

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20639

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 20-639

Sponsor: Zeneca

Drug: Seroquel (quetiapine)

Material Submitted: Safety Update and Response to Approvable Letter

Date Submitted: Safety Update (6/30/97); Response to Approvable Letter (7/31/97)

Date Received: Safety Update (7/1/97); Response to Approvable Letter (8/4/97)

Medical Officer: Andrew Mosholder, M.D.

1. Background

Safety findings from the original Seroquel NDA submission and the 4 month safety update were reviewed in the NDA clinical review. These two sources together provided data on patients exposed to quetiapine in clinical trials through 3/1/96. The sponsor's "pre-approval safety update" submitted 6/30/97, and the sponsor's response to the Seroquel Approvable Letter submitted 7/31/97, provide additional safety data that is the subject of this review.

The sponsor's response to the agency's Approvable Letter will also be reviewed here.

2. Updated Clinical Data

The original NDA clinical review covered the sponsor's primary integrated safety database, comprising 2387 quetiapine treated patients who received the drug in Phase II-III clinical trials. This primary integrated database incorporated both the original NDA submission and a four month safety update. The cutoff date for safety data on these 2387 quetiapine patients was 3/1/96.

Updated Primary Integrated Database

This submission updates the primary integrated database with a new cutoff date of 11/7/96. Included are data on all adverse experiences, including serious adverse experiences, premature discontinuations and deaths, for 504 quetiapine treated subjects. Of these, 136 are new patients and 368 are previously reported patients with added exposure time. Note that clinical laboratory, vital signs, and EKG data was not updated in this submission. Data on adverse experiences was provided in electronic SAS format. All new safety data was from outpatient uncontrolled trials, and there were no new data from placebo or active control treated patients. The updated primary integrated database does not include any additional Phase I trial data, reportedly because the additional Phase I trials were not yet analyzed.

The table below displays the total number of patients and the exposure in patient years for the primary integrated database, with the new cutoff date of 11/7/96, by treatment group.

TREATMENT GROUP	N	PT-YEARS
Quetiapine	2523	1103.2
Placebo	206	14.6
Haloperidol	320	42.5
Chlorpromazine	100	9.2

The additional quetiapine exposure for this submission amounts to 237.9 patient years. As noted, the exposure for the control groups did not change with this submission.

Clinical Trials Not Included in the Primary Integrated Database

This submission includes data from 14 trials not incorporated in the primary integrated database, chiefly because they were still ongoing or not yet analyzed. For these studies, the sponsor reported deaths, serious adverse events, and adverse events leading to dropout. While 5 of these trials were described in the NDA clinical review, 9 were new trials.

Secondary Data Cutoff

In the pre-approval safety update Zeneca provided a listing of all deaths and serious adverse events among quetiapine treated patients during the period 11/8/96 to 5/30/97, with narrative case summaries. Case report forms were also provided for patients who died. These data are not included in the primary integrated database, however, and case report forms were not always available to the sponsor.

Tertiary Data Cutoff

In the response dated 7/31/97 to the approvable letter, the sponsor provided line listings and narrative summaries for deaths and other serious adverse events occurring from 5/30/97 to 7/15/97. The case report form for the one patient who died was also provided under separate cover (submitted 8/6/97).

Demographic Profile for primary integrated database

With the updated primary integrated database (n=2523) for quetiapine exposed patients in Phase II-III trials, the percentage composition by age group, gender and racial background changed very little (not more than about 1% in any category). I have not included a revised demographic profile table here, because the overall changes are so minimal, but the interested reader is referred to the sponsor's Table T3.2.7.3.

Deaths

The following table displays a listing of all deaths among quetiapine treated patients in the safety update period. This table is adapted from the sponsor's electronic submission.

Table Subjects who died during or within 30 days after discontinuation of trial treatment, 3/1/96 to 7/15/97*

Trial/center/ subject number	Age (y)	Sex	Last recorded dose (mg/day)	Duration of trial treatment (days)	Primary cause of death
0048/0003/0310*	77	M	500	292	Myocardial infarction; concurrent pneumonia
0048/0007/0712*	64	M	100	252	Aspiration pneumonia; patient with progressive supranuclear palsy
0048/0013/1306*	65	F	175	339	Sepsis, pneumonia, carcinoma of upper esophagus, no autopsy
0048/0013/1310*	81	F	75	189	Sudden death while dancing, deemed "possible cardiopulmonary arrest"
0015/0003/0305	69	M	500	1091	Metastatic pancreatic cancer
0015/0035/3501	47	M	300	1037	Sudden cardiac arrest and death; no autopsy
0048/0001/0105	80	F	50	596	Patient had end stage dementia, was not taking food, liquids or medication, aggressive treatment waived

Table Subjects who died during or within 30 days after discontinuation of trial treatment, 3/1/96 to 7/15/97*

