[f]Positive control.
[g]Mean of solvent controls.

Repeat of MLP/TK report 17

TABLE 1. RESULTS OF THE MOUSE LYMPHOMA FORWARD MUTATION ASSAY WITH LY170053. STUDY 840509MLA1995.

Treatment	Concentration (µg/ml)	Day 1 Cell Counts (x106/ml)	Day 2 Cell Counts (x106/ml)	Percent Suspension Growth[a]	No. Colonies On Selective Plates (Mean)[b]	No. Colonies On Non-Selective Plates (Mean)[b]	Percent Cloning Efficiency[a]
NON-ACTIVATED TEST							
LY170053	250	Dead	---	---	---	---	---
LY170053	225	Dead	---	---	---	---	---
LY170053	200	0.023	0.015	< 1[e]	---	---	---
LY170053	175	0.023	0.053	< 1[e]	---	---	---
LY170053	150	0.180	0.600	8[e]	---	---	---
LY170053	125	0.563	1.298	31	10	80	88
LY170053	100	0.945	1.298	52	7	68	75
LY170053	75	1.575	0.990	66	12	89	98
DMSO[c]	(1%)	1.688	1.380	100	12	91	100
DMSO[c]	(1%)	1.898	1.260	100	14	99	100
DMSO[c]	(1%)	1.823	1.305	100	12	83	100
EMS[d]	620	1.163	1.223	60	216	60	66

[a]Calculated as indicated in Appendix D.
[b]Mean of triplicate plates.
[c]Solvent control.
[d]Positive control.
[e]Culture not cloned due to severe toxicity.

TABLE 2. RESULTS OF THE MOUSE LYMPHOMA FORWARD MUTATION ASSAY WITH LY170053. STUDY 840509MLA1995.

Treatment	Concentration (µg/ml)	Day 1 Cell Counts (x106/ml)	Day 2 Cell Counts (x106/ml)	Percent Suspension Growth[a]	No. Colonies On Selective Plates (Mean)[b]	No. Colonies On Non-Selective Plates (Mean)[b]	Percent Cloning Efficiency[a]
ACTIVATED TEST							
LY170053	250	0.030	0.045	< 1e	---	---	---
LY170053	225	0.098	0.338	6[e]	---	---	---
LY170053	200	0.293	1.553	26	11	108	94
LY170053	175	0.675	1.530	57	10	76	66
LY170053	150	0.728	1.703	69	14	98	85
LY170053	125	1.223	1.658	112	13	83	72
LY170053	100	1.260	1.875	131	10	81	70
LY170053	75	1.553	1.755	151	13	70	61
DMSO[c]	(1%)	1.125	1.350	100	17	124	100
DMSO[c]	(1%)	1.200	1.575	100	13	120	100
DMSO[c]	(1%)	1.200	1.680	100	17	100	100
3MC[d]	2	0.488	1.433	39	115	69	60

[a]Calculated as indicated in Appendix D.
[b]Mean of triplicate plates.
[c]Solvent control.
[d]Positive control.
[e]Culture not cloned due to severe toxicity.

TABLE 3. A SUMMARY OF RESULTS FOR THE MOUSE LYMPHOMA FORWARD MUTATION ASSAY WITH LY170053. STUDY 840509MLA1995.[a]

Treatment	Concentration (μg/ml)	Percent Total Survival[b]	Mutation Frequency[c]		Mutation Index[d]
NON-ACTIVATED TEST					
LY170053	250	—	—		—
LY170053	225	—	—		—
LY170053	200	—	—		—
LY170053	175	—	—		—
LY170053	150	—	—		—
LY170053	125	27	2.5		0.9
LY170053	100	39	2.1		0.8
LY170053	75	65	2.7		1.0
DMSO[e]	(1%)	100	2.6		
DMSO[e]	(1%)	100	2.8	2.8[g]	(1.0)
DMSO[e]	(1%)	100	2.9		
EMS[f]	620	40	72.0		25.7
ACTIVATED TEST					
LY170053	250	—	—		—
LY170053	225	—	—		—
LY170053	200	24	2.0		0.7
LY170053	175	38	2.6		0.9
LY170053	150	59	2.9		1.0
LY170053	125	81	3.1		1.1
LY170053	100	92	2.5		0.9
LY170053	75	92	3.7		1.3
DMSO[e]	(1%)	100	2.7		
DMSO[e]	(1%)	100	2.2	2.8[g]	(1.0)
DMSO[e]	(1%)	100	3.4		
3MC[f]	2	23	33.3		11.9

[a]Consult Appendix D for calculations.
[b](Suspension growth) x (cloning efficiency).
[c]$TK^{-/-}$ mutants per 1 x 10^5 colony forming cells.
[d](Mutation frequency of treated culture)/(control mutation frequency).
[e]Solvent control.
[f]Positive control.
[g]Mean of solvent controls.

- The effect of olanzapine on the induction of DNA repair synthesis in primary cultures of adult rat hepatocytes/Report# 8/Study#s 830712UDS1995&830719UDS1995/Lilly labs, IN/Feb 1984/GLP.
lot# 56786

Primary cultures of adult Fischer 344 rat hepatocyte were used. Criteria for a positive response was at least 2 consecutive conc produce net nuclear grain count (NNC) exceeding that of the negative control by 3 s.d. Induction of UDS was measured by autoradiography, positive controls included the pro-carcinogen 2AAF and the carcinogen MNNG. Eight olanzapine conc were tested ranging between 0.5 to 1000nmol/ml; basis for selecting these conc was not provided. **The results showed that olanzapine did not induce DNA repair synthesis at any conc tested** however, a marked incr in UDS was induced by 2AAF and MNNG; the assay was repeated with similar results. Note that individual data were not provided and the basis for selection of conc was not provided as well.

- The effect of olanzapine on in vivo induction of micronuclei in bone marrow of ICR mice/Report# 33/Study# 911021MNT1995/Lilly Labs, IN/Apr 1992/GLP.
Lot# 58962

Olanzapine was administered by gavage (as a suspension in 10% w/v aqueous acacia) to male and female ICR mice at 11.5, 23, or 46mg/kg for 2 days. The doses were selected based on a preliminary tox study# 911014MTT1995, at doses 62.5, 125, 250, and 500mg/kg and estimation of the median lethal dose (see table below from sponsor). The median lethal dose was 125mg/kg with no deaths at 62.5mg/kg and the estimated mini lethal dose was approximately 92mg/kg. Five mice/sex were administered olanzapine or cyclophosphamide (the positive control). Animals were killed 24hr after the 2nd dose and bone marrow collected and 1000 PCE/animal were examined. Criteria for a valid test: the drug dose should be the MTD and both the negative and positive controls should produce MN (PCE/NCE ratio) within the historical data. Criteria for a positive response: dose-related incr in PCE where the no. of MN is statistically higher than the concurrent cont value. **The results showed no incr in MN at any conc of olanzapine**, a sig incr noted in CP compared to the neg control (table below from sponsor). The HD tested could have been higher based on the results of the preliminary study.

Summary of Results from a Preliminary Dose Range-Finding Study with Olanzapine (LY170053) Given by Gavage to ICR Mice. Study 911014MTT1995.

Chemical Treatment	Dose (mg/kg)	No. Dead/No. Dosed[a] Males	Females
Vehicle (10% Acacia)	20 ml/kg	0/5[b]	0/5[b]
LY170053	62.5	0/5[c]	0/5[c]
LY170053	125	5/5[d]	4/5[d]
LY170053	250	5/5[e]	5/5[e]
LY170053	500	5/5[f]	5/5[f]

Estimated MLD[g] (males/females combined): 91.858 mg/kg

[a]Two equal treatments approximately 24 hours apart, with observations recorded periodically through study termination.
[b]All animals appeared normal throughout the observation period.
[c]All animals were observed with lethargy 1 hour after first dose. Animals showed the same clinical signs of toxicity following the second dose.
[d]Five males and three females died within 3 hours of the first dose. Four males and one female died within 2 hours after the second dose. The remaining female was observed with lethargy, ocular discharge, hunched posture, hypoactivity, and poor grooming throughout the study.
[e]Four males and all females died within 1 hour after first dose. The remaining male died within 20 minutes after second dose.
[f]All animals died within 1 hour after first dose.
[g]MLD=Median Lethal Dose; estimated using logarithmic interpolation.

Table 1. Summary of the Incidence of Micronucleated Polychromatic Erythrocytes in ICR Mice Given LY170053 by Gavage. Study 911021MNT1995.

Sex	Treatment[a,b]	Dose (mg/kg)	PCE/NCE[c] Ratio	MPCE[d] per 1000 PCE	Trend Te two-tail p-value
Male					
	Vehicle[e]	0	1.1±0.4	1.4±1.1	
	LY170053	11.5	0.7±0.3	1.4±2.1	
	LY170053	23	1.0±0.5	0.4±0.9	
	LY170053	46	1.0±0.4	1.0±0	
	CP[f]	25	1.0±0.5	10.2±3.6**	0.28
Female					
	Vehicle[e]	0	1.3±0.5	2.0±2.1	-
	LY170053	11.5	1.1±0.4	0.6±0.5	
	LY170053	23	1.1±0.2	1.2±0.8	-
	LY170053	46	1.7±0.3	0.8±0.8	
	CP[f]	25	1.0±0.4	12.2±2.9**	0.16
				pooled[g] p = 0.08	

[a] Two equal treatments ~24 hours apart with harvest ~24 hours after the second treatment.
[b] Values are mean ± SD for 5 animals/treatment group.
[c] PCE: polychromatic erythrocyte; NCE: normochromatic erythrocyte.
[d] MPCE: micronucleated polychromatic erythrocytes.
[e] 10% aqueous acacia given in a dose volume of 20 ml/kg.
[f] Cyclophosphamide (CP) served as the positive control.
[g] Pooled: Mantel-Haenszel pooled across sex.
**Significant increase in the incidence of MPCE, p< 01

- The effect of olanzapine on the in vivo induction of SCE in bone marrow of Chinese hamsters/Report# 10/Study# 840320SCE1995/Lilly Labs, IN/Sep 1984/GLP.

Adult female Chinese Hamsters (32-39g) were used. BrdUrd tablets were implanted s.c. into the shaved abdomen of these hamsters. Three hamsters were tested per treatment gr, 2 animals for neg cont and 1 for positive control (CP); the use of 2 and 1 hamsters for the neg and positive control gr was deemed sufficient based on historical data from the sponsor's lab. Five hrs after implantation of BrdUrd tablets, olanzapine was orally dosed by gavage at 12.5, 25, 50, or 100mg/kg; animals were killed 21hr postdose and bone marrow was removed and processed. For cytotoxicity, 100 metaphase cells per animal were scored for 1st, 2nd, or 3rd division, incr in cell division during the 1st phase with a decr in the number of cell dividing in the 2nd and 3rd divisions indicated abnormalities in cell cycle. A cpd to induce SCE i.e. a positive response, is that which can induce a dose-related incr in SCE in 2 doses with statistical difference from the neg cont using Dunnett's t-test. For all olanzapine grs, CP, and the neg control groups, 25 metaphases/animal were scored. **Olanzapine did not induce SCE in bone marrow when admnistered orally to Chinese Hamsters at doses upto 100mg/kg dose.**

SUMMARY AND CONCLUSION OF MUTAGENICITY:

The mutagenicity potential of olanzapine was evaluated in 2 in vitro and 2 in vivo assays: the MLP/TK forward mutation and the UDS for the in vitro tests and bone marrow MN in mice and bone marrow SCE in chinese hamsters for the in vivo assays. **Olanzapine was non mutagenic in any of these assays** under these experimental conditions.

Dr. R. Hollenbeck reviewed the Ames bacterial assay and stated that **olanzapine was not mutagenic** in bacteria at conc ranged between 0.1-1000ug/ml (Original summary Aug 20 1986).

Dr. L. Freed reviewed Ames assay in E.coli, in vitro chrom. Abs in CHO cells, and in vivo induction of MN in bone marrow of ICR mice (also reviewed above by Dr. Atrakchi). In the Ames assay, the only tester strain assayed was E. coli wp2uvrA⁻ at conc between 250-4000ug/plate in -S9 and in presence of S9 conc ranged between 312-5000ug/plate; **olanzapine was not mutagenic in this assay.** Olanzapine **did not induce chrom. abs in the in vitro CHO cells** at conc upto 375ug/ml; Dr. Freed indicated that this assay failed to follow the OECD guidelines and may not be adequate (no data showing cytotoxicity and only 100 metaphases/dose were analyzed instead of the recommended 200/conc). In the in vivo bone marrow MN test in mice, **olanzapine did not induce MN** at the doses tested; Dr Freed similar to Dr. Atrakchi, indicated that the HD could have been higher since no bone marrow tox was evident.

Carcinogenicity Studies And Dose-Range Finding

Selection of doses for the carcinogenecity studies for mice and rats was based on 2-wk and 3-mo tox studies in each species. The 2-wk and 3-mo dose-range finding studies for the mouse are reviewed below, the corresponding studies for the rat were reviewed by Dr. Hollenbeck and are included in attachment A.

Mouse

- 3-month toxicity study by oral gavage/study# M01090/Tox report# 32/Lilly Res. Labs-IN/1991/GLP.

Lot#	58962/purity 100.2%
Species/wt/Age:	CD-1 mouse/initial mean wt±s.d. 24.7±1.8g males and 20.4±1.3g females/ 5-6wk initial age.
Dose/duration:	3, 10, 30mg/kg/day for 3months by oral gavage; control gr administered the vehicle 10% w/v aqueous acacia solution. Few drops of simethicone emulsion were added to drug and control suspensions to decrease foaming.
No./sex/dose:	10/sex/dose.

Parameters measured: clinical signs and survival (daily), B.wt (weekly), hematology (at 2months (5/sex/dose) and, end of study (surviving rats); orbital sinus puncture; non-fasting at 2months and fasting mice at end of study), clinical chemistry (end of study; fasted mice), enzyme induction (by measuring the activity of hepatic p-nitroanisole O-demethylase (end of study 5/sex/dose), organ wt (kidneys, liver, heart, spleen, uterus, and testes), gross exam and histopath (all grs). Statistics by Dunnett and Bartlett tests.

Results:

Survival: 100% in MD&HDf and LD&MDm, only 70% in LDf (7/10) and 80% in HDm* (8/10); also 1 each m and f of control mice died. Deaths were accidental and occurred early in the study.

* one of these males was killed moribund and its the one with histopath findings in the spleen (see histopath section).

Clinical Signs: hypoactivity and sternal recumbancy noted in all drug grs during 1st wk of study, and remained in the two high doses till end of study. Other signs mainly noted in males included rough hair coat and soiled genital area.

B.wt: no change in mean wt or wt gain in males but a significant increase in mean wt at end of study and wt gain of all female drug grs (non-dose dependent)(table below from sponsor).

TABLE SUMMARY OF GROWTH AND SURVIVAL OF MICE RECEIVING LY170053 BY GAVAGE FOR 3 MONTHS STUDY M01090

Dose (mg/kg/day)	Mean Weight at Start (g)	Number of Survivors	Mean Weight at Termination (g)	Mean Weight Gain (g)
		MALES		
0	24.6	9	35.4	10.8
3	24.4	10	35.0	10.6
10	25.5	10	35.3	9.7
30	24.4	8	34.0	9.7
		FEMALES		
0	20.4	9	28.1	7.6
3	20.4	7	32.1**	11.6**
10	20.4	10	30.1*	9.7*
30	20.2	10	30.0*	9.8*

*Significantly different from control, p≤.05, Dunnett's two-tailed "t".

Hematology: **after 2months**, the only effect was a **significant decrease in RBCs** (8.5%), **Hb** (6.5%), and **PCV** (6%) noted in **HDf** relative to the control values; this was not found in males and the values for Hb and PCV were comparable to those of the control at termination. The **WBC count was moderately reduced** in **HDm** after 2months (non significantly, 47% of control). **At termination, HDf** had a **significant decrease** (9%) in **RBC** relative to the control. The **WBC count was dose-dependently reduced in MD&HDm** expressed as reduced leukocytes (59&72%), lymphocytes (52&68%), and neutrophils (also noted in LD; 48, 71, and 80% in LD, MD, and HD respectively). In females at termination, the data were inconsistent since a significant increase in leukocytes was noted at MD but a significant decrease at HD, lymphocytes however, were significantly reduced in HDf relative to the control. Also, noted was a significant reduction in the # of monocytes in MD&HDm at termination.
Clinical Chemistry: non-dose dependent and scattered findings were observed. In HDm, there was a **significant increase in BUN** (58±21 vs. 27.6±8.8 control; $p<0.05$) and an increase in **total protein levels**, perhaps due to increase in Alb. BUN was also increased significantly in HDf (35.7±13.8 vs. 19.4±5.5 in control; $p<0.05$) and the **AST** level was significantly elevated in HDf (160±74 vs. 93±22.5 in control); $p<0.05$). No other findings were observed. There was a great deal of interanimal variation in clinical chemistry parameters.
Hepatic Enzyme Activity: no increase was measured in p-nitroanisole O-demethylase mean activity of any drug gr. indicating that LY 170053 did not induce enzymes in mice at doses upto 30mg/kg.
Organ wts. There was a high variability in the absolute and relative wt of the spleen in all male grs including the control. In females, some of the changes noted were related to the increase in mean wt of mice in drug grs; a significant increase was measured in the absolute liver wt of LD&MDf but not in HDf.
Gross Morphology: there were no drug-related gross findings in any gr. Esophageal rupture was observed which was considered secondary to gavage accidents that contributed to the deaths.
Histopathology: main finding included **lymphoid depletion of the spleen** in all drug grs with severity ranging between marked (2/10HDf), moderate (3/10 each HDm&HDf), minimal (2/10LDm, 1/10LDf, 2/10 each MDm&MDf), (slight 3/10 each control m&f, 2/10LDm, 3/10LDf, 3/10MDm, 4/10MDf, 6/10HDm, 7/10HDf) ; slight hemosiderosis noted in all grs including the controls. Also in the spleen, minimal to moderate **multifocal lymphoid necrosis** noted in HD mice (1-3 of 10 mice). **Mammary gland** moderate acinar hypertrophy in MDf (3/10) and HDf (5/10), moderate **ductal ectasia** MDf (1/10), HDf (4/10), cont. f (2/10), and slight **ductal epithelial hypertrophy** in LDf (1/10), MDf (6/10), HDf (6/10), and cont. f (3/10).

Summary and Conclusions:
Oral administration of LY 170053 to male and female mice at 3, 10, or 30mg/kg for 3 months produced CNS clinical signs such as sedation and hypoactivity during 1st wk of study in all drug grs. These signs disappeared in LD but remained in MD&HD mice till end of study Hematology findings noted after 2months and end of study included significant decrease in RBC and WBC parameters in HD mice. There were no gross findings and histopath was limited to some lymphoid depletion and necrosis of the spleen, slight epithelial hypertrophy and moderate ductal ectasia of mammary gland in MD&HDf. It is concluded that **3mg/kg is the NOEL and 10mg/kg is a LOEL** due to slight histopath findings and hematology findings.

Comment:
Concurrent with the above study, a 2-week pilot toxicity study (#M15390) was conducted to determine MTD in mice; a summary was attached as Appendix J, to the 3-month study report. CD-1 mice (5/sex/dose) were orally administered LY 170053 at **45, 70, or 100mg/kg/d for 2wks**. Mice were 5-6wks of age at study initiation with mean wt (±s.d.) 27.3±2g m and 22±1.5g f.
Survival: All HDm and 4/5HDf died on day 3 of the study, 3/5MDm and 2/5MDf died by day4; all LD and cont mice survived till end of study.

Clinical Signs: 1st 3days: hypoactivity in LD, semicomatose in MD, and comatose in HD; these signs lasted several hr postdosing. Days 4-6 all surviving mice were semicomatose immediately after dosing then hypoactive for several hrs postdose. From day7-end all surviving mice were hypoactive after dosing.
B.wt(2x per wk): mean wt and wt gain were significantly decreased throughout the study in LD&MDm however, LD&MDf mean wt and wt gain were similar to the controls. Note HD animals died early.
Hematology: significant dose-related decrease in lymphocytes and neutrophils in male and female mice. These decreases led to depletion of total leukocyte count. Platelet count was slightly increased (non dose-dependently).
Clinical Chemistry: a trend toward increase in BUN and hepatic enzyme activities (ALP, AST, ALT) in both sexes from LD&HD. The enzyme changes were also elevated in the single surviving 100mg/kg dosed female mouse.