0048/0002/0207	70	F	300	592	Death from pneumonia following surgery for bowel obstruction
0048/0004/0406	77	M	200	618	Aspiration pneumonia, dysphagia, dementia. Also receiving olanzapine 5 mg/d.
0048/0006/0609	96	M	75	571	Bronchopneumonia in patient with vascular dementia; family elected not to treat pneumonia
H-15-34/1311/H-003	65	M	400	47	Died after febrile illness with respiratory distress; suspected pneumonia
H-15-37/4018/016-001	28	M	75	3	Suicide
H-15-37/4003/012-001	38	m	200	220	Found approximately 10 d after death, body too decomposed for autopsy
H-15-31/0201/013-001 BLINDED (QUETIAPINE OR HALOPERIDOL)	27	F	blinded	57	Suicide
H-15-31/0105/080-001 HALOPERIDOL	55	F	0.75 Haloperidol	1	Sudden death
H-15-31/0402/015-003 HALOPERIDOL	40	M	9 Haloperidol	46	Sudden death (found in bathroom); no autopsy; investigator suspected water intoxication

* Additionally, 2 subjects (0048/0001/0102 and 0048/0018/1811) died (aspiration pneumonia and unknown cause, respectively) more than 30 days after discontinuation of quetiapine treatment and 1 subject (0050/0092/0001) committed suicide more than 30 days after discontinuation of blinded treatment (quetiapine or haloperidol).

NA Not applicable.

*Included in primary integrated database

In my judgement, none of these deaths are directly attributable to the effects of quetiapine. (Drug related dysphagia and aspiration may be contributing factors in the development of pneumonia, however, as discussed in the NDA clinical review.) The following table provides the updated all cause mortality in the primary integrated database.

Table Overall mortality in the updated integrated Phase II-III database (adapted from sponsor's electronic submission)

Treatment	Number of subjects	Patient-years exposure ^a	Number of deaths ^b	Crude mortality rate	Mortality per 100 patient-years
Quetiapine	2523	1103.2	12	0.48	1.09
Haloperidol	320	42.5	1	0.31	2.35
Chlorpromazine	100	9.2	0	0.00	0
Placebo	206	14.6	0	0.00	0

^a Patient-years is defined as the sum of all subjects' days on treatment (duration) divided by 365 days.

^b Deaths occurring within 30 days after trial treatment ended (excludes one death from Trial 0031, for which treatment assignment remains blinded).

Overdose Experience

The sponsor defined overdose to be ingestion of 900 mg or more of quetiapine. In the original database the small number of known overdoses of quetiapine did not point to any unusual toxicity. The following provides a listing of quetiapine overdoses reported in the safety update.

Table Summary of overdoses with quetiapine 3/1/96-5/30/97

Trial;subject	A g e	S e x	over-dose mg	Concomitant drugs	Comments
0048/0010/1006	79	f	900/d x 14 d		Inadvertent administration by caregiver; no significant effects other than slight hypotension and dizziness
0056/0044/0007	27	f	~1000		Developed Tachycardia, nonspecific T wave changes, Qtc 402 msec; received lavage, recovered
0061/0001/0130	28	f	3000		Treated with charcoal and lavage; experienced sedation, tachycardia (180 bpm) and was administered diltiazem and adenosine; treated in intensive care setting, recovered; no ECG data provided
0053/0521/0001	48	f	5100 or pbo.		Received overdose of quetiapine or placebo due to dispensing error (blind was not broken); pt. asymptomatic
0053/0544/0001	39	m	700-900/d or risperidone 16 mg/d x 1 wk		Dispensing error resulted in overdose; blind not broken; pt. asymptomatic
0054/0253/0001	62	m	10,000 or pbo.		Accidental overdose; blind not broken, pt. slightly hyponatremic (131 mmol/l) but otherwise asymptomatic
0054/0253/0002	57	m	10,000 or pbo.		Accidental overdose; blind not broken, pt. developed dry mouth, urinary retention and incontinence, sedation, hematuria, myoclonus, dry skin, flushing, delirium, no ECG findings. Treated with diazepam; recovered in 2 days.
0053/0573/0001	25	m	1700		Accidental overdose; pt. developed sedation, dizziness, rigidity, lower blood pressure and heart rate. Treated with charcoal and lactulose; recovered in 12 hours.
0056/0008/0002	21	m	18,000 to 20,000	fluoxetine 400-600 mg	Sinus tachycardia, confusion; treated with lavage and IV fluids
0056/0022/0005	26	f	12,000 to 19,200		Treated with gastric lavage, hydration; became obtunded and required intubation; recovered
0056/0044/4410	24	m	2400	risperidone, benztropine	Treated with charcoal; no symptoms or ECG findings. Pt overdosed a second time (see below)
0056/0044/4410	24	m	1900		Second overdose by this patient. Experienced stupor, dysarthria; ECG normal; treated with charcoal, recovered
Not a subject	51	m	200		Family member took patient's medication by mistake; developed hypotension, slurred speech, lethargy, dry mouth, recovered in 7 hrs.
0056/0009/0003	32	m	1800		Sedation noted; treated with lavage and charcoal, recovered within hours

0050/0071/0007	25	f	1000-1200		Developed sopor, tachycardia (140 bpm) and hypotension (85/60); treated with gastric lavage with saline solution, recovered by next day
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The most notable clinical features from the cases above are the prominent sedative effects and anticholinergic effects. The latter is somewhat surprising since quetiapine is not believed to possess much anticholinergic activity.

Adverse Events

As the only additional exposure reported was from uncontrolled studies, no information of consequence on the common adverse event profile was provided by the new data. Hence, the focus of this review is on significant adverse events, primarily deaths and other serious adverse events, and in some cases adverse events that lead to dropout. The primary source of information for this section was the sponsor's clinical narrative summaries of the cases; in certain cases the CRF was consulted or the sponsor provided additional information upon my request.

In the following, I will highlight the adverse events of significance by body system. Events referable to the patient's psychiatric illness will not be discussed here.

Cardiovascular

Deaths: Patient 0048/0003/0310 died of an MI. Patient 0048/0013/1310 (81 y.o.) died suddenly while dancing. Patient 0015/0035/3501 died suddenly (47 y.o., no autopsy). See table above for details.

Other adverse events: There were 5 cases of syncope or postural hypotension reported among quetiapine treated patients and another 6 such cases among patients who were not unblinded. In addition, there were 2 cases of deep vein thrombophlebitis, 2 cases of angina/chest pain, one case of congestive heart failure, one case of hypotension and left bundle branch block, and one case of arterial thrombosis which required surgery.

Thrombotic adverse events continue to be reported with quetiapine treatment, as was noted in the NDA clinical review; please refer to the discussion there under Cardiovascular system.

Similarly, please refer to the NDA clinical review discussion of syncope/postural hypotension. These new data do not lead me to revise my previous interpretations. The incidence of syncope (i.e., adverse events with this COSTART term found by electronic search) for the updated primary integrated database was 28/2523 quetiapine treated patients (1.1%), compared to 2/420 active control patients (0.5%) and no placebo patients. The median duration of quetiapine treatment at the time of syncope for these patients was 17 days.

Gastrointestinal

The following adverse events were reported in patients receiving quetiapine or whose treatment was blinded but could have been receiving quetiapine: bloody diarrhea requiring hospitalization, intestinal obstruction secondary to adhesions, appendectomy for carcinoid tumor of appendix, abdominal pain of unknown cause, esophagitis (3 cases), fecal impaction (2 cases), paralytic ileus, increased liver enzymes, appendectomy, cholecystectomy (2 cases, one of which also involved cirrhosis of unknown cause), gastroenteritis, diarrhea, rectal fistula, hemorrhage from a benign colonic ulcer. One notable case is summarized below, although the randomization code was not broken:

0053/0534/0007

BLINDED 40 y.o. male developed jaundice, increased LFTs (ALT 324 iu/l), hepatopathy, and portal hypertension on day 18 of quetiapine or risperidone. Prior history of hepatitis C, with positive antibodies to hep B and C. Resolved after d/c of treatment

This patient became symptomatic with hepatic dysfunction and recovered after drug was discontinued; however, the patient had evidence of exposure to viral hepatitis.

Hemic and Lymphatic

The following adverse events were reported in patients receiving quetiapine or whose treatment was blinded but could have been receiving quetiapine: leukopenia (ANC 1010), pernicious anemia, prolonged bleeding times resulting in postponement of elective surgery, ecchymosis (but with normal platelet count). These new reports do not alter the previous conclusions regarding this body system, in my opinion.

Genitourinary

The following adverse events were reported in patients receiving quetiapine or whose treatment was blinded but could have been receiving quetiapine: urinary tract infection (6 cases), pyelonephritis (2 cases), renal calculus, surgery for urethral stricture. In my opinion, a drug related cause of urinary tract infections seems unlikely.

Metabolic and Endocrine

The following adverse events were reported in patients receiving quetiapine or whose treatment was blinded but could have been receiving quetiapine: Neuroleptic malignant syndrome and similar events (4 cases, blind unbroken in all 4), weight loss requiring hospitalization, dehydration, acute hypoglycemia of unknown cause, diabetic ketoacidosis. One patient, 0050/0031/0003, whose treatment remained blinded, was withdrawn and treated with thyroid replacement, although the TSH remained normal. Please refer to the NDA clinical review for a discussion of thyroid findings with quetiapine treatment.

Musculoskeletal

The following adverse events were reported in patients receiving quetiapine or whose treatment was blinded but could have been receiving quetiapine: fracture of maxilla in a fall, hip fracture (2 cases), bone graft of hip for osteoporosis, fracture of ankle, fracture of radius, herniated lumbar disk. With respect to hip fracture, there was one additional case in the primary integrated database in a patient over age 64 (0048/0008/0801). Please refer to the NDA clinical review for a discussion of falls and fractures, which could be drug related via postural hypotension.