There were no organ wt, gross morphology, or histopath done except gross exam was done on the animals that died; no findings were observed.

It is concluded that a NOEL could not be established and the LOEL is <45mg/kg based on decrease in B.wt, hematology findings, and changes in enzyme activity.

- Oncogenic and blood levels in CD-1 mice given olanzapine daily by gavage for the duration of their life span//Report 49/Study# M02691, M02791(collectively referred to as MC2627), and M02691/Lilly Res Labs-IN/Report Date: Sep 1994/Study initiation Nov 1991/GLP.

Study M02691 was conducted to measure plasma levels and hematology throughout the study and assess morphologic changes in lymphoid tissues and bone marrow at 3mo.

Studies M02691 and M02791 are identical in protocol, animal #, and doses they were initiated 3wks apart to facilitate dealing with large # of animals.

Lot# 58962, purity: 100%
Species/wt/Age: CD-1 mouse/initial mean wt±s.d. males 28.5±2.5g and 22±2g for females study# MC2627 and for study# M02891 males wt was 28±1.8g and for females: 21.5±1.3g/6-7wk initial age.
Dose/Duration: 3, 10, 30/20*mg/kg/19m for males and 21mo for females study MC2627 and 15mo for both sexes study M02891/oral gavage (2.5ml/kg volume; gavage was selected over food admixture because the drug was not stable in food); control gr administered 10ml/kg of the vehicle (10% w/v aqueous acacia solution). Few drops of simethicone emulsion were added to drug and control suspensions to decrease foaming.
No./sex/dose: 15/sex/control gr and 42/sex/dose for drug grs for study# M02891. 60/sex/gr for study# M02791&M02691 (MC2627).

* dose decr to 20mg/kg on day 100 due to mortality specially in males and incr neutropenia in these mice.

Due to drug-related aggressiveness, mice were housed individually after 7mo of dosing; initially there were 3mice/cage.

Parameters measured: clinical signs and survival (daily with thorough exam weekly), B.wt (weekly for the 1st 3mo then every 2wks), food intake (weekly for the 1st 3mo then every 3mo), hematology (3, 6, 12, and 15mo (M02891) and in survivors at necropsy (MC2627); 3/sex/dose for #M02891 and 20/sex/dose for #M02791&M02691; orbital sinus puncture), clinical chemistry (at necropsy), toxicokinetics (0.5 and 24hr at 6, 12, and 15mo; blood bled from the orbital sinus (non-fasting mice) will be collected from 3/sex/dose/time point), organ wt, gross exam and histopath (all grs).
Statistics: Dunnett's t-test/ANOVA; for tumor incidence, dose-response test after adjustment for mortality (Peto's trend test).

Basis for dose selection: subchronic 3m tox and PK studies.

Results:
Survival: in males ranged between 68% in cont to 22% in HD and, in females, 58% in cont to 32% in HD (see attached table and figure from the sponsor).

study # MC2627 Oncogen. study in mice NDA 20-592/Olanzapine

Table F-2. Summary of Growth, Survival, and Food Consumption for CD-1 Mice Receiving Olanzapine by Gavage for Their Life Span. Study MC2627.

Dose (mg/kg/day)	Mean Body Weight at Start (g)	Number of Survivors[a] (%)	Final Mean Body Weight[b] (g)	Mean Body Weight Gain (g)	Mean Daily Food Consumption (g/mouse/day)
			Males		
0	28.6	68	39.4	10.5	5.53
3	28.1	67	39.3	11.3	5.87
10	28.7	40	38.4	9.8	6.19
30/20	28.5	22	39.3	11.0	6.67
			Females		
0	22.0	58	34.5	12.2	5.52
3	22.0	50	34.9	12.8	6.22
10	22.4	40	34.7	12.3	6.25
30/20	22.0	32	36.2	13.9	6.45

[a]Number of males surviving 19 months and females surviving 20 months.
[b]Approximately Day 575 for males and Day 637 for females.

Figure F-2.1 Survival.

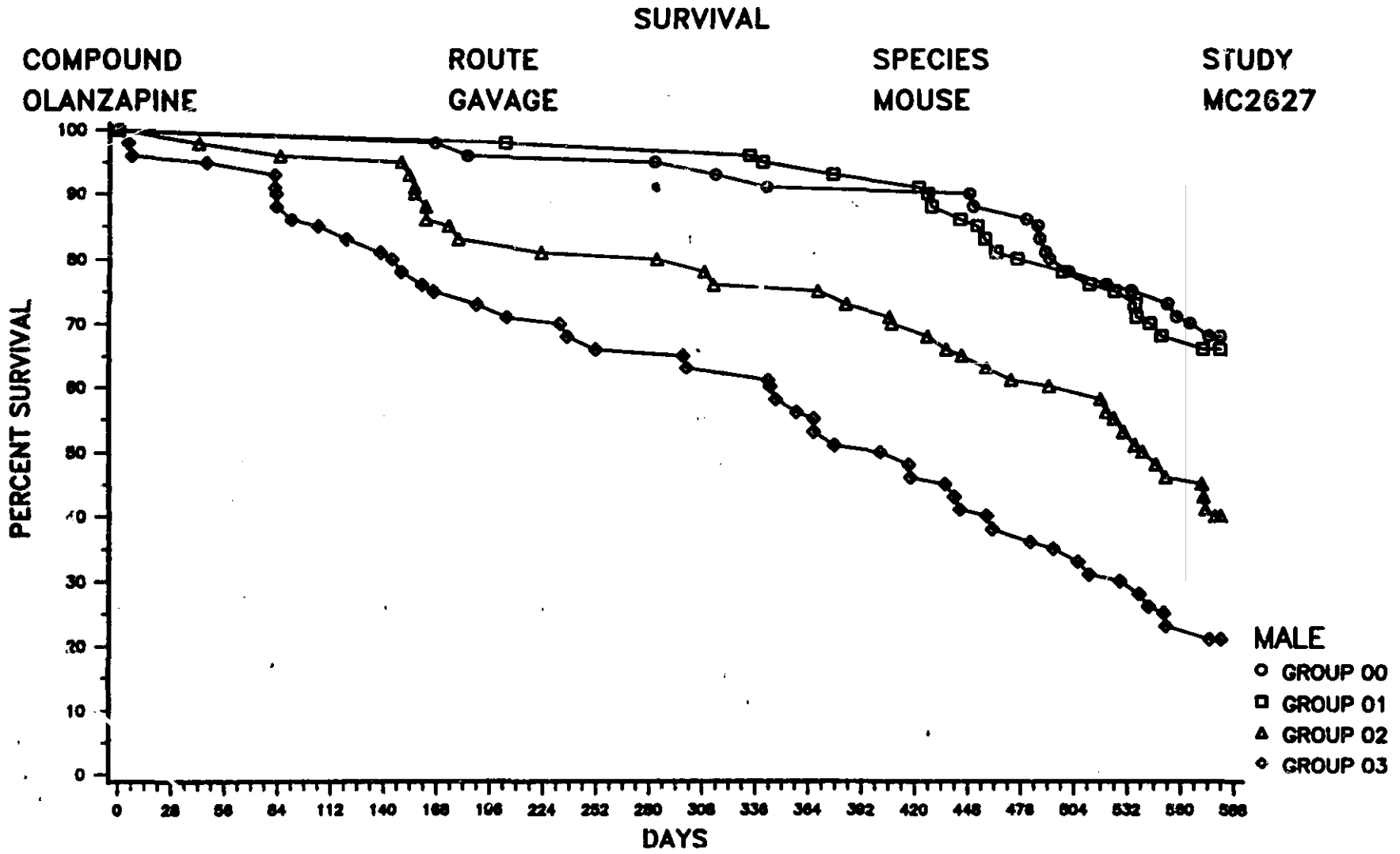
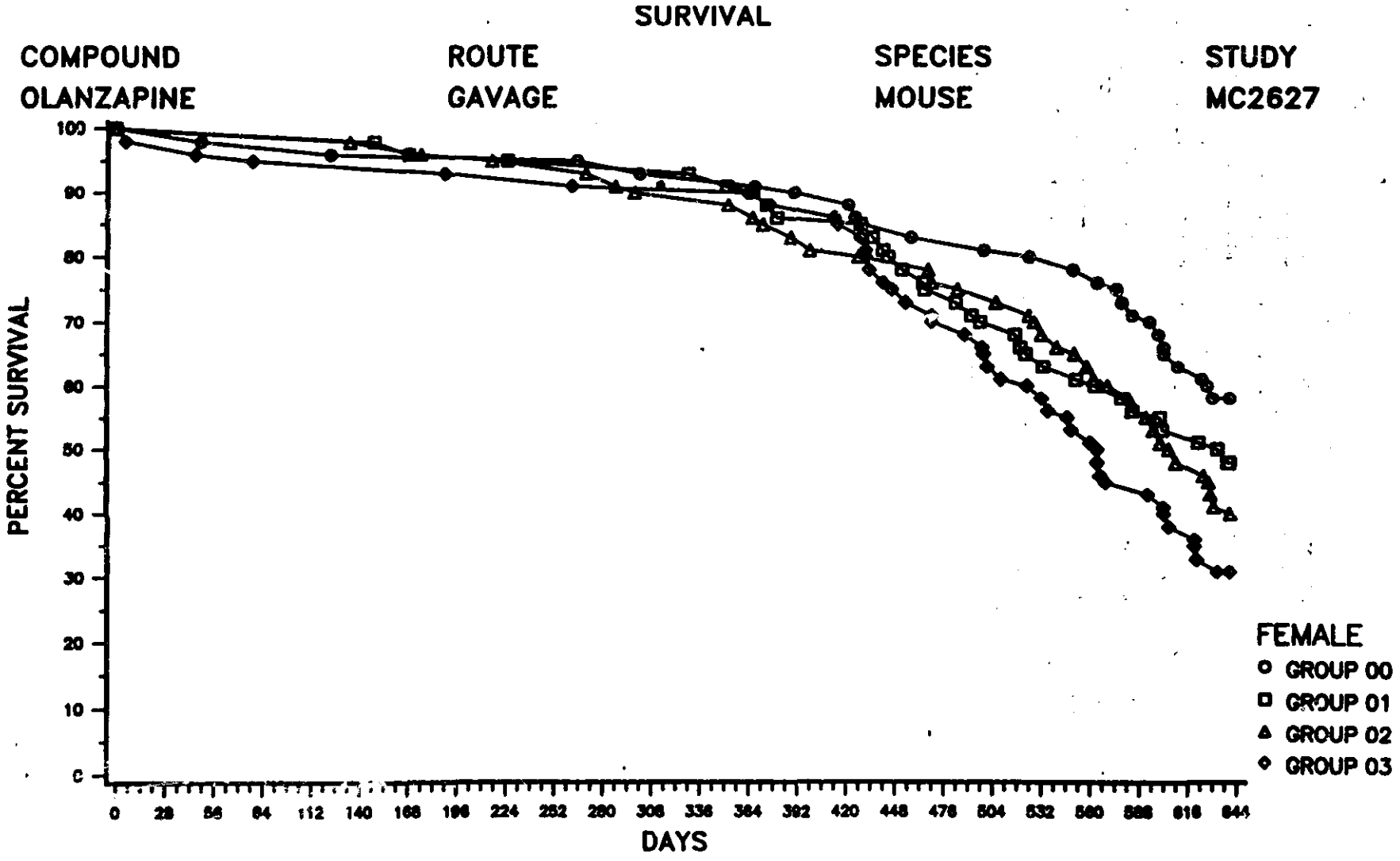


Figure F-2.2 Survival.



Clinical signs: hypoactivity noted in all animals in the drug grs within 15min of dosing, and severity was dose-dependent. Mice dosed LD or MD showed hypoactivity during the 1st 2-3mo, those dosed HD, mice remained hypoactive till end of study; reducing dose to 20mg/kg had no effect on this sign. Mices in the MD and/or HD showed aggressiveness noted as increased biting, rough hair coat, and soiling. Rough coat and soiling were observed till end of study in MD and/or HDm. Other signs in males included high incidence of distended penis and palpable abdominal mass relative to the control gr. Females of MD and/or HD had high incidence of nodules relative to the control. Other signs were common among all drug and control grs or seen only in very few mice in the drug gr.

Body wt: final mean wt or wt gain were similar between cont and drug grs (see attached figures from sponsor). Mean wt and wt gain was sig reduced in MD&HDm starting after 1mo of dosing and until month 13 of the study. Mice reach max B.wt (males) around the 9th month of life, at this time, MD&HDm had 7 and 10% reduction in mean wt respectively, relative to the control. Mean wt in females dosed 30mg/kg, was reduced and occasionally reached statistical sig. However, when the dose was reduced to 20mg/kg the B.wt and wt gain were similar to the cont. In LDf, mean wt was sig incr during the 1st 5mo and month11 of treatment. Mean wt and wt gain in LDf incr 4 & 12% during month 11. Also in MDf, mean wt was incr during the 1st 10wks.

Figure F-1.1 Mean Body Weight.

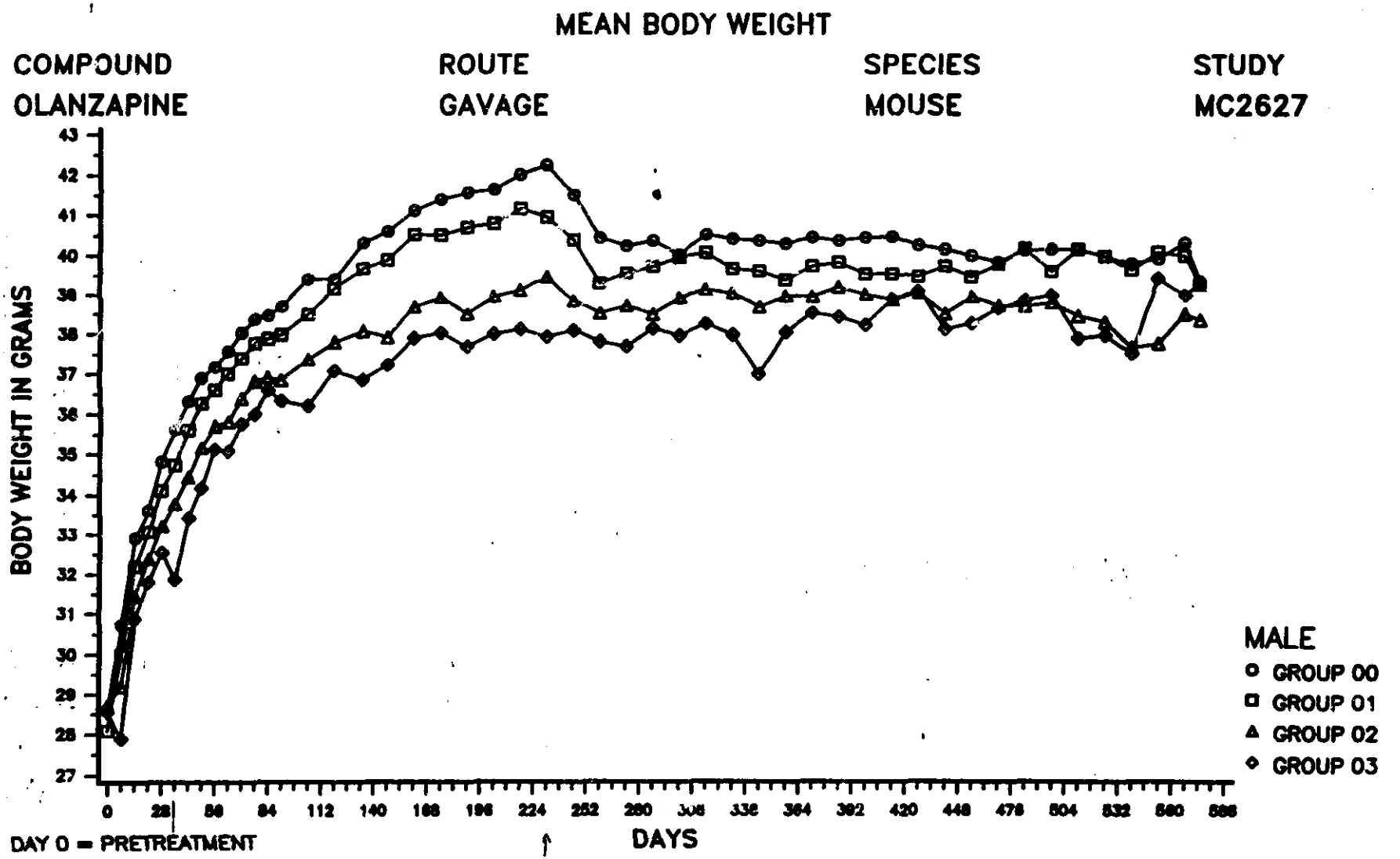
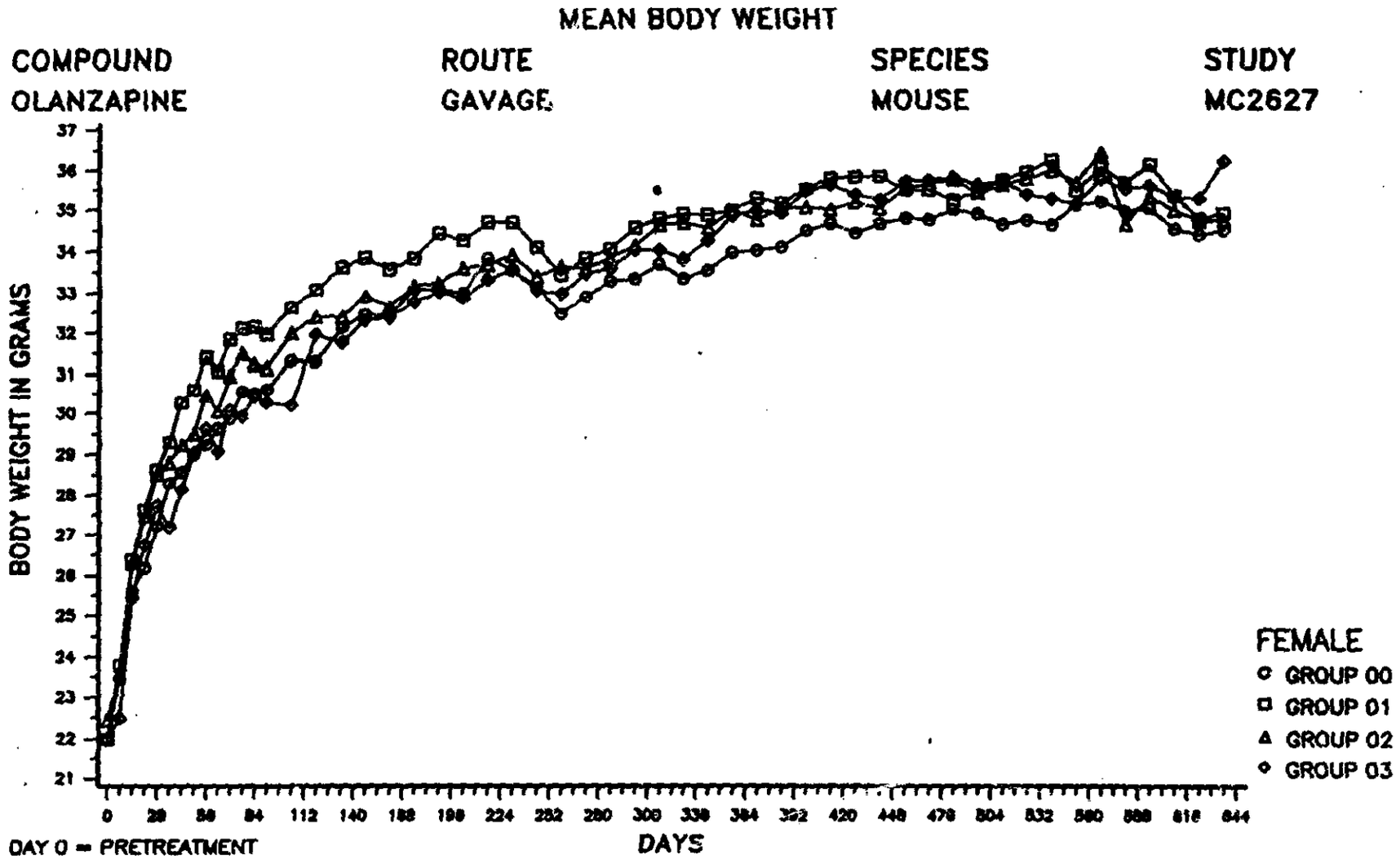


Figure F-1.2 Mean Body Weight.



Food Intake: food intake was measured weekly upto wk13 then every 3mo till end of study. The sponsor analyzed the data based on 2 phases: the 1st 13wks and, wk40 after study initiation till end of study; note that the dose was reduced from 30 to 20mg/kg during the 1st 3mo of study. Also, food intake during the 1st 13wks was based on gm per cage per wk (3 mice/cage) that was converted to gm/mouse/day prior to analysis. However, after wk13, food intake was based on individual mouse consumption. During the 13wks, males in HD consumed sig more food than the corresponding cont (22%). Food intake was also incr in MDm during wks 1,8,9,11, and 13 however, this incr did not reach statistical sig. From wk40 till end, mean daily intake for males in all dose gr was more than the cont by 7, 14, and 20% respectively for 3, 10, and 30/20mg/kg. Females during the 1st 13wks (few exceptions), ate sig more than the cont by 12, 11, and 11% for 3, 10, and 30/20mg/kg doses respectively. From wk 40 till end of study, the average daily intake for females was sig more than that for the cont by 13, 14, and 19% respectively. Therefore, a correlation between wt loss and food intake did not exist.

Hematology: drug-related effects included: dose-related (MD&HD mainly), decr in WBC (60-70%) in males resulting from a decr mainly in lymphocytes and neutrophils, also, some RBC parameters were decr dose-dependently though the changes did not reach statistical sig. The lymphocyte count was decr 70&87% in MD&HDm respectively, and the neutrophil count was decr 34&29% respectively. The monocyte and eosinophil counts were also reduced sig and dose-dependently in MD&HDm (80&84% and 90% respectively). In females however, there was a sig incr in WBCs and lymphocytes in HDf although there was a great deal of interanimal variation in values. A dose-dependent decr was noted in eosinophils (sig only in HDf, 90%).

In the supplemental study# M02891, mice were administered olanzapine at the same doses above (3, 10, 30/20mg/kg) and monitored for TK and hematology at 3, 6, 12, and 15mo. There was a dose-dependent decr in WBCs (mainly lymphocytes and neutrophils) this time in both males and females at 3, 6, and 12mo but, no effect in either sex was measured at 15mo and also in males at 12mo (see attached tables from the sponsor). Also, the Monos and Eos count was decr in both sexes several times reaching sig in MD&HD at 3, 6, and 12mo. The changes in RBC parameters were random and usually non-dose-dependent.

Mouse Oncog. Study #103

Appendix H (Continued).

Lymphocyte and Neutrophil Counts in Female Mice at Various Sampling Intervals.

	Month							
	3		6		12		15	
Dose (mg/kg)	Lyms (th/µl)	Neuts (th/µl)	Lyms (th/µl)	Neuts (th/µl)	Lyms (th/µl)	Neuts (th/µl)	Lyms (th/µl)	Neuts (th/µl)
0	3.93	0.700	6.03	0.967	4.583	1.833	3.13	1.58
3	4.08	0.667	2.75*	0.733	2.917	0.717*	2.90	1.85
10	2.72	0.517	2.18*	0.333*	1.950*	0.667*	1.88	1.42
30/20	0.98*	0.320	1.66*	0.520*	2.000*	0.750*	2.43	1.42

*P<0.05, Two Tailed Trend T on Ranked Data

The decreases which occurred in other leukocytic parameters, e.g. monocytes and eosinophils, were not considered intrinsically important because they were anticipated with the decreases in lymphocyte and neutrophil counts and were therefore of secondary significance.

Administration of Olanzapine (LY170053) was associated with slight to moderate reductions in leukocyte, lymphocyte, and neutrophil counts at the 3-, 6- and 12-month time points but not the 15-month time point. In males, these changes were observed in the mid- and high-dose groups at 3 and 6 months, and in all dose groups at 12 months. In females, the high-dose was affected at 3 months, and all dose groups were affected at 6 and 12 months. The means of lymphocyte and neutrophil counts are tabulated below:

Lymphocyte and Neutrophil Counts in Male Mice at Various Sampling Intervals.

	Month							
	3		6		12		15	
Dose (mg/kg)	Lyms (th/µl)	Neuts (th/µl)	Lyms (th/µl)	Neuts (th/µl)	Lyms (th/µl)	Neuts (th/µl)	Lyms (th/µl)	Neuts (th/µl)
0	4.03	1.017	4.98	1.000	6.97	3.97	4.67	2.42
3	3.95	0.717	3.28	1.867	3.33*	1.33	2.80	1.74
10	1.45*	0.300*	3.13*	0.667	2.13*	1.17	3.45	2.37
30/20	1.22*	0.250*	2.58*	0.650	2.20*	1.53	—	—

*P<0.05, Two Tailed Trend T on Ranked Data

Clinical Chemistry: glucose was decr dose-dependently in MD&HD mice. BUN incr dose-dependently in MD&HD mice, enzyme levels in general were incr sig in both sexes and those that did not reach statistical sig showed high variability. BUN levels incr 41-94% in males and 26-89% in females. This incr was accompanied by an incr in inorganic phosphate levels (17-27% in HDm&f).

Dose	Glu	BUN
0	150±6 (135±5)	32±3.0 (27±2)
MD	99±9 (102±7)	45±3 (34±6)a
HD	61±10 (70±7)	62±7 (51±8)

Dose	ALT	ALP	AST	CPK	TG	Chol
0	43±5 (33±2)	50±5 (59±4)	67±5 (85±6)	121±12 (154±19)	64±4 (53±3)	136±10 (90±3)
MD	74±13 (33±3a)	46±3a (58±5a)	112±10 (108±10)	449±122 (273±74a)	34±3 (52±4a)	106±7 (86±5a)
HD	53±6 (50±9)	55±7 (57±5a) •	108±8 (150±13)	413±90 (345±58)	21±3 (36±4)	81±8 (80±6a)

values are means±s.e.m. () are values for females
- All values are statistically sig different from the cont unless indicated otherwise.
a not sig different from the cont.

Electrolyte levels were also affected in males and females including small but sig decr in Ca in MD&HD mice (3-8%). In males, total proteins and Alb levels were decr in dose-dependent manner in MD&HD animals ($p<0.05$; 6-18%)(also globulin in HDm). Some of these parameters were similarly affected in females but the values did not reach statistical sig.

TK Analyses (ADME report#20): plasma conc. incr with dose this incr was non-linear, there seem to be no sex difference at the 2 low doses. Drug was not detectable by 24hr postdose in any gr indicating no accumulation. Due to high mortality, plasma levels were not measured in HDm at 15mo and there was a large interanimal variation in females, the no. of animals was small (n=2) or drug was BLQ. Table below presents mean plasma levels over the 15mo period (±s.d.):

Dose (mg/kg)	plasma conc (ng/ml) males	females
3	40±16	31±8
10	160±36	157*
30/20	**	377±166

* s.d. not reported.
** data not calculated for males due to very low values at 6mo and absence of data at 15mo due to high mortality.

Table below provides mean±s.d plasma levels for each time period:

Mean Plasma Concentrations (ng/ml ± SD) of LY170053 Following the Oral Chronic Administration of LY170053 to Male and Female CD1 Mice for 15 Months (Toxicology Study M02891)

Dose (mg/kg)	Time (hrs)	Month 6		Month 12		Month 15	
		Male	Female	Male	Female	Male	Female
3	0.5	51.1 ± 20.4	29.7 ± 22.6	46.8 ± 5.93	39.7 ± 8.25	21.8 ± 1.49	24.9 ± 7.03
	24	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
10	0.5	179 ± 38.7	197 ± 26.5	182 ± 47.9	NC	119 ± 11.1	116[a]
	24	BLQ	BLQ	BLQ	BLQ	NS	BLQ
20	0.5	34.9 ± 28.4	462[a]	505 ± 16.1	484[a]	NS	186[a]
	24	BLQ	BLQ	BLQ	BLQ	NS	BLQ

BLQ = Below Limit of Quantitation (1 ng/ml)
NC = Not Calculated (values outside of standard curve)
NS = No Samples
[a] n=2

Table below presents range of plasma conc (males and females combined):

Dose	time(hr)	Range of Plasma Levels (ng/ml) 6months	12months	15months
3	0.5	4-73	31-54	19-33
	24	BLQ-5.5	BLQ	BLQ
10	0.5	143-220	153-237*	101-131
	24	BLQ	BLQ	BLQ
20	0.5	8-614	483-523*	8&364**
	24	BLQ-3.2	BLQ-2.0	BLQ

BLQ below detection limit of 1ng/ml
* some values were not calculated because they were outside the standard curve.
** only 2 values.

Organ wts: the following organs were weighed: kidneys, liver, heart, spleen, ovaries, testes, and brain. The absolute wt of testes was decr in all 3 drug gr but the relative wt was decr only in HD. These decr ranged between 12-24%. The absolute wt of the brain was sig decr in MD&HDm but no change in females or in the relative wt. The relative wt of the ovaries showed large variations in MD&HDf; none of the values reached sig level. No other changes were observed. In general, the changes in organ wt were minimal.

Gross Morphology: no sig drug related changes.

Histopathology: non-neoplastic lesions included a dose-related incr in the incidence of mouse urologic syndrome (MUS) in males (all drug grs), and neoplastic lesions included incr in mammary gland tumors (adenocarcinoma and adenomas) in MD&HDf, and lymphosarcoma in females from all doses. Urologic syndrome was defined by the sponsor as the collective combination of the following lesions: cystitis, prostitis, nephritis, distended bladder, renal tubular cysts, and hydronephrosis. MUS was found mainly in males though one HDf died from this syndrome. The incidence in males was 6, 12, 13, and 24 out of 60 mice in each dose gr (0, 3, 10, 30/20mg/kg, respectively); this syndrome contributed to 40% of all deaths in males.

Statistical analysis by the sponsor showed a sig increase in the following neoplastic lesions: mammary gland adenocarcinomas, lymphosarcomas, and lung alveolar/bronchiolar carcinomas, all in females.

The combined incidence of mammary gland adenocarcinomas (fatal+incidental) was 0, 2, 4, and 6 of 60 mice in each gr for cont, 3, 10, and 30/20mg/kg respectively, and the combined incidence adjusted for mortality was 0, 11, 18, and 24% respectively. From the table below by the sponsor, a sig incr was noted in fatal tumors in MD&HDf; no fatal tumors in the cont therefore, producing mortality adjusted rates of 14&13% for MD&HDf. Time to onset was also incr sig in these 2 grs. There was one adenoma in HDf the rest were adenocarcinomas causing the mortality adjusted rate in HD to be 24% for fatal and incidental tumors combined.

Table [illegible] *Summary of Peto's Trend Test for Adenocarcinoma and Adenoma Occurring in Mammary Glands in Female Mice from Studies M02691 and M02791 (Combined Number MC2627).*

		Dose Level of LY170053 (mg/kg)				
Tumor Type	Statistic	0	3	10	30/20	30/20*
combined	N	0	2	4	4	6
(onset)	p_r	0	.03	.07	.07	.08
	p_a	0	.11	.18	.19	.24
	Z_T		1.541	2.221	2.199	2.552
	P		.062	.013	.014	.005
fatal	N	0	0	3	3	3
(mortality)	p_r	0	0	.05	.05	.05
	p_a	0	0	.14	.13	.13
	Z_T		—	2.269	2.305	2.303
	P		—	.012	.011	.011
incidental	N	0	2	1	1	2
(prevalence)	p_r	0	.03	.02	.02	.03
	p_a	0	.11	.04	.06	.13
	Z_T		1.541	.862	.638	1.249
	P		.062	.194	.262	.106

N = tumor incidence.
p_r = raw tumor rate.
p_a = tumor rate adjusted for mortality.
Z_T = test statistic for increasing trend in rate of tumor incidence.
P = 1-tailed p-value for trend test.
*: results from analysis of adenocarcinoma and adenoma combined.

Lymphosarcomas were found in many tissues and were analyzed as a *whole animal finding* rather than a tissue-specific finding. The combined (fatal+incidental) incidences for 0, 3, 10, and 30/20mg/kg in females were : 4/60, 10/60, 9/60, and 10/60 respectively, and in males: 4/60, 3/60, 0/60, and 1/60 respectively. Although there was no sig difference in the fatal incidecne, a sig incr was found in incidence of fatal + incidental combined in all 3 female grs (see table below from the sponsor). Fatal tumors were further analyzed using ANOVA and there was no sig difference in the mean time to death among the grs. The mean time to death due to fatal lymphosarcomas was 59, 62, 71, and 69 weeks for the cont, 3, 10, and 30/20mg/kg respectively. The lymphosarcoma incidence in females was stated to be within the published historical level for CD-1 female mice: 3-22% (Sher et al., 1982), 31% (Homburger et al., 1975), 8-27% (Malta et al., 1988), and 9-13% (Engelhardt 1993). The lymphosarcoma historical incidence in cont female CD-1 mice from the in-house data is approximately 8-15% and the adjusted incidence for survival is 10-22%. Therefore, the sponsor indicated that the incidecne of lymphosarcoma in the cont females in this study was low compared to their historical lab data as well as being within those in the published literature (see above). Also, the incidence of lymphosarcoma was not incr in male mice nor in the male or female rats (see report# 42 to follow). Lymphosarcoma in this study affected 9% of all mice and produced 71% fatality index and contributed to 11% of all fatalities. [detailed discussion of this finding is found in the overall summary for the carcinogenicity studies]

Table K-5. Summary of Peto's Trend Test for Whole Animal Lymphosarcoma in Female mice from studies M02791 (Combined Number MC2627).

M02791/R

Tumor Type	Statistic	Dose Level of LY170053 (mg/kg) 0	3	10	30/20
combined	N	4	10	9	10
(onset)	p_r	.07	.17	.15	.17
	p_a	.09	.24	.24	.36
	Z_T		1.878	1.673	2.178
	P		.030	.047	.015
fatal	N	3	7	7	5
(mortality)	p_r	.05	.12	.12	.08
	p_a	.06	.15	.17	.13
	Z_T		1.453	1.433	1.046
	P		.073	.076	.148
incidental	N	1	3	2	5
(prevalence)	p_r	.02	.05	.03	.08
	p_a	.03	.10	.06	.26
	Z_T		1.222	.865	2.363
	P		.111	.194	.009

N = tumor incidence.
p_r = raw tumor rate.
p_a = tumor rate adjusted for mortality.
Z_T = test statistic for increasing trend in rate of tumor incidence.
P = 1-tailed p-value for trend test.

The incidence of lung alveolar/bronchiolar carcinomas and combined carcinomas + adenomas was sig incr in LD (see table below from sponsor). Mortality adjusted rate for carcinnomas was 3&17% for cont and LD, and for the combined tumors, the rates were 12&33% respectively.

Table K-7. Summary of Peto's Trend Test for Alveolar/Bronchiolar Carcinoma and Adenoma Occurring in Lungs in Female Mice from Studies M02691 and M02791 (Combined Number MC2827).

Alveolar/bronchiolar carcinoma

Tumor Type	Statistic	Dose Level of LY170053 (mg/kg) 0	3	10	30/20
Incidental	N	1	5	1	0
(prevalence)	P_r	.02	.08	.02	0
	P_a	.07	.17	.04	0
	Z_T		1.903	.376	-.643
	P		.029	.353	.740

Alveolar/bronchiolar carcinoma and adenoma combined

Tumor Type	Statistic	Dose Level of LY170053 (mg/kg) 0	3	10	30/20
Incidental	N	6	15	8	3
(prevalence)	P_r	.10	.25	.13	.05
	P_a	.12	.33	.21	.11
	Z_T		2.295	.732	-.909
	P		.011	.232	.818

N = tumor incidence.
P_r = raw tumor rate.
P_a = tumor rate adjusted for mortality.
Z_T = test statistic for increasing trend/in rate of tumor incidence.
P = 1-tailed p-value for trend test.

Other statistically sig tumors included pheochromocytoma and combined hepatocellular carcinoma and adenoma in MDm. In the former tumor only 3 tumors were found, and in the latter, the incidence was sig different only when the adenomas were combined with the carcinomas. The mortality adjusted rate for the combined hepatocellular tumors was 19&7% for the MD and cont respectively.

The table below summarizes all lesions with incidences higher than the cont (may/may not be statistically sig)(all incidences are of 60 male and 60 female mice per gr unless specified otherwise):

Finding	cont	LD	MD	HD
whole animal				
lymphosarcoma	4m, 4f	3m, 10f	9f	1m, 10f
mammary gland				
Adenocarc.	0	2/39f	4/39f	4/44f
Adenoma	0	0	0	2/44f
lung alveolar/bronch.				
Carcinoma	1m, 1f	1m, 5f	1/59m, 1f	0
Adenoma	8m, 5f	6m, 10f	6m, 7f	3f
Hepatocellular				
Carcinoma	1m	3m	3/59m	0
Adenoma	2m, 1f	4m	3m	1m
Ovary granulosa-theca/malignant	0	0	0	1/59f
Thyroid follicular cell adenoma	0	0	1/56m	0
Pituitary adenoma	0	0	0	1/53f
Metastatic neoplasia	1f	2m, 2f	7f	7f

The 0 value refers to absence of finding in male and female.

Summary and Conclusions:

Daily oral administration of olanzapine to male and female mice at 3, 10, and 30/20mg/kg for up to 21mo caused death in HD (22% males and 32% females). Consequently, the 30mg/kg dose was reduced to 20mg/kg on study day 100. The main clinical sign was hypoactivity noted in all drug grs occurring within 15min of dosing and severity incr with dose. The final mean B.wt and wt gain of drug grs was similar to that of the cont. However, B.wt and wt gain were reduced in MD&HDm starting at 1mo postdosing and until mo13 (decreasing 7&10% of the cont at 9mo); no sig effect in females. The changes in B.wt were not correlated with the changes in food consumption since the latter was incr from start to end of study both in males and females. The main drug effect on hematology was a dose-dependent decr in WBC count in males and females due to the decr in lymphocytes and neutrophils as well as the monos and eos when blood analyzed at 3, 6, and 12mo but the values were comparable to the cont at 15mo. Drug effect on clinical chemistry was inconsistent however, some changes seem to be drug related since they've been reported in other tox studies: dose-dependent decr in gluc, dose-dependent incr in BUN&IP, sig incr in ALT, AST, and CPK, and decr in TG and Chol. Also, total protein levels and Alb were reduced dose-dependently in MD&HD mice. Plasma conc incr non-linearly with incr in dose and there was no sex difference; the levels ranged between 4-523ng/ml and at some points values were BLQ of 1ng/ml. The drug was absorbed rapidly since

conc were measurable by 0.5hr postdose in all doses, this time is also when C_{max} was reached. The only change in org wt that could be drug related was a decr in absol and rel wt of the testes in HD. There were no changes in gross morphology. Non-neoplastic findings included dose-related incr in mouse urologic syndrome mainly in males. This was evident from the changes in BUN and electrolyte levels as well as the higher rate of infection due to the decr in WBC count. Neoplasia included incr incidence of mammary gland adenocarcinomas in females (0, 2, 4, and 6 out of 60 mice in each gr of cont, 3, 10, and 30/20mg/kg respectively). Also lymphosarcoma incidence was incr in females but was stated by the sponsor to be within the historical data (not provided) and non-dose dependent incr in lung tumors. Based on these data, it can be concluded that olanzapine caused mammary gland tumors in mice at plasma levels that were 2.6x the max human exposure based on a ng/ml basis (mean plasma level of MD was 157ng/ml; max conc in humans was 60ng/ml after a single dose of 20mg/d).

In this study, the sponsor concluded that the MTD was exceeded because the increased mortality in HD mice was not entirely due to fatal tumors in the animals that died. Therefore, another study was conducted in mice at lower doses (discussion to follow).