Nervous

Deaths (see table above for details): Suicide (patients H-15-37/4018/016-001, H-15-31/0201/013-001 (blinded))

End stage dementia (patient 0048/0001/0105)

The following adverse events were reported in patients receiving quetiapine or whose treatment was blinded but could have been receiving quetiapine: cerebrovascular accident, breast carcinoma metastatic to brain, seizure (12 cases, 5 on quetiapine and 7 blinded), akathisia (4 cases), hypertonia, severe somnolence/stupor (3 cases), tremor, hemiparesis of unknown cause, delirium, ataxia, severe EPS. Please refer to the original NDA clinical review for a discussion of nervous system adverse events. Concerning seizures, Zeneca has agreed to labeling with the incidence of seizures from the previous primary integrated database, i.e., 0.8%, and did not conduct a search to update this incidence.

Respiratory

Deaths: Pneumonia was involved in the following fatal cases, either as a cause or a complication: 0048/0007/0712, 0048/0013/1306, 0048/0002/0207, 0048/0004/0406, 0048/0006/0609, H-15-34/1311/H-003. See table above for details.

The following adverse events were reported in patients receiving quetiapine or whose treatment was blinded but could have been receiving quetiapine: pneumonia (10 cases), dysphagia (choking on food), respiratory dyskinesia, bronchitis.

As noted in the NDA clinical review, and the draft labeling, dysphagia and aspiration pneumonia may be drug related.

Dermatological

Two patients underwent surgical removal of skin cancers. One patient had a severe skin allergy:

0051/0216/0007 42 y.o. male hospitalized for photoallergy of skin after 70 days on quetiapine 600 mg/d. Concomitant medications were tropatepine and alprazolam; continued open label quetiapine.

Special Senses

One patient suffered traumatic retinal detachment (when struck by another patient.)

Miscellaneous

Deaths: pancreatic carcinoma (0015/0003/0305). Another patient was found dead, and the body was considered too decomposed for autopsy (H-15-37/4003/012-001).

The following adverse events were reported in patients receiving quetiapine or whose treatment was blinded but could have been receiving quetiapine: alcohol intolerance, cellulitis (2 cases), burn injury suffered in kitchen fire, surgery to remove uvula polyp, chronic otitis, breast cancer, fever of unknown origin, leg ulcer, chest pain of unknown etiology, surgical drainage of abscess on arm, food allergy.

In addition, the sponsor reported a case of psuedotumor cerebri in a 14 year old boy receiving quetiapine, the first instance of psuedotumor cerebri in a patient treated with quetiapine. The investigator attributed this to concomitant minocycline (IND safety report 7/28/97).

Additional Clinical Data on Cases Reviewed in NDA Clinical Review

In response to our request (fax 6/5/97), Zeneca provided additional clinical information on certain cases of serious adverse events for which the originally submitted information was incomplete (submissions dated 6/19/97 and 6/16/97). On balance, this additional clarifying information does not provide evidence of additional adverse drug reactions to quetiapine. Briefly, the information provided is as follows:

0013/0016/1605: This patient had a DVT which was attributed to concomitant oral contraceptives; her anemia was determined to be iron deficiency.

0012/0091/9143: This 46 year old man who developed a left ventricle thrombus and a resulting cerebrovascular accident did in fact have a history of myocardial infarction with a residual left bundle branch block, although Zeneca did not include this information originally.

0048/0002/0201: This patient developed acute renal failure and anemia while on quetiapine, among other disorders; he apparently had a history of chronic renal failure and the sponsor attributes his acute renal failure to multifactorial causes. No specific cause for the anemia was stated but Zeneca denied that there was any evidence of hemolysis.

0012/0019/1903: No other cause of this patient's renal failure was found, and the investigator attributed it to quetiapine; however, the patient was not rechallenged with the drug.

0048/0004/0405: No additional information on this patient's anemia was available; apparently the investigator ignored it.
0015/0005/0502: The patient's anemia was attributed to cancer chemotherapy, which was not made clear in the original submission.

0014/0046/4609: This patient was hospitalized for his anemia, and was found to have gastritis; he was treated with folate. The case report form was submitted but provided little additional information.

Conclusions: The additional safety data in the pre-approval safety update and the final safety update submitted after the approvable letter do not substantively alter the previous conclusions about quetiapine safety. If desired, the sponsor could be asked to update the incidence of key adverse events such as seizures and syncope, which was not done for these submissions.

3. Zeneca's Response to the Approvable Letter

Labeling

I have the following comments on the sponsor's counter-proposals to the approvable letter labeling. Regarding the interaction with phenytoin cited under Clinical Pharmacology, I favor retaining the cross-reference to the Dosage and Administration section; Zeneca's proposal is to delete the cross-reference. Under Clinical Trials, I favor retaining the description of the possible age interaction, which Zeneca proposed to delete. For the precaution about cataracts, Zeneca has proposed deleting the recommendation for periodic slit lamp exams and replacing it with a recommendation for "careful ocular examination." The sponsor's response has been reviewed by our ophthalmology consultant, Dr. Wiley Chambers, who disagrees. (Dr. Chambers explained to me in a telephone conversation that a routine examination of the eye with a handheld ophthalmoscope does not permit thorough visualization of the lens, partly because the bright light constricts the pupil and partly because the instrument cannot focus effectively on the lens.) Regarding cholesterol elevations, Zeneca has declined to conduct further analyses of these data on the grounds that the samples were non-fasting and therefore are not definitive.

Zeneca proposes a recommended dose range of 300-400 mg/d (the agency's interpretation was that the target dose should be 400-450 mg/d). In my opinion, this is a matter of judgement, as I do not believe the clinical trial data are precise enough to distinguish whether 300 or 400 mg daily should be the target dose. The sponsor has revised the "Other Events..." table as requested.

Post-Marketing Studies: Zeneca has agreed to conduct the studies requested in the approvable letter, but has not submitted any proposals.

World Literature Update: Zeneca conducted a literature search covering the period 4/16/96 through 7/14/97, using their in-house library database, and provided abstracts of publications pertaining to quetiapine. Dr. Lisa Arvanitis from Zeneca has certified that there are no publications that would adversely affect conclusions about the safety of quetiapine. My own review of the abstracts provided leads me to the same conclusion. There is some new information about the pharmacology of the drug, however: Seeman and associates (Japanese Journal of Pharmacology 71(3):187-204, 1996) provided K_i values for quetiapine binding to human dopamine and serotonin receptors (see page 215 of submission). The values they obtained were 78 nM for D2, 3000 nM for D4 and 2500 nM for 5HT2A. The proposed labeling has IC50 values; these appear to be the first K_i values reported for the compound. Additionally, Zeng and associates concluded that quetiapine has almost no effect at the muscarinic m4 receptor (European Journal of Pharmacology 1997:321(3):349-354, on page 238 of the submission).

World Regulatory Update: Seroquel has neither been approved nor rejected for marketing elsewhere. A number of foreign applications are pending.

4. Conclusions and Recommendations

The additional clinical data provided by Zeneca subsequent to the NDA clinical review do not substantively

alter the previous conclusions about quetiapine safety or efficacy. I recommend approval of the drug, with appropriate revisions to the sponsor's draft labeling.

Andrew Mosholder 8/19/97

Andrew Mosholder, M.D.
Medical officer, Division of Neuropharmacologic Drug Products

NDA 20-639
Div File
HFD-120:Laughren/Hardeman/Mosholder

8-21-97

I agree that this NDA can now
be approved. However, we have not
reached agreement on the issue of
labeling language for extracts, and
I will forward a package that includes
our originally proposed language.
See memo to file for more
detailed response.

Thomas P. Laughren, MD
TL, PDA

8A LIST OF INVESTIGATORS

All investigators who received trial drug shipment up to the secondary data cutoff date (1 March 1996) are included in the following list:

NAME/ADDRESS	TRIAL NUMBER/ CENTER***	TYPE OF TRIAL**	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT FORMS*
Addington, Donald E.N., MD Foothills Hospital 1403-29th Street NW Calgary, Alberta T2N 2T9 CANADA	5077IL/0013:0019	D-B Comp	1.117/1, 1.148/1, 1.308/1	1.398/1	CANDA
	5077IL/0013:0019	O-L E	1.262/1	1.442/274	CT Report
Ahnlund, Dr. N.G. Vuxen Psyk Mottagningen Vallonvagen 15 812 00 Finspang SWEDEN	5077IL/0014:0058	D-B Comp	1.243/1 1.354/1	1.431/1	CANDA
	5077IL/0014:0058	O-L E	1.262/1	1.442/274	CT Report
Alphs, Larry D., MD, PhD Lafayette Clinic 951 East Lafayette Avenue Detroit, MI 48207 USA Detroit VA Medical Center Southfield and Outer Drive Allen Park, MI 48101 USA	5077IL/0006:0004 (APS 0-A31-1/0004)	D-B Comp	1.132/1, 1.301/1	1.384/1	CANDA
Anderson, Cheryl, PharmD University of Texas Health Science Center at San Antonio San Antonio State Hospital Clinical Pharmacy Programs 7703 Floyd Curl Drive San Antonio, TX 78284 USA	5077US/0001:0009 ¹¹ (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Anderson, Dr. T. Psyk Kliniken Universitetssjukhuset 901 85 UMea SWEDEN	5077IL/0014:0060	D-B Comp	1.243/1 1.354/1	1.431/1	CANDA
	5077IL/0014:0060	O-L E	1.262/1	1.442/274	CT Report
Apter, Jeffrey T., MD Princeton Biomedical Research 256 Bunn Drive, Suite 6 Princeton, NJ 08540 USA	5077IL/0015:0001	D-B Comp	1.171/1, 1.314/1	1.408/1	CANDA
	5077IL/0015:0001	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0048:0001	O-L	1.258/1	1.442/272	CANDA
Aschauer, Dr. H.H. Psychiatrische Universitätsklinik Wahringer Gurtel 18-20 A-1090 Wien AUSTRIA	204636/0008:0027 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA

See footnotes on Pages 53 and 54.