Oncogenic and blood level studies in CD-1 mice given olanzapine (LY170053) daily by gavage for the duration of their life span/Report# 67/Studies# M09393, M09493 (together referred to as study#MC9394), and M09593/Lilly labs, IN/Report Date: /Study initiation Aug 1993/GLP.
Lot# 029JD3, purity: 99%

This study was conducted because, as the sponsor stated, the doses in the previous study (# M02691, M02791, and M02891) exceeded the MTD. Therefore, the sponsor initiated the present study at lower doses to better characterize the carcinogenic potential of olanzapine.

Studies M09393 and M09493 are identical in protocol, animal #/sex/dose. These studies were initiated 1wk apart and the animals were from 2 different shipments from the same supplier.

Species/wt/Age: CD-1 mouse/initial mean wt±s.d. males 29.6±1.9g and 22.9±2g for females study# M09393&M09493 and for study# M09593 male wt was 31.4±2.4g and female wt, 24.5±2g/6-7wk initial age.
Dose/Duration: 0.5, 2, 8mg/kg/d/duration: 19m for males and 21mo for females study MC2627 and 15mo for both sexes study M02891/oral gavage (10ml/kg volume), control gr administered the same vol of the vehicle (10% w/v aqueous acacia solution). Few drops of simethicone emulsion were added to drug and control suspensions to decrease foaming.
No./sex/dose: 9/sex/control gr and 15/sex/dose for drug grs for study# M09593. 60/sex/gr for study#s M09393&M09493 (MC9394).

Parameters measured: clinical signs and survival (daily with thorough exam weekly), B.wt (weekly for the 1st 13-14wks then every 2wks), food intake (weekly for the 1st 13-14wks then every 2wks), food efficiency (B.wt gain per 100g food ingested), hematology (from survivors at necropsy for study#s M09393 and M09493 (fasting); and for study# M09593 from 6/sex/dose at 6 and 12mo (non-fasting); orbital sinus puncture), clinical chemistry (from survivors at necropsy for study#s M09393 and M09493; fasting; orbital sinus), toxicokinetics (0.5hr at 6 and 12mo; blood bled from the orbital sinus (non-fasting rats) will be collected from 6/sex/dose), organ wt, gross exam and histopath (all grs).
Statistics: Dunnett's t-test/ANOVA. Tumor incidence, onset, and mortality rates will be analyzed statistically by Peto's dose-response test after adjustment for mortality; Tarone test (1975) analyzes dose-related trend in mortality which incorporates stratum defined by time of death. Significance at the 0.05 level was used and 1-sided for increasing mortality.

Results:
Survival: there was no drug-related effect on survival, for studies M09393 and M09493 by end of study at month 21. Survivability was 67, 57, 62, and 53% for males and for females, 53, 47, 53, and 60% at 0, 0.5, 2, and 8mg/kg gr, respectively. Only 2MDm and 1HDm died in study# M09593.

Clinical Signs: included hyperactivity in all HDm and 31/60 HDf compared with 2/60 each in male and female cont, palpable mass in abdomen, rough hair coat, and soiling. Other signs were common to all mice or had small incidences.
**B.wt: (studies M09393&M09493): sig decr noted in mean wt and wt gain in HDm starting at 3rd wk through study month19. The max difference occurred during month11 when mean wt and wt gain were 7&23% lower than the corresponding values in cont, respectively. Mean wt in MDm was reduced during the1st 3mo reaching statistical sig occasionally, however, the wt was comparable to the cont thereafter. In contrast to males, MD&HDf had an incr in mean wt and/or wt gain. Mean wt and wt gain were sig incr in HDf from mo1 through 18 or 19 and maximum incr for mean wt and wt gain was 9 and 93% more than the cont during mo1, respectively. MDf, mean wt was sig incr from mo1 through 12 and months 15&16 whereas, wt gain was sig incr between months1 through 19. Maximum incr in mean wt and wt gain for MDf was 6 and 30% more than the cont, respectively. There were no sig effect on either parameter for LD males or females (see attached figures from sponsor).

olanzapine/NDA 20-5[illegible]
Mouse oncog. study - 2nd study/ #M09393 & M09493

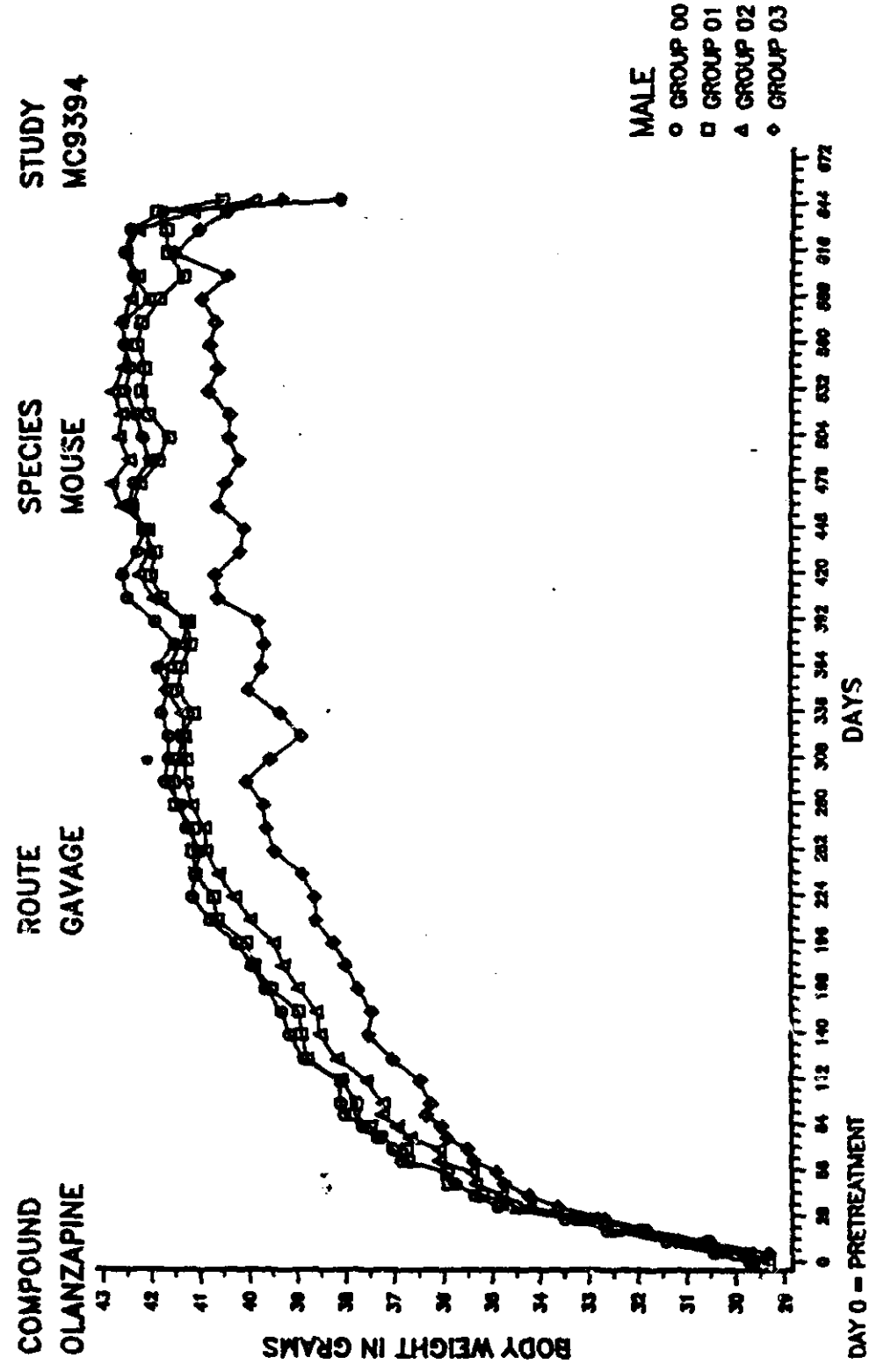
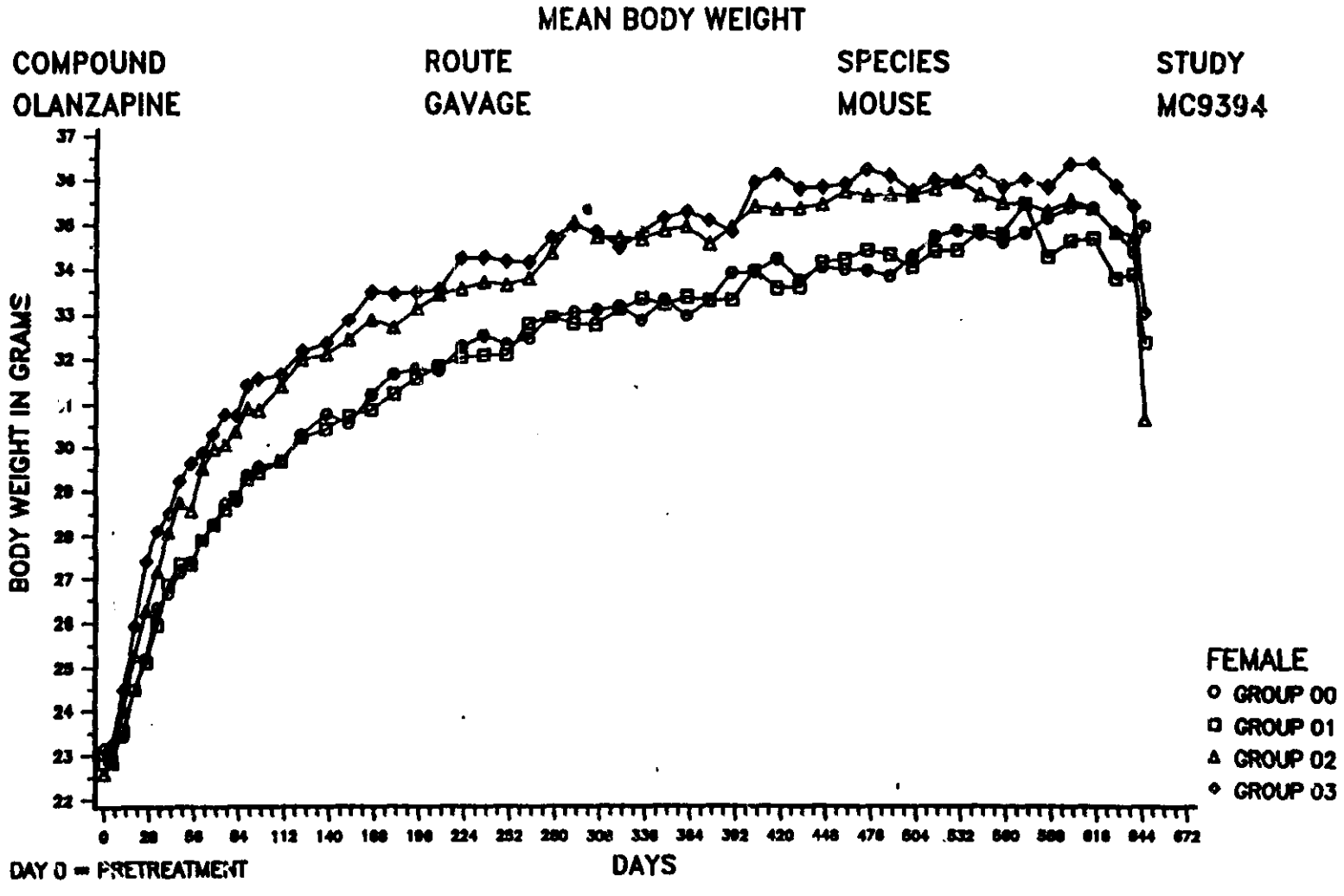


Figure F-1.1. Mean Body Weight.

Figure F-1.2. Mean Body Weight.



Food Intake: cummulative food intake was sig incr in MD&HD mice; this is in contrast to the decr in B.wt of MD&HDm. Relative food intake was sig incr in males from all drug grs and HDf. At end of study, cummulative food intake was incr 5&10% for MD&HDm and 5&8% for MD&HDf respectively. Relative food intake at termination was incr 7&13% in MD&HDm above the cont; for females, the incr was sporadic throughout the study, sometimes reaching statistical sig in MD&HDf. Efficiency of food utilization (EFU) was sig decr in HDm but sig incr in MD&HDf. Cummulative EFU at end of study, was sig decr in HDm at 15% less than the cont. Cummulative EFU in MD&HDf was sporadically but sig incr throughout the study but comparable to the cont at termination. There were no sig drug effect on cummulative EFU for LD or MDm and LDf.

Hematology (Studies M09393&M09493): the only sig changes were a 32% decr in total WBCs in HDm relative to the cont that was attributed to a 35% decr in lymphocyte count and 27% decr in neutrophils of HDm. Eosinophils were also reduced in HDm (62% less than the cont) but did not reach statistical sig. There were no corresponding changes in females.

The following parameters were affected in study# M09593 (6/sex/dose/time point):
6&12months: No change in any RBC parameter in males or females except for a slight but sig incr in MCH of HDm (6%). All effects on WBCs noted in 6months (see below) were absent at 12months in males and females.

6months: WBCs (all comparisons relative to the cont):

total WBC	dose-dependent decr in all 3 male gr (33-54%)/non-dose dependent decr in all 3 female gr (35-60%).
lymphos	decr in all 3 male gr (dose-dependent in the 2 high doses)(49-61%)(3.6±0.5; 3.8±0.5; 2.9±0.6 in 0.5, 2, and 8mg/kg doses respectively, vs. 7.4±1.6 in cont)/no effect in females.
Neutr	decr in MD&HDm (non-dose dependent)(31&18% respectively)/dose-dependent decr in all female grs (47-55%).

Clinical Chemistry: the following were statistically sig changes noted only in HD relative to the cont:

HDm		HDf	
glucose	14% ↓	Creatinine	10% ↑
BUN	54% ↑	AST	38% ↑
Ca	4% ↓	Globulin	9% ↑
P inorg	7.5% ↓		

TK: blood was pooled from 2 mice therefore, producing a total of 3 samples per dose.

Dose (mg/kg)	sex	Plasma conc. (ng/ml) 6months	12months
0.5	m	4.8±0.3	8.4±2.3
	f	4.0 ±0.3	5.0 ±0.64
2	m	24.2±5.4	37.6±13.7
	f	20.5±4.5	30.0±5.7
8	m	258±10.0*	227.3±33.3
	f	162±26.0	170±31.6

values are means±s.d.; n=3; detection limit (dl) 1ng/ml
* extrapolated value since original values were outside the range of standard curve (1-100ng/ml).

Plasma conc ranges were (ng/ml):

	6months	12months
LD	3.8-5.2	4.3-8.6
MD	17-25.6	25-52
HD	139-269*	149-254

* value outside standard curve (1-100ng/ml) so it had to be extrapolated.

Plasma levels increased linearly between the 0.5 and 2mg/kg doses but non-linearly between these 2 doses and HD. The values for HD were several fold higher than those at the 2 lower doses (6-10x higher than those at 2mg/kg). There was no sex difference except in HD at 6mo where males had values outside the standard curve i.e. higher than the conc in females (250, 255, and 269ng/ml for the 3 male samples vs. 139, 157, and 190ng/ml for the 3 female samples); no difference at 12mo. Note that the mean for HD at 6mo had to be extrapolated because the values fell outside the range for the standard curve (1-100ng/ml). Also note, that these conc were relatively comparable to those recorded in the previous mouse oncogenicity study at doses 3 and 10mg/kg (see above). The sponsor indicated that the sex difference noted in HD at 6mo and the much higher values for HD than those predicted from the 0.5mg/kg could be related to the small sample size and the fact that some of the values had to be extrapolated.

Organ wts: changes in organ wts were non-dose dependent and random occurring mainly in HD.

Liver	decr absol. in HDm (15%) but incr in HD&MDf (14%); incr rel/B.wt MD&HDf (12&10% respectively, non-dose dependent).
spleen	decr absol (28%); decr rel/B.wt in HDm (not sig 29%).
testes	incr absol (89%; not sig, high variation (large s.d.); 391±175 vs. 206±7.5 in cont); incr rel/B.wt HDm (80%; not sig; large variation: 90±36 vs. 50±2 in cont).
heart	incr absol in HDf (12%); incr rel/B.wt in MD&HDm (9%; non-sig in MDm); incr rel/B.wt HDf (10%).
ovaries	incr in absol HD&MDf (64&113& % respectively, non-dose dependent and not sig); incr in rel/B.wt in all 3 female gr non-dose dependent and not sig (64-100%).
brain	incr absol in HDf (2%).
kidney	incr rel/B.wt MD&HDm (dose dependently, 6&12% respectively).

Liver wt relative to brain wt was sig decr in HDm (14%) but sig incr in HDf (11%), spleen wt rel to the brain was sig reduced in HDm (26%), and heart wt rel to brain wt was sig incr in HDf (8.6%).

Gross Morphology: no sig drug-related findings. Alopecia, rough hair coat, and soiled mice were noted in all gr including cont but slightly higher incidence in HD.

Histopathology: no sig drug-related findings in any gr. There was heart degeneration noted as follows (out of 60 mice/sex/gr): 1m cont, 1MDm, 5HDm; 0f cont, 3MDf, 1HDf; heart fibrosis was seen in: 1LDm, 1MDm, 4HDm, 1MDf, 5HDf; and 0 incidence in male and female cont mice. There was also a dose-dependent incr in slight histiocytosis in females: 7 cont, 10LDf, 11MDf, and 12HDf.

Neoplasia:
Incidence of non-neoplastic findings (all incidences are for 60 male or 60 female mice):
The following findings occurred at high incidences in drug gr relative to the cont; when incidences are reported only for 1 sex, they may mean either they did not occur in the other sex, or the incidence was low and not different from the cont.

Finding	cont	LD	MD	HD
amyloidosis	10m/10f	13m/15f	11m/16f	5m/13f
MUS*	8m	9m	14m	20m
Hydroneph.	7m	2m	7m	13m
Kid. Dilation	6m	9m	13m	20m
Urin.bladder Inflammation	0	0	3m	4m
Heart Degen.	1m	0	1m	5m
Heart fibrosis	0	1m/0f	1m/1f	4m/5f
Vagin. Change**	11f	6f	17f	28f
Prost. Inflam.	2m	0	5m	5m
Semin. Vesic. Inflam.	0	0	1m	4m
Mammary gl. Hyperplas.	0	0	1f	1f
Eye Keratits	7f	8f	9f	13f

* Mouse urologic Sundrome.
** changes unspecified.

Benign neoplastic lesions:				
Pituitary adenoma	1f	1f	1f	3f
Malignant neoplasia:				
Lymphosarcoma	14f	7f	13f	11f
Hemangiosarcoma	0	1f	1f	3f
Mammary gl. Adeno-carcinoma	0	0	3f	6f

Statistical analyses of tumors showed a sig and dose-dependent increase in adenocarcinoma of mammary glands in MD&HDf for onset and prevalence but not for fatal incidence (see attached table fron sponsor). These tumors were also incr sig in the previous mouse car. study (MC2627) at doses ≥10mg/kg. The difference between the 2 studies, is that in MC2627, the incr was contributed to fatal tumors however, in the present study, these tumors were incidental. Note also, the zero incidence in the cont gr in both studies.

In study MC2627, the combined incidence (fatal and incidental) of lymphosarcoma in female mice was sig incr at doses ≥3mg/kg. However, there is no sig trend in the present study (MC9394) regarding lymphosarcomas (tumor incidence: 14, 7, 13, and 11 in 0, 0.5, 2, and 8mg/kg respectively, vs. the original study: 4, 10, 9, and 10 in 0, 3, 10, and 30/20mg/kg respectively). The sponsor indicated that the sig result in study MC2627 was due to the low incidence in the cont and not to the increased rate in drug grs. This is seen from the similar mortality adjusted rate for the two studies (28 and 26% for MC2627 and MC9394 respectively, whereas the adjusted rate for the controls in these 2 studies were 9 and 31% respectively.

The combined (fatal and incidental) incidence of hemangiosarcoma in the livers of female mice was sig incr in MD&HDf (see attached table from sponsor). However, the rate of fatal hemangiosarcomas was too small to analyze and that for prevalence did not show a trend. Therefore, it was concluded that this finding was not drug related.

Summary and Conclusions:
This study is a repeate for the mouse oncogenicity study because the sponsor felt that the MTD was exceeded in the previous mouse study discussed above (#MC2627). Olanzapine was orally administered to male and female mice at 0, 0.5, 2, and 8mg/kg for 18 or 21mo. The drug had no effect on survival at any dose and the high dose did not exceed the MTD. The main clinical sign was, as in previous studies, hypoactivity in HD animals. A **sig decr in mean wt and wt gain noted in HD** mice starting at wk3 through mo19 with the maximum decline occurring during month 11 when the 2 parameters were 7&23% lower than the corresponding cont value; the wt was comparable at end of study. **In contrast to the males, MD&HDf showed a sig incr in mean wt and wt gain**; these parameters were unaffected by treatment in LD. There was no correlation between food intake and B.wt, since food consumption was incr in MD&HD mice and at end of study, cummulative food intake was incr 5-10%. The drug effect on cummulative FEU was inconsistent between males and females. The effect of olanzapine on hematology was similar to those reported in previous tox studies i.e. **decr in total WBC count** (at the 6mo sample) mainly due to **decr in lymphocytes and neutrophils**. The effect on WBC was mainly observed in male mice, also the decr seemed to be transient since the values were comparable to the cont at 12mo measurement. The clinical chemistry parameters affected included in HDm: decr in glucose level and incr in BUN and in HDf, incr in AST, creatinine and globulin. Changes in organ wts were inconsistent and non-dose dependent some of the changes that seemed to be drug related include: **incr in absol and relative wt of the liver in MD&HDf, decr in absol and relative wt of the spleen, incr in absol and rel wt of the hea[illegible] in HDf, incr in absol and rel wt of the ovaries in MD&HDf, incr in absol.and rel wt of the testes in HDm, and incr in rel wt of the kidney in MD&HDm.** Plasma drug concentration was measured at 6&12mo, levels incr linearly with dose between the LD&MD but non-linearly between these doses and the HD with the HD being 6-10x higher than the MD. There was no difference in conc. between the 6&12mo measurements and no sex difference except at 6mo where males had higher values than the females. This sex difference may be caused by the small sample size and that some values had to be extrapolated since they were outside the standard curve. **Plasma conc ranged between 3.8-269ng/ml.** Non-neoplastic findings included MUS in males, hydronephrosis and kidney dilation in MD&HDm, heart degeneration in HDm and fibrosis in HDm&f, unspecified vaginal changes in HDf, mammary gland hyperplasia in MD&HDf, and eye keratitis in HDf. Neoplastic findings that reached statistical sig included **mammary gland adenocarcinoma and adenomas in MD&HDf for onset and prevalence** but not for fatal incidence (this tumor was also incr in the previous mouse carcinogenicity study), the combined incidence of female lymphosarcoma that was seen in the previous study (MC2627) was absent in this study; the **combined incidence of liver hemangiosarcoma in female mice was incr in this study.** It can be concluded that olanzapine caused mammary gland tumors in mice at exposures that are 0.4-4x the maximum human exposure of 60ng/ml measured after a single dose of 20mg/d.

2 yr. Mouse carcino. (Repeate)

Table 4. **Summary of Peto's trend test for adenocarcinoma occurring in mammary glands in female mice from Study MC0394.**

Tumor Type	Statistic	Dose Level of LY170053 (mg/kg) 0	0.5	2	5
combined	N	0	0	3	6
(onset)	p_r	0	0	.05	.10
	p_a	0	0	.10	.17
	Z_T		NT	1.962	2.719
	P		--	.025	**.003**
	P_x		--	.055	**.003**
fatal	N	0	0	1	2
(mortality)	p_r	0	0	.02	.03
	p_a	0	0	.03	.06
	Z_T		NT	NT	1.580
	P		--	--	.059
	P_x		--	--	.101
incidental	N	0	0	2	4
(prevalence)	p_r	0	0	.03	.07
	p_a	0	0	.07	.13
	Z_T		NT	NT	2.228
	P		--	--	**.013**
	P_x		--	--	**.016**

N = tumor incidence.
p_r = raw tumor rate.
p_a = tumor rate adjusted for mortality (strata for Weeks 92 and 93 combined).
Z_T = test statistic for increasing trend in rate of tumor incidence.
P = 1-tailed p-value for trend test.
P_x = exact 1-tailed p-value for trend test.
NT = no test according to sequential trend test or due to sparseness in tumor incidence.
The values in bold font indicate dose levels where trends in the adjusted tumor rates were statistically significant.

House carcinog - (Repeate)

Table 6. Summary of Peto's trend test for hemangiosarcoma occurring in livers in female mice from Study MC9394.

Tumor Type	Statistic	Dose Level of LY170053 (mg/kg) 0	0.5	2	8
combined	N	0	1	1	3
(onset)	p_r	0	.02	.02	.05
	p_a	0	.04	.02	.08
	Z_T		NT	NT	1.699
	P		--	--	.045
	P_x		--	--	.066
fatal	N	0	0	0	1
(mortality)	p_r	0	0	0	.02
	p_a	0	0	0	.03
	Z_T		NT	NT	NT
	P		--	--	--
	P_x		--	--	--
incidental	N	0	1	1	2
(prevalence)	p_r	0	.02	.02	.03
	p_a	0	.04	.02	.06
	Z_T		NT	NT	1.260
	P		--	--	.104
	P_x		--	--	.155

N = tumor incidence.
p_r = raw tumor rate.
p_a = tumor rate adjusted for mortality.
Z_T = test statistic for increasing trend in rate of tumor incidence.
P = 1-tailed p-value for trend test.
P_x = exact 1-tailed p-value for trend test.
NT = no test according to sequential trend test or due to sparseness in tumor incidence.

- A chronic toxicity and oncogenic study of olanzapine in Fischer 344 rats given daily oral doses for 2yrs/Report 42/Study# RC1740 (replicate studies# R11790 and R14090*)/Lilly Res Labs-IN/Report Date: Jan 1994/Study initiation Nov 1990/GLP.

* study RC1740 was divided into 2 replicate studies R11790&R14090 to facilitate scheduling for studies with large number of animals. These 2 studies were 3wks apart but were identical in protocol and animal number.
Lot# 58962, purity: 100%

Species/wt/Age: Fischer 344 rats/initial mean wt±s.d. 108.8±7.6g males and 90±5.4g females/ 5-7wk initial age.
Dose/duration: Males only: 0.25, 1, 2.5, 4mg/kg, Females only: 0.25, 1, 2.5/4, 4/8mg/kg (on day 211 for females only, the 2.5 and 4mg/kg doses were increased to 4 and 8mg/kg respectively*) /2yrs by oral gavage (2.5ml/kg volume; gavage was selected over food admixture because the drug was not stable in food); control gr administered the vehicle at 10% w/v aqueous acacia solution. Few drops of simethicone emulsion were added to drug and control suspensions to decrease foaming.
No./sex/dose: 60/sex/dose.

* the reason for increasing the dose was because after 6months of dosing, the wts of females did not change considerably relative to the control gr.

Parameters measured: clinical signs and survival (daily with thorough exam weekly), B.wt and food intake (weekly), food efficiency (weekly using wt gained (g) per 100g food consumed), hematology (6, 12, 18, and 24 mo; 20/sex/dose; orbital sinus puncture; non-fasting samples except for those at study termination), clinical chemistry (6,12,18, and 24months; 20/sex/dose; see hematology for other info.), urinalysis (6,12,18, and 24months; 20/sex/dose; collect urine for 5hr), toxicokinetics (blood bled from the orbital sinus (non-fasting rats) will be collected from 3/sex/dose/time point at 0.5 and 7hr postdosing on months 6, 8, 12, and 18), organ wt, gross exam and histopath (all grs)(see below for detail provided by the sponsor).*

20. ORGAN WEIGHTS

Weigh:

Kidneys	Ovaries	Thyroids W/parath
Liver	Testes	Brain
Heart	Prostate	
Spleen	Adrenals	

at termination of study.

21. ANATOMIC PATHOLOGY

Gross examination and histopathologic evaluation of:

Kidney	Stomach	Skeletal Muscle
Urinary Bladder	Duodenum	Bone
Liver	Jejunum	Bone Marrow
Heart	Ileum	Adrenal
Aorta	Colon	Thyroid
Trachea	Ovary	Parathyroid
Lung	Uterus	Pituitary
Spleen	Vagina	Cerebrum
Lymph Node	Testis	Cerebellum
Thymus	Prostate	Brain Stem
Salivary Gland	Seminal Vesicle	Spinal Cord
Pancreas	Skin	Sciatic Nerve
Tongue	Mammary Gland	Eye
Esophagus	Harderian Gland	

Sternum and femur will be collected for bone and bone marrow.
Lung will include bronchi.

Gross lesions will also be collected if present.

Schedules approximately for the following study days (animals):

728(45)	730(45)	732(40)	736(40)
729(45)	731(45)	735(40)	

Statistics: Dunnett's t-test/ANOVA; linear treatment contrasts will be tested in a sequential manner to determine dose-response (Tukey analysis), mortality was tested using the method of Tarone (1975), Peto's survival adjusted trend test for tumor incidence.

Doses for this study were selected based on 2wk and 3mc tox studies in rats. The doses used in the 2wk were 2, 6, 18, 54mg/kg and those in the 3mo were 2.4, 7.5, 22.5mg/kg.

Results:
Survival: high survival rate was noted in all gr. (See table and figures from sponsor). It ranged between 40-65% in males and 57-83% in females relative to the control (83% was noted in HDf). Two-tailed p value for females showed a sig decr in mortality (p=0.036).

2 yr. Rat carcing. Olanzapine N20-592

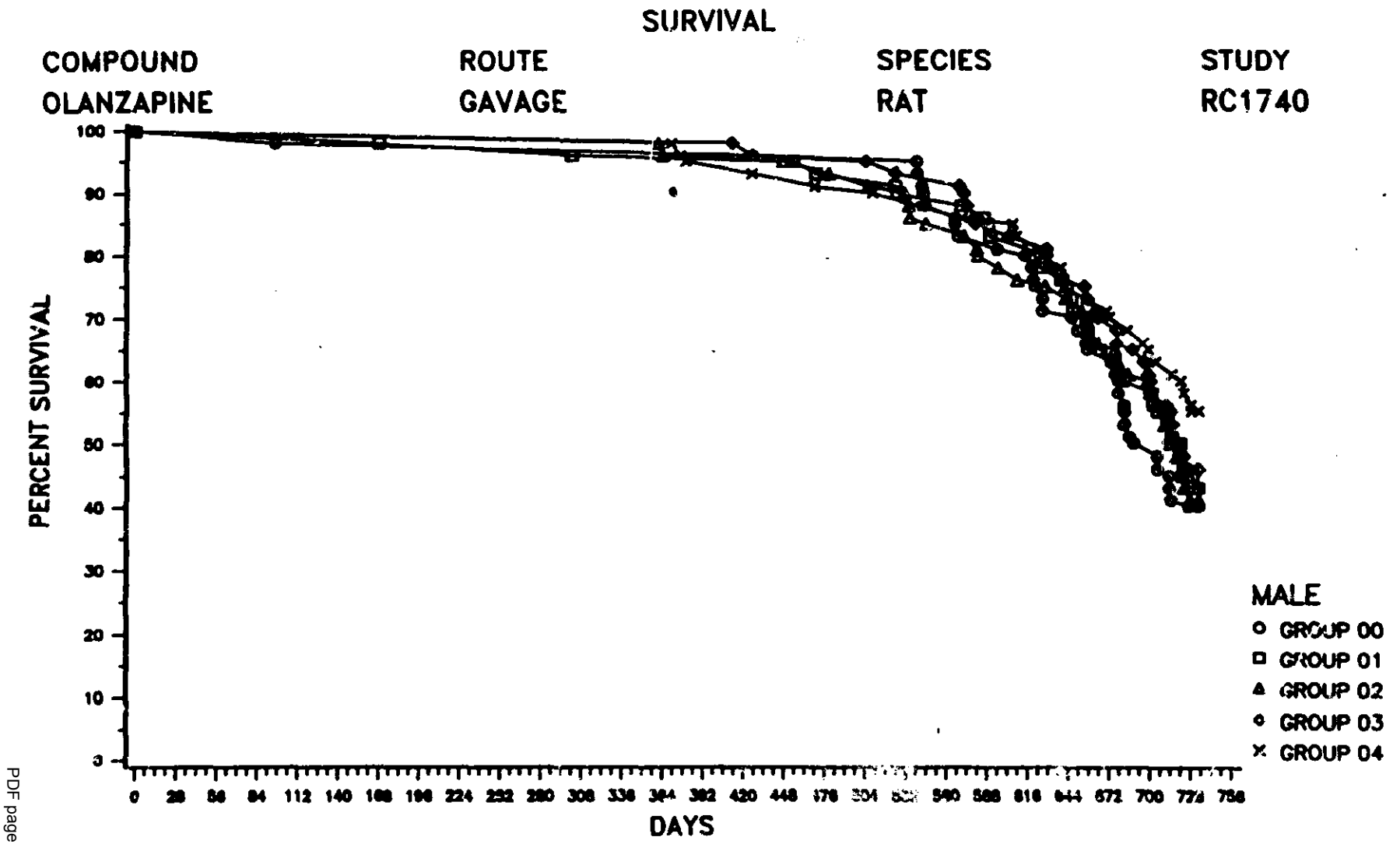
Table E-2. Summary of Growth, Survival, Food Consumption, and Efficiency of Food Utilization for Fischer 344 Rats Receiving Olanzapine by Gavage for 2 Years. Study RC1740.

Dose (mg/kg/day)	Mean Body Weight at Start (g)	Number of Survivors	Final Mean Body Weight[a]	Mean Body Weight Gain (g)	Mean Daily Food Consumption (g)	Mean EFU[b]
			Males			
0	108.5	24 40	395.1	286.4	18.5	2.1
0.25	107.6	26 43	390.4	282.9	18.6	2.1
1.0	109.7	25 42	380.6	272.1	19.4	1.9
2.5	108.7	28 47	394.0	284.8	18.7	2.1
4.0	109.7	33 55	362.3	253.5 11%	17.5*	2.0
			Females			
0	90.8	39 65	306.6	215.5	14.6	2.0
0.25	90.3	34 57	315.1	224.3	14.8	2.1
1.0	89.0	35 58	313.4	223.9	15.0	2.1
2.5/4.0[c]	89.0	37 62	266.1*	176.6* 18%	14.6	1.7*
4.0/8.0[c]	91.6	50 83	235.4*	143.8* 33%	14.2*	1.4*

[a]Mean body weight on Day 721.
[b]EFU = Efficiency of food utilization = grams of body weight gained per 100 g of food consumed.
[c]Dose increased on Test Day 211 → 2.5 mg/kg
*Significantly different from control, p≤.05, Tukey's trend test.

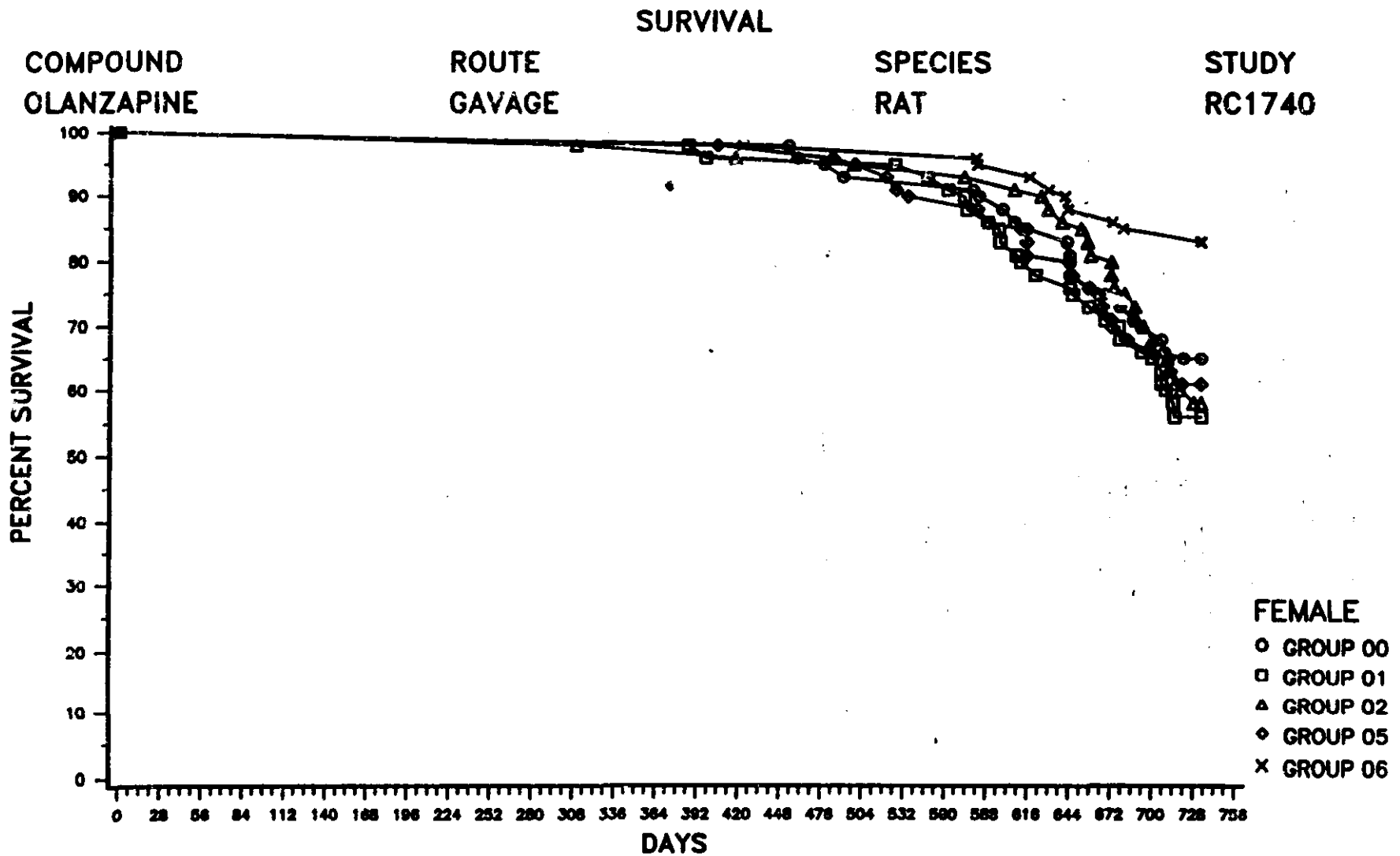
2yr rat carc./olanzapine/N20-592

Figure E-3.1. Survival.



2yr. rat carcin -/c olanzapine/N. 20-592

Figure E-3.2. Survival.