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT FORMS*
Ashcroft, G.W., Professor Department of Mental Health University Medical Buildings Foresterhill Aberdeen, England AB9 2ZD UK	50771L/0005: UK-0005	O-L	1.254/1	1.439/272	CANDA
Asserson, Dr. S. Helleveien 65 Sandviken Sykehus 5035 Bergen NORWAY	50771L/0014:0043	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	50771L/0014:0043	O-L E	1.262/1	1.442/274	CT Report
Avnon, Dr. M. Psychiatric Center Doar NA Chefer Shaar Menashe ISRAEL	50771L/0012:0046	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0046	O-L E	1.262/1	1.442/274	CT Report
Ayuso, Prof. Hospital Clinico Universitario Servicio de Psiquiatria San Carlos Madrid SPAIN	204636/0007:0011	D-B Comp	1.217/1, 1.348/1	1.415/1	CANDA
Azorin, Prof. J.M. C.H.U. La Timone Clinique de Psychiatrie Rue Saint-Pierre 13385 Marseille Cedex 4 FRANCE	50771L/0012:0033	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0033	O-L E	1.262/1	1.442/274	CT Report
Baker, Robert Special Studies Center South 2, Ward 4B 1601 Mayview Road Bridgeville, PA 15017 USA	50771L/0031:0009z	D-B Comp	1.261/333	1.442/273	CANDA
Ballus-Pascual, Dr. C. Servicio de Psiquiatria Hospital Clinico y Provincial Villarreal 170 08036 Barcelona SPAIN	204636/0007:0014	D-B Comp	1.217/1, 1.348/1	1.415/1	CANDA
	50771L/0014:0054	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
Banki, Dr. C. Department of Psychiatry Regional Neuropsychiatric Institute Nagykallo, PO Box 37 H-4321 HUNGARY	50771L/0012:0092	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0092	O-L E	1.262/1	1.442/274	CT Report

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT FORMS*
Bark, Nigel, MD Bronx Psychiatric Center Ward 19 - Research 1500 Waters Place Bronx, NY 10461 USA	5077IL/0031:0006	D-B Comp	1.261/333	1.442/273	CANDA
Barnes, T.R.E., Dr. Horton Hospital Long Grove Road Epsom Surrey KT19 8PZ UK	204836/0008:0001 ¹⁶ (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Bartko, Dr. G. Department of Psychiatry South-Pest Hospital Budapest Koves, ut 2-4 H 1204 HUNGARY	5077IL/0012:0091	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0091	O-L E	1.262/1	1.442/274	CT Report
Bassi, Dr. M. Servizio di Salute Mentale Via Berenini 153-43036 Fidenza ITALY	5077IL/0012:0074	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0074	O-L E	1.262/1	1.442/274	CT Report
Bastani, Bijan, MD Portage Path Community Mental Health Center, 340 South Broadway Street Akron, OH 44304 USA	5077IL/0015:0034	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0034	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0048:0002	O-L	1.258/1	1.442/273	CANDA
Beau, Dr. J. Center Hospitalier Malartic 1141 Rue Royale Malartic Quebec J0Y 1Z0 CANADA	5077IL/0012:0062	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0062	O-L E	1.262/1	1.442/274	CT Report
Bech, Prof. Per Hellerod Sygehus Helsevej 2 3400 Hillerod DENMARK	5077IL/0005: UK-0017	O-L	1.254/1	1.439/272	CANDA
	5077IL/0014:0018	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
Beckers, Dr. G. Medister Jagersdreef 100 2950 Kapellen BELGIUM	5077IL/0012:0023	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0023	O-L E	1.262/1	1.442/274	CT Report