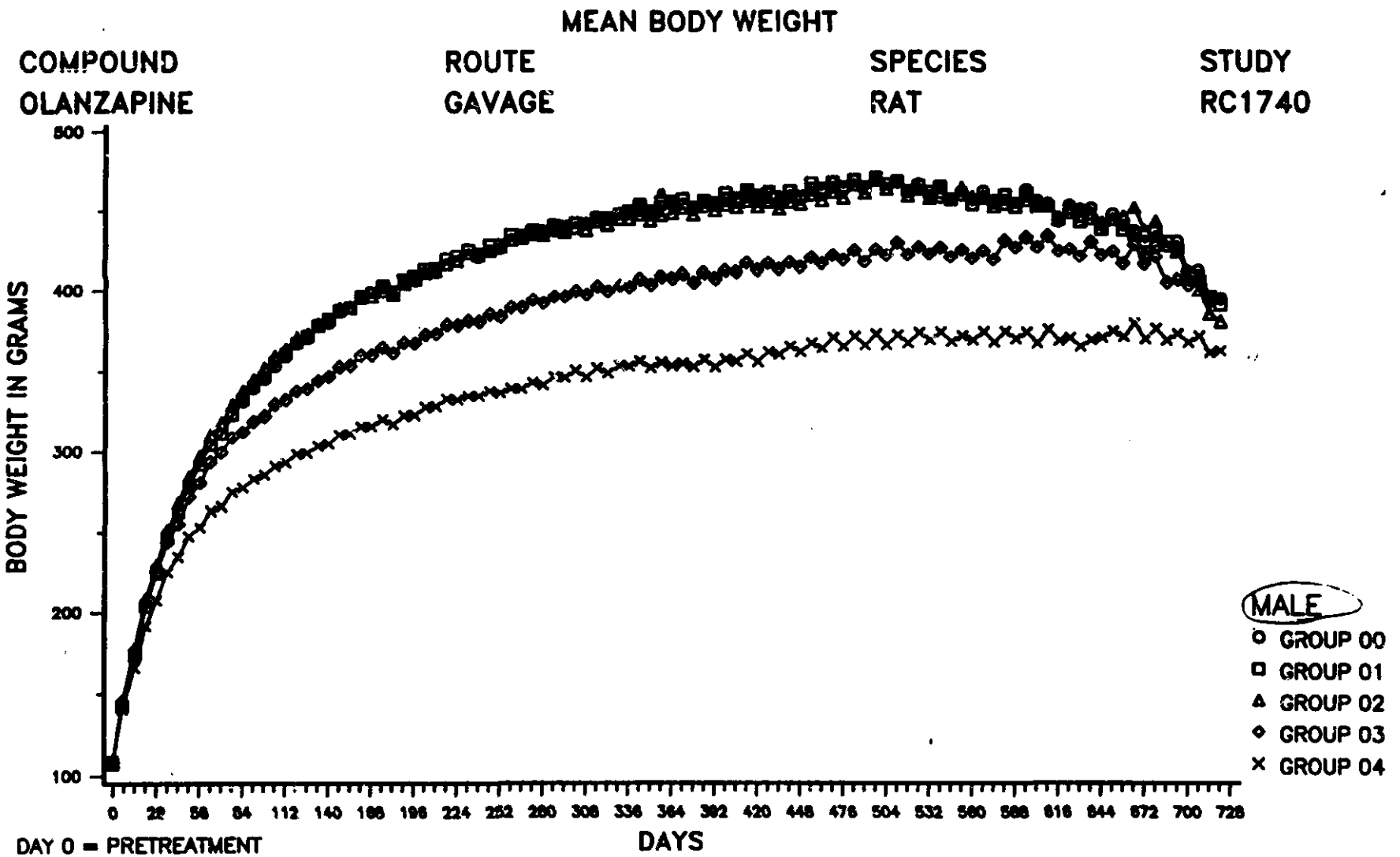
Clinical signs: hypoactivity noted in all drug grs and severity was dose-decendent. It lasted for 1wk, 3wks, 2mo, and 3mo in rats dosed 0.25, 1, 2.5, or 4mg/kg respectively. In females where the dose was increased from 4 to 8mg/kg, hypoactivity continued till end of study. Convulsions were seen in females dosed 4/8mg/kg (11/60 vs. 1/60 cont f) after 11m of dosing. Other signs were common among all drug and control grs or seen only in very few rats in the drug gr.

Body wt and Food Intake: a significant decrease in mean wt and wt gain noted in rats dosed ≥2.5mg/kg (see table from sponsor on previous pages and attached figures from sponsor). Males dosed 2.5mg/kg started losing wt during the 2nd month through month 22 and HDm lost wt during 1st month till end of study. At termination, males in the HD showed 12% decrease in wt gain relative to the controls but at 17months (peak of max wt), the decrease in wt gain was 13 and 27% of the control in MD&HDm. No wt effect in 0.25 or 1mg/kg dose gr. In females, a significant reduction of 10% was noted in mean wt gain in females dosed the 2 high doses (2.5 and 4mg/kg) during the 1st 7months of dosing. The sponsor decided to increase dose in females because of the small decrease in wt and/or wt gain. Within 1month of increasing dose, mean wt and wt gain in 4/8mg/kg gr declined significantly and remained low till end of study. Females dosed 2.5/4mg/kg showed decrease in wt and wt gain as of the 11th month till end of study. At termination, mean wt gain was reduced in females dosed 2.5/4 or 4/8mg/kg by 18 and 33% respectively, relative to the controls.

Food was decreased 5% ($p<0.05$) in HDm from the 3rd month till termination of study. In females dosed 4/8mg/kg, food was significantly reduced (3%) relative to the cont starting on month 19 till end of study. Some increases however, were noted in food intake in males and females during the beginning of the study. The cummulative efficiency of food utilization (EFU) was also significantly reduced in MD&HDm within the 1st month of dosing and in males dosed 1mg/kg starting from the 4th month through month 20. In females, EFU was decreased significantly at the 4/8mg/kg throughout the study, and from month9 till end of study in the 2.5/4mg/kg gr. The decrease in EFU relative to the cont at termination of live phase, was 15&30% for females dosed 2.5/4 and 4/8mg/kg respectively.

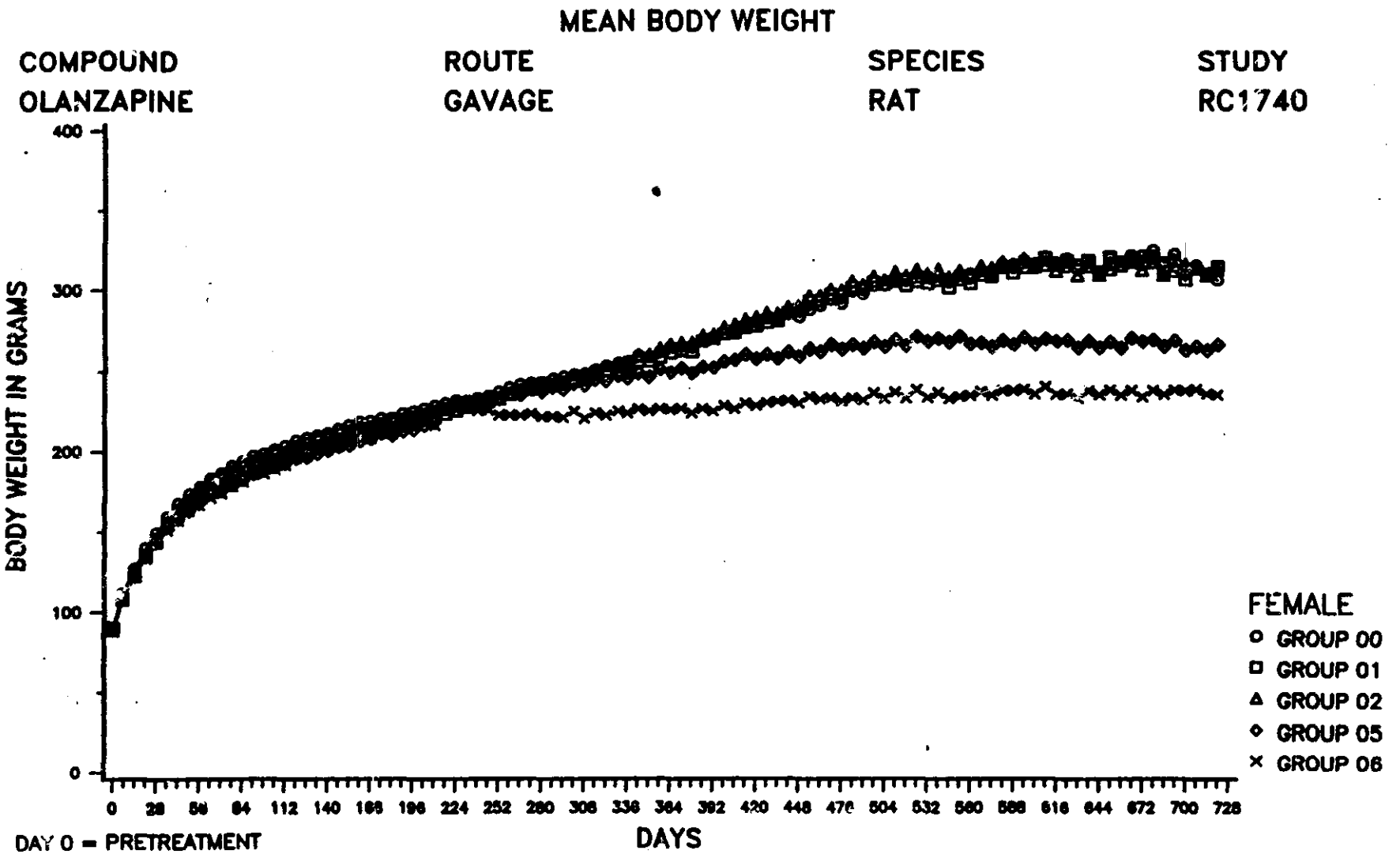
2 yr. rat carc. / Olanzap. / N20-592

Figure E-1.1. Mean Body Weight.



2 yr. rat carc./olanzapine/N20-592

Figure E-1.2. Mean Body Weight.



Hematology: statistically significant increases in various parameters noted at all time points both in males and females generally those administered the higher doses. Parameters affected included RBC count, Hb, PCV, MCH, MCV, and MCHC, elevations ranged between 0.2% to 14% (see table below)(all changes are relative to the corresponding controls:

6-month
The following were dose-dependent increases noted at 2.5 and 4mg/kg doses in males:
Hb (2.5&6% respectively)
PCV (1.8&2.6% respectively)
MCH (3&4% respectively)
MCV (2.4&3.1% respectively, and in 1mg/kg at 0.63%)

MCHC incr 1.4% in 4mg/kg.

In females incr noted only in HD (4/8mg/kg):
MCH 2% MCV 1.3%

1-yr
The following were dose-dependent increases noted at 2.5 and 4mg/kg in males:
Hb (1.8&4% respectively)
PCV (1.6&4% respectively)

Non-dose-dependent at 2.5 and 4mg/kg:
MCV (3.8&3.7% respectively)
MCH (4.3&4% respectively)

In females, dose-dependent incr at 2/4 and 4/8mg/kg in the following parameters:
Hb (2.6&3.2% respectively)
PCV (2.6&2.7% respectively)
MCV (0.2&1.1% respectively) but als at 1mg/kg dose (0.4%)

MCH incr 1.6% in females dosed 4/8mg/kg

18-months:
The following were dose-dependent increases noted at 2.5 and 4mg/kg in males:
RBCs (3.4&4.3% respectively; but at 2mg/kg was not significant)
Hb (5&5.7% respectively)
PCV (4.5&5% respectively)
MCH (1.3&1.6% respectively)

MCHC incr 0.6% in HDm

In females, incr noted in MCHC at 2/4 and 4/8mg/kg (1.6&1% respectively), and MCH incr 1% at HDf.

2-yrs:
Males/changes recorded only in HD (incr):
RBCs 14%
Hb 14%
PCV 12%

In females, incr noted in 2/4mg/kg and 4/8mg/kg included:
RBCs 3.8&2.6% respectively
Hb 5&4.8% respectively
PCV 5.8&3.7% respectively

At 4/8mg/kg only:
MCHC 1.8%

Effect on WBC parameters were inconsistent and non-dose-dependent. Some of these effects included thrombocytes (decr. and incr.), and leukocytes and lymphocytes (decr. and incr. respectively).

Clinical Chemistry: the changes were inconsistent and mostly non-dose-dependent.
6-months:
In males administered HD incr. noted in: glucose (4.8%), BUN (4%), ALP (9%), and Chol. (9.5%). Decr noted in T. Bili (28.6%), AST (7.7%), CPK (16.5%), Ca (2.7%), Na (18%), K (6.4%), Cl (11%), and Globulin (5.7%) however, the A/G ratio was incr. (7.3%). Some of the changes that did not reach statistical significance but showed dose-dependency in MD&HD included BUN and ALP. Statistically significant changes in LD&MD that were similar to those in HD included: CPK, Na, K, Chol, Cl (only in MD), and Globulin and A/G ratio (only in MD).

In females, non-dose-dependent incr. in all dose grs in BUN (12-21%) and ALP (17.6-30%). At MD&HD, dose-dependent decr. in T.Bili (15&27%) and GGT (27&28%), and an incr. in Cl (3.8%) and Ca (1.8-4%). In HD, decr. noted in CPK (52%), Chol. (13.6%), Alb (5.7%), and A/G ratio (13%) and an incr. noted in Na (3.4%).

12-months:
In males administered the HD, incr noted in glucose (15%), ALT (1.3%), and Cl (3.8%). A dose-dependent and significant decr. noted in CPK (30-48%) and K (3.2-8%). The following parameters in HDm were also reduced: inorg P(4%), TG (39%), and Globulin (9%).

In females, glucose unlike in males, was decr. in HD (8.6%). Also in HDf, Na level was incr (1.4%) and Globulin (19%). Levels of ALP and GGT were incr. in the 3 higher doses non-dose-dependently (14-23.6% and 46-129% respectively) and Cl incr dose-dependently (1.4-3%), however a non-dose-dependent decr noted in T.Bili (20-24%), Alb (9.5%), and Ca (3.7-6.5%). A dose-dependent decr. were recorded in TG (16-34%), Chol (13.5-19%), and A/G ratio (14-27%).

18-months:
In males at HD, decr. levels noted in Creatinine (7.8%), T.Bili (30%), Chol (27%), and TG (22%). ALT was slightly but sig. incr in HD (11%). A dose-dependent decr. (2 high doses) noted in Ca (3&4.5&) and Na (1.2&2%). Total proteins were reduced (4.6&5.5%) in the 3 high doses in a non-dose-dependent manner and in all drug grs, Globulin levels were decr (17-77%) but the A/G ratio was incr 13.4-27.7% perhaps due to the incr in Alb (sig in the 2 high doses, 3.7-6%).

In females, Gluc was reduced in the 2 high doses (non-dose-dependently, 10-13.5%). ALP, ALT, and AST enzyme levels increased in the 3 high doses non-dose-dependently (for ALT&AST reaching sig in all 3 gr except for ALP sig only in HD)(10.5-42%). TG level was reduced 14% in HD. Unlike the males, total protein level was incr in the 2HD (6&9.6%), the Alb and Glob levels were incr in the 2HD (6-10.6%), but the A/G ratio was reduced reaching sig level in HD.

24-months:
In males, HD/decr noted in BUN (47%), Creatinine (31%), T. Bili (60%; non sig), CPK (29%), Ca (5%), and K (also in MD; 3&5%). Levels of Cl were slightly but sig. incr (1.2%). Dose-dependent incr noted in total proteins in all drug grs (sig only in 2 high doses; 5-6%), and Alb in HD (11%); there was no difference in A/G ratio.

In females at HD, decr noted in Glu (17%), BUN (9%), and K (also in MD; 4-8%). T. Proteins and Alb levels incr dose-dependently in MD&HD (5.7-8%) , as well as Glob level (10%); no change in A/G ratio.

Urinalysis:
No sig drug-related findings.

TK Analyses:
Plasma samples analyzed by validated GC-EC (dl 5ng/ml) and HPLC-electrochemical detection (1ng/ml dl). Plasma levels at 6months ranged between below detection limit of 5ng/ml to **561ng/ml** at 0.5hr postdose and from ND to **96ng/ml** at 7hr postdose. There was no sex difference in drug levels and max concentration was reached at 0.5hr and the drug did not seem to accumulate. Concentrations incr linearly with dose at 6months but non-linearly at 8months. At **8months**, conc. ranged between ND to **684ng/ml** at 0.5hr and at 7hr from ND to **655ng/ml**. Max conc was reached at 0.5hr. At 12 and 18mo, conc increased with dose non-linearly and in females dosed 8mg/kg during month18 measurements, the level was low compared to all other female and male values (see below). In general, females had higher conc than males at months 8-18. At **12months**, conc. ranged between ND to **910ng/ml** at 0.5hr and at 7hr, ND to **658ng/ml**. At **18months**, conc. at 0.5hr ranged between ND to **328ng/ml** and at 7hr, ND to **696ng/ml**. Note that the individual as well as mean conc. was higher in females dosed 4mg/kg than the conc. measured in females dosed the HD of 8mg/kg.

6-months

Dose	Sex	Mean Conc. (ng/ml)(±sd) 0.5hr	7hr
0.25	m	ND	ND
	f	6±0.3	ND
1.0	m	22±10	5*
	f	30±9	8±1
2.5	m	174±77	41±12
	f	132±71	46±13
4	m	335±205	75±21
	f	228±127	77±18

* n=1

8-months
Plasma concentration ranged between ND (<5ng/ml) to 684ng/ml at 0.5hr and at 7hr postdose from ND to 655ng/ml.

Dose	Sex	Mean Conc. (ng/ml)(±sd) 0.5hr	7hr
0.25	m	ND	ND
	f	ND	ND
1.0	m	17±5	5.5a
	f	26±8	7±0.3
2.5	m	95±39	28±3
4	f*	238±43	99±11
4	m	192±69	139b
8	f**	476±187	548±138

a n=1; b n=2
* dose incr from 2.5 to 4mg/kg on day211
** dose incr from 4 to 8mg/kg on day 211

12-months
Plasma conc. ranged between ND (<5ng/ml) to 910ng/ml at 0.5hr and at 7hr postdose from ND to 658ng/ml.

Dose	Sex	Mean Conc. (ng/ml)(±sd) 0.5hr	7hr
0.25	m	5a	ND
	f	8±1.6	ND
1.0	m	26±13	6±1
	f	51±26	7±1.5
2.5	m	187±59	60±26
4	f*	325±140	149±14
4	m	338±46	185±53
8	f**	736±187	533±108

a n=1
* dose incr from 2.5 to 4mg/kg on day211
** dose incr from 4 to 8mg/kg on day 211

18-months
Plasma conc. ranged between ND (<1ng/ml) to 185ng/ml at 0.5hr and at 7hr from ND to 696ng/ml.

Dose	Sex	Mean Conc. (ng/ml)(±sd) 0.5hr	7hr
0.25	m	2±1	ND
	f	3±0.2	ND
1.0	m	19±3	5±2.7
	f	42±19	8±2
2.5	m	119±14	53±25
4	f*	128±50	184±55
4	m	204±108	166±44
8	f**	78±11	657±40

Limit of detection here = 1ng/ml by HPLC
* dose incr from 2.5 to 4mg/kg on day211
** dose incr from 4 to 8mg/kg on day 211

Organ wts: (Means±s.e.) Only those that showed statistical sig are listed in the table below. Mean body wt was sig reduced in HD rats which might have reflected the decr noted in some organ wts (HDm wt decr 5%, females dosed 4&8mg/kg showed 14&24% decr compared with the cont). The following are incr in organ wt relative to the cont gr: rel liver wt of MDf (20%) a decr however, noted in HDf, relative kidney wt in MD&HDf (18%), rel wt of the heart was incr in MD&HD m&f and in males dosed 1mg/kg (5-21%), absolute and rel adrenal wt incr in MD&HDm (25-56%) and the rel wt was incr in MD&HDf (40-78%), rel wt of the spleen was incr in HDf (14%), and the rel wt of the brain was incr dose-dependently in MD&HDf (13&25%). The sponsor contributed the incr in adrenal wt in MD&HD rats to non-specific mechanisms operating in stressed animals due to decr in wt. Also, the decr in absolute kidney wt of HD rats was related to the progressive glomerulonephritis seen in these animals. Regarding the liver, the incr in rel wt in MD&HDf was closley similar to that in 0.25mg/kg female gr and since HDm showed a decr in absol. and rel liver wt, these changes were considered random finding. Heart wt tend to remain constant with changes in B.wt, however, a dose-dependent incr in rel wt noted in the 3 high dose male gr and in MD&HDf but a decr noted in absol. wt of HDf. These findings maybe related to decr in B.wt or, since it was seen in both sexes and was dose-dependent, the change in heart wt maybe drug-related. The spleen absol. wt was decr in MD&HDf but the rel wt was incr only in MDf (4mg/kg); no changes in males therefore, these effects may not be of biological significance. Uterus and testes absol wt were decr in LMD, MD,& HDf and HDm, respectively. Also, rel uterus wt was decr dose-dependently in the 3 high dose grs. Thyroid/para thyr absol wt was decr dose-dependently in MD&HD males and females and rel wt was decr in MD&HDm grs, these effects maybe drug related.

In summary, the changes in organ wt may have been secondary to drug effect on B.wt specially in HD animals. However, changes in the wt (absolute and/or relative wts), of the following organs may be drug related: incr in heart and adrenals, and decr in thyroid/parathyroid and uterus and testes.

gr/sex	organ	Ab. wt of org for the cont gr	Ab.wt	rel/B.wt	rel wt of org for the cont gr
HDm*	liver	13.5±0.6	11±0.37	3.1±0.1	4±0.2
HDf*		9.5±0.3	8±0.2	3.6±0.1	3±0.1
MDf*			NC	3.6±0.1	
HDm	Kidneys	3.3±0.1	3±0.06	NC	
HDf		2.4±0.1	2.2±0.03	952±14	807±22
MDf			NC	952±34	
LMDm*	heart	337±12	NC	375±14	337±12
MDm**			NC	365±13	
HDm			NC	355±6	
MDf			NC	383±7	338±10
HDf		994±16	940±11	410±5	
MDm**	adrenals	76±8	95±8	26±3	22.6±4
HDm			80±2	23±1	
MDf			NC	32±4	23±0.1
HDf			NC	41±8	
MDm**	thyroid/para thyr	30±5	22±1	5.8±0.2	8±1
HDm			21±0.7	6±0.2	
MDf$		20±1	17±0.5		
HDf			16±0.4		
MDf$	spleen	688±121	646±142		
HDf		-	742±180	333±86	292±35
HDm	testes	3±0.4	2±0.1	0.6±33	0.77±0.1
MDf$	uterus	941±28	582±28	227±11	333±44
HDf			530±16	231±7	
MLDf$$			NC	272±11	
MDf	brain		NC	714±11	630±18
HDf			NC	790±10	

NC no sig change/comparable to cont
* B.wt sig <cont
** 2.5mg/kg
$ 4mg/kg (incr from 2.5mg/kg to 4mg/kg for females only on day 211 of study.
$$ 1mg/kg
a LMDm = low mid dose males/1mg/kg dose

Weights were also measured relative to the brain and sig changes noted in: adrenals (incr, MDm/24%; HDm/5%), thyroid/parathyr (decr, MDm/27%; HDm/27%; MDf/15%; HDf/18%), liver (decr, HDm/18%; HDf/8%), kidneys (decr, HDm/12%; HDf/6%), testes (decr, HDm/21%), heart (decr, HDf/3%), spleen (decr, HDf/15%), and uterus (decr, 42%).

gr/sex	organ	Ab. wt of org for the cont gr	Ab.wt	rel/B.wt	rel wt of org for the cont gr
HDm*	liver	13.6±0.6	11±0.37	3.1±0.1	4±0.2
HDf*		9.5±0.3	8±0.2	3.6±0.1	3±0.1
MDf*			NC	3.6±0.1	
HDm	Kidneys	3.3±0.1	3±0.06	NC	
HDf		2.4±0.1	2.2±0.03	952±14	807±22
MDf			NC	952±34	
LMDm[a]	heart	337±12	NC	376±14	337±12
MDm**			NC	365±13	
HDm			NC	355±6	
MDf			NC	383±7	338±10
HDf		994±16	940±11	410±5	
MDm**	adrenals	76±8	95±8	26±3	22.6±4
HDm			80±2	23±1	
MDf			NC	32±4	23±0.1
HDf			NC	41±8	
MDm**	thyroid/para thyr	30±5	22±1	5.8±0.2	6±1
HDm			21±0.7	6±0.2	
MDf$		20±1	17±0.5		
HDf			16±0.4		
MDf$	spleen	*888±121	648±142		
HDf		-	742±190	333±86	292±35
HDm	testes	3±0.4	2±0.1	0.6±33	0.77±0.1
MDf$	uterus	941±28	582±28	227±11	333±44
HDf			530±16	231±7	
MLDf$$			NC	272±11	
MDf	brain		NC	714±11	630±18
HDf			NC	790±10	

NC no sig change/comparable to cont
* B.wt sig <cont
** 2.5mg/kg
$ 4mg/kg (incr from 2.5mg/kg to 4mg/kg for females only on day 211 of study.
$$ 1mg/kg
a LMDm = low mid dose males/1mg/kg dose

Weights were also measured relative to the brain and sig changes noted in: adrenals (incr, MDm/24%; HDm/6%), thyroid/parathyr (decr, MDm/27%; HDm/27%; MDf/15%; HDf/18%), liver (decr, HDm/18%; HDf/8%), kidneys (decr, HDm/12%; HDf/6%), testes (decr, HDm/21%), heart (decr, HDf/3%), spleen (decr, HDf/15%), and uterus (decr, 42%).

Gross Morphology: No remarkable findings on gross morphology.

Histopathology: table below from the sponsor presents the incidence of lesions (non-neoplastic and neoplastic) in all grs. It can be seen that there was no sig incr in lesions/tumors except for a non-dose-dependent incr in malignant mammary gland in the 2 HD female grs (9/60 and 7/60 respectively, vs. 2/60 in the cont.).

Appendix H (Continued).

Survival, Body Weight, and Incidence of Spontaneous Lesions Affected by Treatment
(each group has 60 animals)

Males

Dose (mg/kg)	0	0.25	1.0	2.5	4.0
Number Survived	24	26	25	28	33
Terminal Body Weight Expressed as % Difference From Control	-	5	-1	2	-5[a]
Severe Progressive Glomerulonephrosis	12	12	19	7	1
Benign Pheochromocytoma	6	10	6	5	0[b]
Interstitial Cell Tumor	26	37	27	12[b]	12[b]

Females

Dose (mg/kg)	0	0.25	1.0	4.0	8.0
Number Survived	35	34	35	37	50
Terminal Body Weight Expressed as % Difference From Control		2	3	-14[a]	-24[a]
Mononuclear Cell Leukemia	19	16	15	7[b]	5[b]
Pituitary Adenoma	39	36	37	38	19[b]
C-Cell Adenoma	10	6	5	6	3[b]
Benign Endometrial Stromal Tumor	7	11	4	5	1[b]
Clitoral Gland Adenoma	3	4	0	0[b]	1[b]
Benign Mammary Gland Neoplasia	15	15	17	12	14
Malignant Mammary Gland Neoplasia	2	3	3	9[c]	7[c]
Total Mammary Gland Neoplasia	17	18	20	21	21

[a]P<=.05, two tailed trend T on ranked data.
[b]Significant decrease based on Peto's trend test
[c]Significant increase based on Peto's trend test

The sponsor listed age-related lesions/pathological changes in the rat. The following 3 lesions contributed to the death of animals: glomerulonephritis in males, mononuclear cell leukemia in females, and pituitary adenoma or adenocarcinoma. The incidences of these tumors were actually decr with incr dose and occasionally reached statistical sig. The incidence of interstitial cell tumors was on the low end of historical data from this lab (data not provided). The incidence of benign mammary gland neoplasia (adenomas and fibroadenomas) and the total mammary gland neoplasia did not reach statistical sig. However, the incidence of malignant mammary gland neoplasia (adenocarcinomas) was sig incr in the 2 high dosed female grs but the incr was not dose-dependent (see attached tables from the sponsor). This tumor affected 24 females and the tumors were detected in rats killed at end of study.

Summary and Conclusion:
Oral administration of olanzapine to male and female F344 rats for 2yrs at doses between 0.25mg/kg and upto 8mg/kg had no effect on survival. Doses in male rats were 0.25, 1, 2.5, and 4mg/kg and those in females were 0.25, 1, 2.5/4, and 4/8mg/kg. The 2.5 and 4mg/kg doses in females were increased to 4 and 8mg/kg respectively, on day 211 because of the small effects on B.wt. Mean wt and wt gain at termination were sig reduced at doses ≥2.5mg/kg (12-33%). Mean food intake at termination in HDm was sig reduced (5%) but the EFU was unaffected. In MD&HDf, mean food intake and EFU were reduced at termination (15-30% of the cont.). Similar to other tox studies and studies in mice and dogs, changes were observed in hematology parameters at all time points and in both sexes mainly at the higher doses. The affected parameters included RBC, Hb, PCV, MCH, MCV, and MCHC, elevations ranged between 0.2-14% of the control and many were dose-dependent. There seem to be some time-of-treatment factor since values measured at 2yrs tended to be higher than those measured during the 1st yr. Plasma levels were similar in males and females and the drug did not appear to accumulate at least during the 1st 6months of treatment. The increase in drug conc was linear at the 6mo measurement but non-linear thereafter (last measurement on the 18th month). Plasma conc ranged between BLQ of 5ng/ml to 910ng/ml. **The hematology changes occurred at plasma levels 1-12x the max clinical plasma level of 60ng/ml measured after a single dose of 20mg/d.** There were some statistical significant changes in organ wt such as decr in thyroid/parathyroid 15-30% of cont (absol and rel), dose-dependent decr in absol and rel wt of the uterus, testes HDm absol wt decr, and the rel wt of the brain in MD&HDf was incr. There was no gross morphological findings. There was no sig incr in incidence of neoplastic lesions in any gr except a non-dose dependent incr in mammary gland adenocarcinoma of MD&HDf at an incidence of 9/60 and 7/60 respectively, vs 2/60 in cont. There was no drug effect on Non-neoplastic lesions. **The mammary gland tumors in females occurred at plasma levels that are equivalent to 1-11x the max clinical plasma level of60ng/ml measured after a single dose of 20mg/d.** The incidence of other tumors actually was lower as the dose was incr. This decr was contributed to the decr in mean wt or wt gain of these rats. Note that the mammary gland tumors were also seen in the mouse oncogenicity studies (see above).

Attachment Table H-6. Summary of Peto's trend test for total mammary gland neoplasia[b] in female rats from Study RC1740. Numbers shown are number of tumor-bearing animals/number of animals at risk.

Tumor Type	Detection Interval (weeks)	Treatment Group 00	01	02	03	04
Fatal	72	0/51	0/47	1/54	0/54	0/55
	78	0/51	0/48	0/53	1/52	0/55
	86	0/49	1/42	0/52	0/50	0/53
	91	0/46	0/39	1/51	0/47	0/52
	95	0/42	0/37	0/47	1/45	0/49
	97	0/41	0/35	2/46	2/43	0/49
	98	0/41	1/34	0/43	0/40	1/49
	100	0/40	0/32	1/42	0/40	0/47
	101	0/38	0/32	0/36	1/40	0/47
Incidental	82 - 92	0/10	0/7	0/4	0/7	2/6
	93 - 103	3/7	2/10	1/10	2/7	1/2
	104- 104	3/10	4/9	2/10	1/11	4/12
	105- 106	11/26	9/19	10/25	11/25	12/35

	Results of Peto's Trend test					
	Mortality		Prevalence		Onset	
Treatment groups	Z	P[a]	Z	P[a]	Z	P[a]
00 - 04	.73	.23	-.46	.68	-.08	.53

a: one-tailed p-values
b: Includes adenocarcinomas, adenomas, and fibroadenomas

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Attachment Table H-5. Summary of Peto's trend test for adenocarcinoma occurring in mammary glands in female rats from Study RC1740. Numbers shown are tumor incidence/number of animals at risk.

Tumor Type	Detection Interval (weeks)	Treatment Group 00	01	02	03	04
Fatal	86	0/49	1/42	0/52	0/50	0/53
	97	0/41	0/35	0/46	1/43	0/49
	101	0/38	0/32	0/38	1/40	0/47
Incidental	97 - 104	0/15	0/16	0/21	1/16	1/14
	105 - 106	2/26	2/19	2/25	6/25	6/35

	Results of Peto's Trend test			
	Mortality		Prevalence	
Treatment groups	Z	P[a]	Z	P[a]
00 - 04	.28	.39	1.91	.03
00 - 03	NT		1.86	.03
00 - 02	NT		.04	.48

a: one-tailed p-values
NT: no test performed

Rat carcinos

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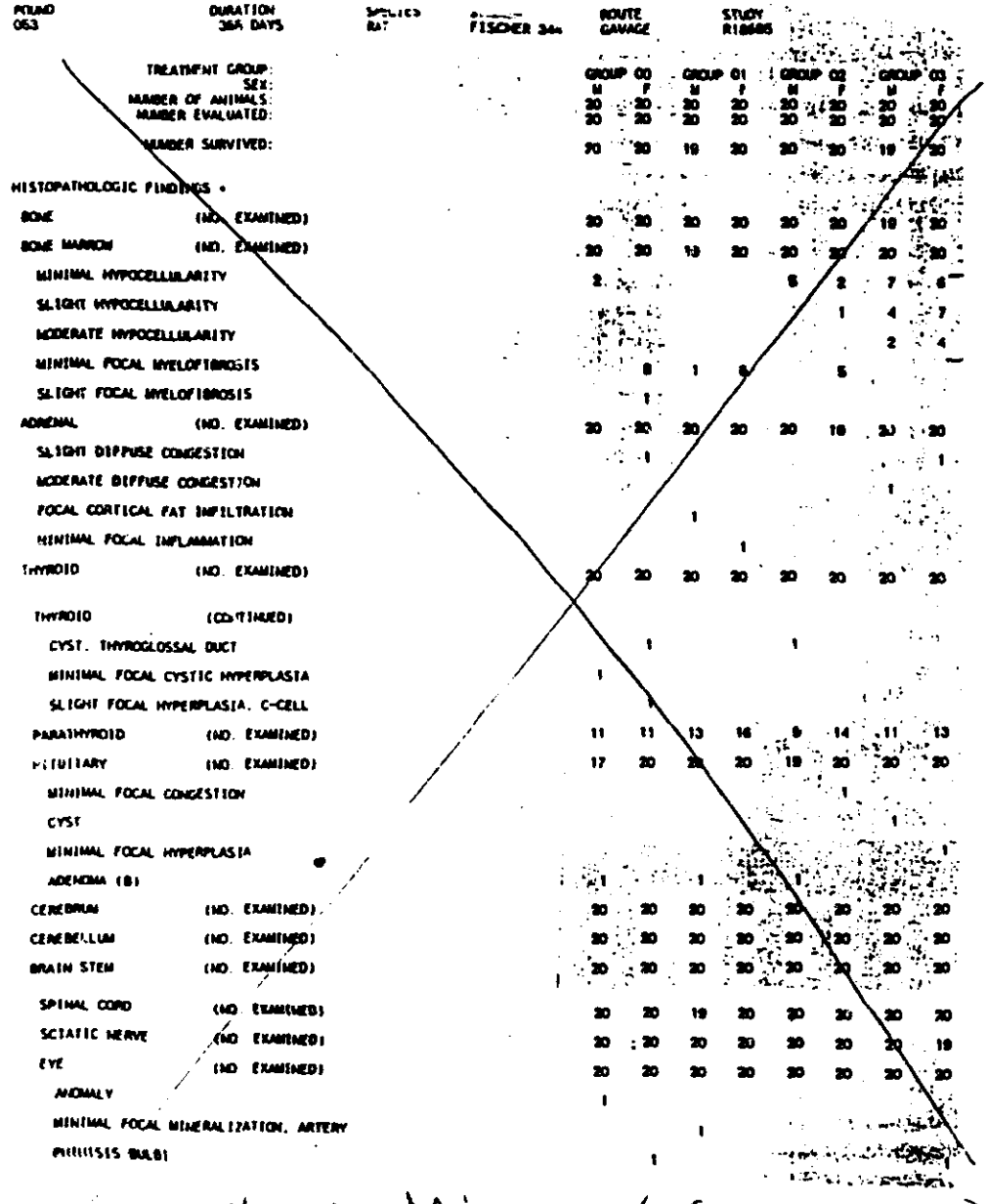
Appendix II



COMPOUND: 053	DURATION: 364 DAYS	SPECIES: RAT	STRAIN: FISCHER 344	ROUTE: GAVAGE		STUDY: R18585		
TREATMENT GROUP:				GROUP 00		GROUP 01	GROUP 02	GROUP 03
SEX:				M	F	M F	M F	M F
NUMBER OF ANIMALS:				20	20	20 20	20 20	20 20
NUMBER EVALUATED:				20	20	20 20	20 20	20 20
NUMBER SURVIVED:				20	20	19 20	20 19	20 20
HISTOPATHOLOGIC FINDINGS *								
BONE	(NO. EXAMINED)			20	20	20 20	20 19	20 20
BONE MARROW	(NO. EXAMINED)			20	20	19 20	20 20	20 20
MINIMAL HYPOCELLULARITY				2			5 2	7 6
SLIGHT HYPOCELLULARITY							1	4 7
MODERATE HYPOCELLULARITY								2 4
MINIMAL FOCAL MYELOFIBROSIS					8	1 5	5	
SLIGHT FOCAL MYELOFIBROSIS					1			
ADRENAL	(NO. EXAMINED)			20	20	20 20	20 19	20 20
SLIGHT DIFFUSE CONGESTION					1			1
MODERATE DIFFUSE CONGESTION							1	
FOCAL CORTICAL FAT INFILTRATION						1		
MINIMAL FOCAL INFLAMMATION						1		
THYROID	(NO. EXAMINED)			20	20	20 20	20 20	20 20
THYROID	(CONTINUED)							
CYST, THYROGLOSSAL DUCT					1	1		
MINIMAL FOCAL CYSTIC HYPERPLASIA				1				
SLIGHT FOCAL HYPERPLASIA, C-CELL					1			
PARATHYROID	(NO. EXAMINED)			11	11	13 16	9 14	11 13
PITUITARY	(NO. EXAMINED)			17	20	20 20	19 20	20 20
MINIMAL FOCAL CONGESTION							1	
CYST								1
MINIMAL FOCAL HYPERPLASIA								1
ADENOMA (B)				1		1	1	
CEREBRUM	(NO. EXAMINED)			20	20	20 20	20 20	20 20
CEREBELLUM	(NO. EXAMINED)			20	20	20 20	20 20	20 20
BRAIN STEM	(NO. EXAMINED)			20	20	20 20	20 20	20 20
SPINAL CORD	(NO. EXAMINED)			20	20	19 20	20 20	20 20
SCIATIC NERVE	(NO. EXAMINED)			20	20	20 20	20 20	20 19
EYE	(NO. EXAMINED)			20	20	20 20	20 20	20 20
ANOMALY				1				
MINIMAL FOCAL MINERALIZATION, ARTERY						1		
PHTHISIS BULBI					1			1

3-month in Mice (G. DeGeorge) Feb. 1991

B. [Toxicology: A Subchronic Toxicity Study and Companion Blood Level Study in $B6C3F_1$ Mice Treated Orally with LY170053 for Three Months. (#007, vol.7.1)] study # M00487 & M00587

$B6C3F_1$ mice (35-42 days old at start of dosing) were assigned to treatment groups as indicated below, and dosed with LY170053 (lot 56786) by gavage. One set of animals was dosed for determination of pharmacokinetic parameters. The pharmacokinetic study was terminated prematurely at 1 month due to a dose-related decrease in survival. Final blood samples (Day 92) were thus collected from animals in the main study.

Dose (mg/kg)	Mean Weight at Start (g)	Number of Survivors	Mean Weight at Termination (g)	Mean Weight Gain (g)
		MALES		
0	22.1	14	32.9	10.6
5	20.5[b]	14	30.2[a]	9.6
15	20.7	14	29.1[a]	8.1[a]
45	20.9	13	28.0[a]	7.1[a]
		FEMALES		
0	17.9	14	25.2	7.3
5	18.0	15	25.5	7.5
15	17.8	12	25.2	7.4
45	17.3	11	24.8	7.3

2. Hematology: There were substantial decreases in WBC counts with dosed M showing greater sensitivity than F. In males dose-related decreases in total WBC counts (↓ 36% LD, 65% MD and 70% HD) with decreases in both lymphocytes and neutrophils (although due to a larger decrease in lymphocytes, the percentage of neutrophils was 2-fold greater at HD than in the CD group). Individual animal data indicated at all doses in males WBC and lymphocyte counts were below the normal range, such that at MD and HD only 2/21 had counts within the normal range.

In females, while only minimal decreases in WBC counts were observed at LD and MD (↓ <12%), at HD, WBC counts were decreased 53%. In contrast to males, females showed a 2-fold increase in neutrophils vs the CD group. Both males and females had small (5%) decreases in RBC counts accompanied by increases in cell volume. These changes in RBC parameters, while consistent with those in other studies, are not biologically significant.