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT FORMS*
Belmaker, Prof. R.H. Psychiatric Center PO Box 4600 Beer Sheva ISRAEL	5077IL/0012:0045	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0045	O-L E	1.262/1	1.442/274	CT Report
Benkert, Prof. O. Psychiatric Clinic Mainz GERMANY	5077IL/0005:UK-020	O-L pilot	1.254/1	1.439/272	CANDA
Bennie, Dr. E. Department of Psychology Leverdale Hospital 510 Crookston Road Glasgow G53 7TU UNITED KINGDOM	204636/0008:0002 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0014:0064	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0064	O-L E	1.262/1	1.442/274	CT Report
Bent, Dr. E. SPDC Oost Bredesodelaan 54 Postbox 50 2080 AB Santpoort-Zuid NETHERLANDS	5077IL/0014:0033	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0033	O-L E	1.262/1	1.442/274	CT Report
Frederik Van Eeden Stichting Amsterdam NETHERLANDS					
Bern, Dr. P.H. C.H. des Chanoux Hotel Dieu 71018 Macon Cedex FRANCE	204636/0007:0031	D-B Comp	1.217/1, 1.348/1	1.415/1	CANDA
	5077IL/0012:0032	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0032	O-L E	1.262/1	1.442/274	CT Report
Bitter, Dr. I. Semmelweis Medical University Balassa utea 6H-1083 Budapest HUNGARY	204636/0008:0017 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0014:0035	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0035	O-L E	1.262/1	1.442/274	CT Report
Bjorling, Dr. G. Psyk Mottagningen Fyren Drottningatan 461 33 Trollhattan SWEDEN	5077IL/0014:0057	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0057	O-L E	1.262/1	1.442/274	CT Report
Bjorck-Thorsen, Dr. G.R. Psykiatrisk Avdeling Sentraljokehuset I Rogalad 4011 Stavanger NORWAY	5077IL/0014:0042	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0042 ¹³	O-L E	1.262/1	1.442/274	CT Report
Bobon, Prof. D. Clinique Notre Dame des Anges Rue Vanderveelde 67 4000 Glain BELGIUM	5077IL/0005:UK-008	O-L pilot	1.254/1	1.439/272	CANDA

NAME/ADDRESS	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F ORMS*
Borison, Richard-L., MD, PhD Medical College of Georgia Dept of Psychiatry & Health Behavior 1515 Pope Avenue Augusta, GA 30912-3800 USA Psychiatry Service 116A-U Augusta VA Medical Center One Freedom Way Augusta, GA 30910 USA	5077IL/0006:0008 ³ (APS 0-A31-1/0008)	D-B Comp	1.132/1, 1.301/1	1.384/1	CANDA
	5077IL/0013:0001	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0001	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0015:0002	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0002	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0031:0001	D-B Comp	1.261/333	1.442/273	CANDA
	5077IL/0044:0001	Clin Pharm	1.90/1	1.377/1	NA
	5077IL/0045:0001	Clin Pharm	1.108/1	1.381/1	CANDA
	5077IL/0045:0001	O-L E	1.262/1	1.442/274	CT Report
	Botte, Dr. Psychiatric Hospital of Manage 7170 Manage BELGIUM	204636/0007:0035	D-B Comp	1.217/1, 1.348/1	1.415/1
Bowden, Charles L., MD Department of Psychiatry Audie L. Murphy Veterans Memorial Hospital 7400 Merton Minter Boulevard San Antonio, TX 78284 USA	5077US/0001:0002 (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Boza, Ramon, MD VA Medical Center Department of Psychiatry 1201 NW 16th Street Miami, FL 33125 USA	5077IL/0015:0022 ⁴	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0022 ⁴	O-L E	1.262/1	1.442/274	CT Report
Braconnier, Dr. A. Centre de L'Eau Vive 8 Avenue du Gal de Gaulle 91450 Soisy-sur-Seine FRANCE	5077IL/0012:0037	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0037	O-L E	1.262/1	1.442/274	CT Report
Bredbacka, Dr. P.E. Paijat Hame Central Hospital Keskussairaalankatu 7 15 850 Lahti FINLAND	5077IL/0014:0023	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0023 ¹⁹	O-L E	1.262/1	1.442/274	CT Report
Brown, Walter A., MD Clinical Programs Ltd. 4 Richmond Square Providence, RI 02906 USA	5077IL/0015:0031	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0031	O-L E	1.262/1	1.442/274	CT Report

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F ORMS*
Buchkremer, Prof. G. Psychiatrische Universitätsklinik 72076 Tübingen Osianderstrasse 22 72076 Tübingen GERMANY	5077IL/0012:0050	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0050	O-L E	1.262/1	1.442/514	CT Report
Burns, Prof. T. Department of Mental Health Sciences Jenner Wing Cranmer Terrace Tooting London SW17 0RE UNITED KINGDOM	5077IL/0012:0015	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0015	O-L E	1.262/1	1.442/274	CT Report
Busse, Erhard, MD Psychopharmacology Research Training Center Hamilton Psychiatric Hospital 100 West 5th Street Hamilton, Ontario L9C 3N6 CANADA	5077IL/0031:0007s	D-B Comp	1.261/333	1.442/273	CANDA
Canive, Jose M., MD VA Medical Center Building 1 2100 Ridgecrest Drive, SE Albuquerque, NM 87108 USA VA Medical Center 3695 Hot Springs Boulevard Las Vegas, NM 87701 USA	5077IL/0015:0003	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0003	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0031:0002	D-B Comp	1.261/333	1.442/273	CANDA
Carman, John S., MD Brawner Psychiatric Institute 3180 Atlanta Street SE Smyrna, GA 30080 USA Carman Research 4000 Cumberland Parkway Building 100, Suite A Atlanta, GA 30339 USA	5077IL/0006:0002 (APS 0-A31-1/002)	D-B Comp	1.132/1, 1.301/1	1.384/1	CANDA
	5077IL/0015:0030	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0030	O-L E	1.262/1	1.442/274	CT Report