DURATION: 90 DAYS | SAMPLE PERIOD: 92- 93 DAYS | SPECIES: MOUSE | STRAIN: B6C3F1 | ROUTE: GAVA

MALE

TRT	STATISTIC	ERYS MILL/UL	HGB G/DL	PCV %	MCV FL	MCH PG	MCHC %
00	MEAN	9.885	16.127	48.21	48.782	16.164	33.485
	STD	0.287	0.415#	1.27	0.853	0.334	0.350
	STDERR	0.087	0.125#	0.38	0.182	0.070	0.089
	N	11	11	11	11	11	11
01	MEAN	10.118	16.430	48.87	48.800	16.220	33.800
	STD	0.214	0.258#	0.82	0.632	0.168	0.371
	STDERR	0.068	0.082#	0.28	0.800	0.053	0.117
	N	10	10	10	10	10	10
02	MEAN	9.885	15.827	47.19	48.818	16.000	33.573
	STD	0.515	0.988#	3.08	0.823	0.328	0.369
	STDERR	0.185	0.298#	0.92	0.182	0.088	0.111
	N	11	11	11	11	11	11
03	MEAN	9.497	10.000	47.10	49.700+	16.800+	33.800+
	STD	0.677	1.117#	2.72	0.948	0.357	0.952
	STDERR	0.182	0.353#	0.86	0.300	0.113	0.176
	N	10	10	10	10	10	10

DURATION: 90 DAYS | SAMPLE PERIOD: 92- 93 DAYS | SPECIES: MOUSE | STRAIN: B6C3F1 | ROU: GA

FEMALE

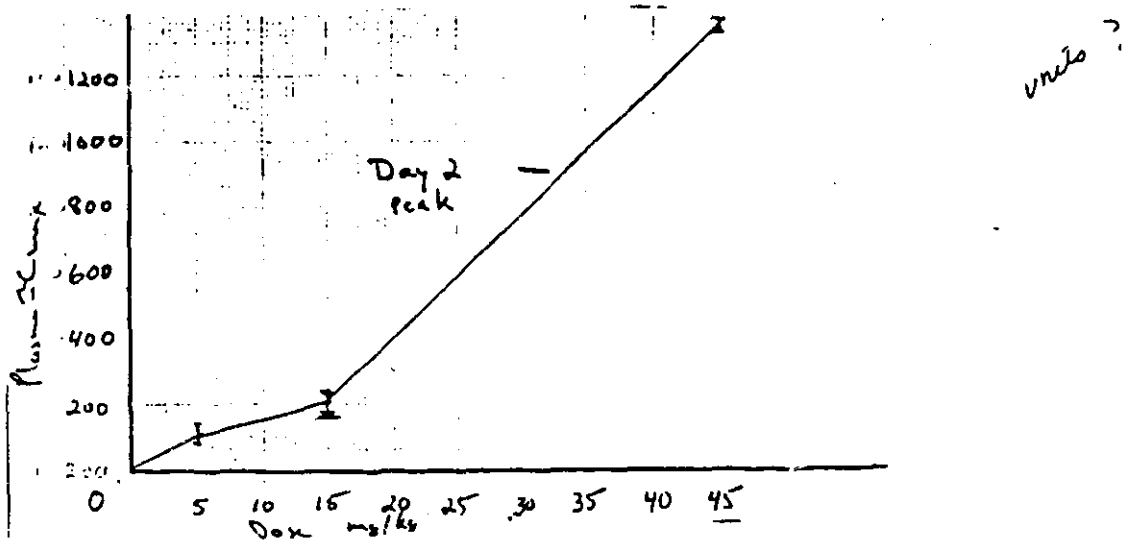
TRT	STATISTIC	ERYS MILL/UL	HGB G/DL	PCV %	MCV FL	MCH PG	MCHC %
00	MEAN	10.088	16.473	48.16	47.908	16.384	34.191
	STD	0.391#	0.637#	1.56	0.701	0.157	0.455
	STDERR	0.079#	0.182#	0.47	0.211	0.047	0.136
	N	11	11	11	11	11	11
01	MEAN	10.244	17.017	49.88	48.333	16.800	34.827
	STD	0.286#	0.486#	1.45	0.351	0.210	0.304
	STDERR	0.077#	0.131#	0.42	0.108	0.061	0.088
	N	12	12	12	12	12	12
02	MEAN	10.201	17.222	50.08	49.000+	16.956+	34.344
	STD	0.275#	0.360#	1.34	0.500	0.151	0.353
	STDERR	0.080#	0.120#	0.45	0.167	0.050	0.118
	N	9	9	9	9	9	9
03	MEAN	9.974+	16.113	46.87	46.875+	16.025+	34.387
	STD	0.771#	1.203#	4.10	0.641	0.188	0.304
	STDERR	0.375#	0.456#	1.45	0.227	0.070	0.136
	N	9	9	9	9	9	9

DURATION: 90 DAYS | SAMPLE PERIOD: 92- 93 DAYS | SPECIES: MOUSE | STRAIN: B6C3F1 | ROUTE: GAVAGE | CODE: 170

MALE

TRT	STATISTIC	LEUKS TH/UL	LYMS TH/UL	NEUTS TH/UL	BNDS TH/UL	MONOS TH/UL	EOS TH/UL	BASOS TH/UL	THRMBS TH/UL
00	MEAN	4.508	3.381	1.073	0	0.0384	0.0182	0	1188.5
	STD	1.340	1.120	0.368	0	0.0674	0.0406	0	83.3
	STDERR	0.404	0.338	0.117	0	0.0203	0.0122	0	20.2
	N	11	11	11	11	11	11	11	17
01	MEAN	2.900+	2.100+	0.780	0	0.0000	0.0000	0	1188.6
	STD	0.814	0.691	0.222	0	0.0000	0.0000	0	110.4
	STDERR	0.257	0.206	0.070	0	0.0000	0.0000	0	34.9
	N	10	10	10	10	10	10	10	10
02	MEAN	1.800+	1.088+	0.540+	0	0.0000	0.0000	0	1173.0
	STD	0.933	0.772	0.338	0	0.0000	0.0000	0	78.0
	STDERR	0.281	0.219	0.102	0	0.0000	0.0000	0	23.5
	N	11	11	11	11	11	11	11	11

concentrations occurred 0.5 -1.0 h post dosing, indicating rapid absorption of drug. Parent compound decreases in plasma suggests at least 2 rates of elimination (or distribution) a rapid phase shortly after achieving peak concentration, with a $t_{1/2}$ of 1 h or less, followed by slow elimination with a $t_{1/2}$ of $\geq$ 12 h. There appeared to be a non-linear increase in C_{max} at HD on day 2. However, by day 92 the 2 h concentration at HD (but not at MD) was reduced relative to the 2 day value, suggesting that the apparent non-linearity may not be significant. Given the possible variability in the data, M and F showed little difference in peak concentrations.



6. Necropsy General: Mean organ weights and organ to body weight ratios indicate that most organs weight reductions (observed only in males) were correlated with decreased body weight. There were no exceptions with the 5 tissues measured, kidney, liver, heart, spleen, and reproductive tissues. The lack of an effect on reproductive tissues is in contrast to the effects observed in rat.

8. Gross Pathology: Several animals in the dosed group had black, mottled, heart (3/15 HDM) or intestinal contents (4/15 HDM and 3/15 HDF), suggestive of hemorrhages. In the heart, microscopic examination revealed normal tissues and the lesions may have occurred during the blood collection at necropsy. There were no lesions to the intestine identified. Thus, the toxicologic significance of the lesions (apparent hemorrhages) is unclear.

9. Histopathology: Histological findings were limited. Diffuse organ congestion was observed in 3/15 HDF and 3/15 MDF and is likely associated with death. Lymphoid depletion was also observed in MDF and HDF which died during the study. That females with depressed lymphocyte levels died prior to the hematology sampling, likely suppressed the depression in lymphocyte counts in females at HD and MD.

Summary and Evaluation of Toxicity Studies

The toxicity of LY170053 was assessed in a chronic toxicity study in rat (1-year; 1, 4, and 16 mg/kg) and a subchronic toxicity study in mouse (3-month; 5, 15, 45 mg/kg). The effects in both species were generally similar, although the effects occurred at higher doses in mouse. At low doses pharmacologic effects (sedation and hypoactivity) and small reductions in weight gain were observed in rat, thus no "no effect dose" was found. At higher doses in rat, substantial weight gain suppression was observed. This was accompanied by significant hematological and serum chemistry alterations indicative of malnourishment, particularly at the HD. In mouse these changes were also generally observed at HD, however, there was no effect on weight gain in females. Significantly, both species showed a reduction in WBC counts at HD, primarily, reduced lymphocyte counts (F only in rats). This change was associated with hypocellularity of the bone marrow in rat and lymphoid depletion of spleen, thymus and lymph nodes in mouse. The sponsor states that this change is the result of malnutrition, but this is not consistent with the absence of a drug-associated reduction in bodyweight in female mouse. Thus, while malnutrition may have accounted for the change, it is not clear that this reduction in WBC cells is an indirect effect of LY170053. Importantly, the alteration in WBC count has been observed to varying degrees in several previous toxicology, including two separate dog studies (HD, 10 mg/kg). In one instance the response in dog (thrombocytopenia and neutropenia) appeared to be immune mediated (reviewed previously, Hollenbeck). In the rat and mouse studies the effect is associated with plasma concentrations of parent on the order of ≈1 ug/ml. There is no data on the plasma concentration of drug from the 3 month study in dog. In the one year dog study (reviewed previously, Hollenbeck), there was no effect on WBC (one 10mg/kg male had hemolytic anemia). In that study the peak concentration of parent was 0.45 ug/ml given a 10 mg/kg dose. Thus, leukocytes or leukocyte stem cells appear to be adversely effected in several species at doses of LY170053 greater than 10 mg/kg, possibly in association with plasma concentrations of parent in excess of 1 ug/ml.

Teratology

F. Teratology Segment I: A Ten-Week Female Basic Fertility Study of LY170053 Administered by Oral Gavage to CD Rats. (#003, vol.5.1)

LY170053 (Lot# 56786) was given to 20 adult female CD rats/dose group (0, 1,3,10 mg/kg) for two weeks prior to mating and throughout lactation (day 21 postpartum) via gavage. All females were allowed to deliver; males were not dosed. LY170053 was prepared daily as a suspension in 5% aqueous acacia. Dosing suspensions for the HD group were consistently 12% lower than those given for the nominal dose 2.0 mg/ml. Thus, the administered dose for the HD group was likely ≈ 9 mg, but does not impact the study findings significantly. However, while the F_1 generation progeny were examined for general physical effects and behavior, breeding was not performed as is required by FDA guidelines.

Reviewer: R. Hollenbeck Aug. 1986

C

TWO WEEK DOSE-RANGING STUDY IN THE RAT

ANIMAL: Fischer 344 rats

DOSE: 0, 2, 6, 18 or 54mg/kg by gavage

DURATION: Two weeks

ANIMALS/GROUP: 5M, 5F

PARAMETERS STUDIED AND RESULTS

MORTALITIES: All HD rats died during the study. In males, deaths occurred after 5, 5, 5, 7 and 10 days on test and for females after 3, 5, 5, 5 and 7 days on test. All other rats survived the study.

OTHER FINDINGS: Dose-related hypoactivity was present in all rats. Doses of 6mg/kg or higher produced a significant depression of growth and food consumption. There were no biologically significant hematologic, clinical chemistry or histologic changes. Toxicologic findings could probably be attributed to an extension of the pharmacologic effects.

54 mg/kg lethal to all rats.

Rat 3 month Study

MEAN BODY WEIGHT - Males

COMPOUND 178853 | ROUTE GAVAGE | SPECIES RAT | STUDY RB86053

Control
LD
MD
HD

0
88
88
88

0 28 56 84 112

DAYS

TABLE 3. BLOOD LEVELS OF LY170053 IN RATS TWO HOURS AFTER DOSE ON DAYS 1 AND 30 OF STUDY R08683.

Sex	Dose mg/kg	Day 1 µ g/ml	∓ ± SE	Sex	Dose mg/kg	Day 30 µ g/ml	∓ ± SE
M	2.5	.09		M	2.5	*	
M	2.5	.14		M	2.5	*	
F	2.5	.16		F	2.5	*	
F	2.5	.11	0.13 ± 0.02	F	2.5	*	
M	7.5	.34		M	7.5	.74	
M	7.5	.58		M	7.5	.94	
M	7.5	.38		F	7.5	.95	
F	7.5	.44	0.44 ± 0.05	F	7.5	.78	0.85 = 0.05
M	22.5	2.03		M	22.5	3.72	
M	22.5	2.57		M	22.5	3.88	
F	22.5	1.80		F	22.5	3.06	
F	22.5	1.68	2.02 ± 0.20	F	22.5	3.51	3.54 = 0.18

*Large interference peak prevented determination.

FINAL

Executive CAC
June 11, 1996

Committee members: James Farrelly, Ph.D., Acting Chair, HFD-530
Alex Jordan, Ph.D., Rotating member, HFD-580
Charles Resnick, Ph.D., HFD-110
Glenna Fitzgerald, Ph.D., Team Leader, HFD-120
Sharon Olmstead, Executive Secretary, HFD-006

NDA 20-592 (Atrakchi; HFD-120)
Zyprex (olanzapine)
Eli Lilly and Co.

The sponsor submitted carcinogenicity study results from a single rat study and two mice studies. The rat carcinogenicity study used doses of 0.25, 1.0, 2.5 and 4.0 mg/kg. Doses for the female rats in the 2 HD groups were increased at day 211 to 4.0 and 8.0 mg/kg, respectively, due to a limited effect on body weight. Decreases in percent of body weight gain were 11% for HD males and 18% and 33% in the two HD female groups. The sponsor reported statistically significant increases in female mammary gland adenocarcinomas; however, the FDA statistician did not agree with the sponsor's analysis. The FDA statistican found no significant increases in tumor types for either sex by any of the statistical tests conducted (trend and pairwise).

The sponsor conducted two separate mice carcinogenicity studies (the second study was conducted at the sponsor initiation). The original study using doses of 3, 10 and 30 mg/kg (lowered to 20 mg/kg due to excessive mortality in males)reported no significant increases of tumors in males. However, for the female mice, significant increases were reported for lung adenomas and carcinomas in the LD group, mammary gland adenomas and carcinomas in the HD group, and a significant but non-dose dependent increase in combined incidence of lymphosarcomas. The validity of this study was questioned by the FDA statistician due to the extreme mortality rate observed within this study.

The second mouse study used doses of 0.5, 2, and 8 mg/kg. The sponsor reported significant increases in the female mice for both mammary gland adenocarcinomas at the MD and the combined onset of liver hemangiosarcomas in the HD group. No significant increases in tumor types were reported in the male mice. The FDA statistician reported a significant increase in lung adenocarcinomas in females not reported by the sponsor.

Recommendations:
The committee found the study design and dose selection acceptable for both the rat and mouse carcinogenicity studies.

1. The committee recommended that historical control data for mouse lung adenocarcinomas, and mouse and rat mammary gland adenocarcinomas and adenomas be obtained from the sponsor, and that our statistician conduct a pairwise comparison for those tumors.

Post-meeting addendum:
Pairwise comparisons did not show the lung tumors to be significantly increased and were found to be within the historical control range. The mammary gland tumors were found not to be significantly increased in the rats; however, the mammary gland tumors were siginificantly increased in both the mouse studies. The mammary gland tumors were higher than historical control data in mice and rats.

James Farrelly, Ph.D., HFD-530
Acting Chair, CAC

cc: NDA file
Division file
HFD-120/GFitzgerald/AAtrakchi
CAC files

NDA 20-592 PG X PHARM/TOX
(O STRAKCHI, PH.D.)

NDA 20-592

Pg X Pharm/Tox

Overall (Summary)

(A. Atrakchi, Ph.D.)

In a separate report (#68) the sponsor further investigated the 1yr dog findings to determine whether serum Ab specific for olanzapine can be detected in dogs with neutropenia. Serum samples from all dog grs including the cont were collected and analyzed by ELISA for development of Ab against olanzapine. Olanzapine IgM Ab was detected in 6/16 cont, 12/28 noncytopenic drug dogs, and 3/3 cytopenic drug dogs. In the cont untreated dogs the level of IgM ranged from bql of ≤2.4 rel.ug/ml to 30rel ug/ml, in the treated grs without the 3 dogs with cytopenia, the IgM level ranged from bql of ≤2.4rel.ug/ml to 76rel.ug/ml. In the 3 cytopenic dogs, the level was from bql to 238rel.ug/ml. This finding was shown to be specific to olanzapine when fixed conc of free olanzapine inhibited portion of the binding. Olanzapine IgG Ab was detected only in sera from 1 dog with cytopenia. This activity was inhibited to 58% with addition of free olanzapine. Also in this dog, high levels of IgM (upto 238rel ug/ml or 5-6x the preexisiting level in other dogs) were detected. This effect was inhibited to · with free drug. The sponsor indicated that the relatively high level of olanzapine IgM and presence of olanzapine IgG suggests a qualitative difference in the type of Ab produced by this dog. It was concluded that the cytopenia observed in at least 1 dog of the 3, may be contributed to olanzapine-specific Ab.

The ophthalmological findings were seen in dogs treated for 2wks, 6mo and 1yr at doses between 2-40mg/kg/d. In the 2wk study, miosis occurred in all drug grs but could not be correlated with dose. There was dose-dependent and sig reduction in lacrimal flow 6hr postdose. These dogs had normal pupil reflexes but pupils of dogs dosed 40mg/kg did not dilate completely in response to application of dilating agents. The mechanism of miosis in this study could not be deduced. No effect on ophthalmology was noted in a 3mo tox study in dogs dosed 2, 5, or 10mg/kg. In a 6mo tox study, dose-dependent miosis, hyperreactivity to pupillary light response, and reduced response to mydriatic drug were seen in dogs dosed 4&8mg/kg/d. Similar to the 6mo study, dogs dosed 2.5, 10mg/kg for 1yr showed dose-dependent miosis, altered pupillary light reflex, and reduced tear production. In HD dogs blepharospasm was also noted. Other findings included conjunctivitis and discharge; tear production was reduced and was irreversible by end of study. The doses used in the 1yr were the same doses used in the 3mo study where no ophthalmological findings were observed. The sponsor related the ophthalmological results to the anticholinergic effect of the drug.

In a 3mo oral gavage mouse study, histopath exam showed **lymphoid depletion of the spleen and moderate multifocal lymphoid necrosis in all drug grs (3, 10, 30mg/kg/d) in addition, non dose-dependent mammary gland acinar hypertrophy, ductal ectasia, and ductal epithelial hypertrophy were seen in these 3 drug grs.** Rats orally dosed for 3mo at 2.5, 7.5, and 22.5mg/kg/d had dose-dependent reduction in relative wts of the ovaries and uteri, without histopath findings. Dogs orally dosed at 10, 20, 40mg/kg/d for 2wks had **lymphoid depletion of the thymus in all drug grs without histopath findings**. The relative wt of the testes was sig reduced in rats dosed 10mg/kg/d for 3mo and histopath exam showed **hypospermatogenesis**. The decr in testes wt in this study might have been secondary to wt loss in this gr. The absolute and relative wt of the ovaries were reduced in female rats dosed 4&16mg/kg/d for 6mo and uterine wt remained depressed in rats dosed 16mg/kg through the 1mo recovery period. Also in this study, the **relative wt of the adrenals in male rats dosed 16mg/kg/d was incr and histopath showed decr in vacuolation of cortical cells that persisted through the 1mo recovery period at which time the vacuolation was also observed in males dosed 4mg/kg/d.** Histopath exam showed mammary gland changes in males and females in this 6mo study. In males dosed 4&16mg/kg/d tissue morphology was changed from the normal lobuloalveolar to tubuloalveolar pattern and secretions were present in female rats dosed 16mg/kg/d. The **incidence and prominance of mucoid metaplasia of vaginal epithelium** were incr in females dosed 4&16mg/kg/d and **ovarian follicular prominance** was also incr in females dosed 16mg/kg/d. These mammary gland changes reversed during the recovery period. Uterine hypoplasia was observed in females dosed 4&16mg/kg/d at end of study and in females dosed 16mg/kg/d at end of recovery. There was thecal prominance in the ovaries of females dosed 4&16mg/kg/d. The findings in the ovaries and uteri were considered secondary to reduced wt in these animals. In a 1yr oral study in