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT FORMS*
Caroli, Dr. F. Hospital Sainte Anne Pavillon Benjamin Ball 1 Rue Cabanis 75674 Paris Cedex 14 FRANCE	204636/0007:0026	D-B Comp	1.217/1, 1.348/1	1.415/1	CANDA
	50771L/0012:0043	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0043	O-L E	1.262/1	1.442/274	CT Report
Casacchia, Prof. M. Universita dell'Aquila Ospedale Santa Maria di Collemaggio 67100 L'Aquila ITALY	50771L/0012:0077	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0077	O-L E	1.262/1	1.442/274	CT Report
Casey, D.E., MD Chief, Psychiatric Research Pharmacology Psychiatry Service 116A VA Medical Center Portland, OR 97207 USA	50771L/0005: US-0005 (APS 9-976-1)	O-L pilot	1.254/1	1.439/1	CANDA
Cervera, Dr. S. Servicio de Psiquiatria Clinica Universitaria de Navarra Avenida Pio XII S/N 31080 Pamplona SPAIN	50771L/0012:0086	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0086	O-L E	1.262/1	1.442/274	CT Report
Chabannes, Dr. J.P. C.H.S. de Bassans BP 1126 73011 Chambéry Cedex FRANCE	50771L/0012:0041	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0041	O-L E	1.262/1	1.442/274	CT Report
Chiles, John, MD University of Texas Health Science Center at San Antonio Department of Psychiatry 7703 Floyd Curl Drive San Antonio, TX 78284-7792 USA	50771L/0015:0013a	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	50771L/0015:0013 ^b	O-L E	1.262/1	1.442/274	CT Report
Chinchilla, Dr. A. Servicio de Psiquiatria Hospital Ramon y Cajal Ctra Colmenar KM 9100 Madrid SPAIN	50771L/0012:0084	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0084	O-L E	1.262/1	1.442/274	CT Report
Clerc, Dr. G. C.H.S. de Pontorson 50170 Pontorson FRANCE	50771L/0012:0040	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0040	O-L E	1.262/1	1.442/274	CT Report

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT FORMS*
Cookson, Dr. I. Department of Psychiatry Defon General Hospital Smithdown Road Liverpool UNITED KINGDOM	204636/0007:0023	D-B Comp	1.217/1, 1.348/1	1.415/1	CANDA
Cooper, Dr. S.J. Department of Therapeutics and Pharmacology Whitla Medical Building Queens University of Belfast 97 Lisburn Road Belfast, Northern Ireland UNITED KINGDOM	204636/0008:0028 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Copolov, Prof. D.L. Mental Health Research Institute of Victoria Oak Street Parkville Victoria 3052 AUSTRALIA	5077IL/0014:0001 5077IL/0014:0001	D-B Comp O-L E	1.243/1, 1.354/1 1.262/1	1.431/1 1.442/274	CANDA CT Report
Corrigan, Dr. F.M. Department of Psychiatry Argyll & Bute Hospital Barbuie Road Lochgilphead Argyll Scotland UNITED KINGDOM	5077IL/0012:0017 5077IL/0012:0017	D-B Comp O-L E	1.225/1, 1.350/1 1.262/1	1.423/1 1.442/274	CANDA CT Report
Corrigan, Mark, MD Clinical Research Unit Edgerton Building Dorothea Dix Hospital 809 Ruggles Drive Raleigh, NC 27603 USA	5077US/0001:0007 (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Covelli, Dr.G. Ospedale Bolognini Via Paderno 1-24068 Seriate ITALY	5077IL/0012:0067 5077IL/0012:0067	D-B Comp O-L E	1.225/1, 1.350/1 1.262/1	1.423/1 1.442/274	CANDA CT Report

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT FORMS*
Crabtree, Brian L., PharmD VA Medical Center 1500 East Woodrow Wilson Avenue Jackson, MS 39216-5199 USA University of Mississippi Medical Center 2500 North State Street Jackson, MS 39216 USA	5077US/0001:0006 ^b (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Creaven, Dr. F. St. Mary's Psychiatric Hospital Caslebar County Mayo EIRE	204636/0008:0023 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Csemansky, John G., MD Washington University School of Medicine Department of Psychiatry 4940 Children's Place St. Louis, MO 63110 USA	5077IL/0015:0004 5077IL/0015:0004 5077IL/0031:0003	D-B Comp O-L E D-B Comp	1.171/1, 1.314/1 1.262/1 1.261/333	1.406/1 1.442/274 1.442/273	CANDA CT Report CANDA
Daniel, David G., MD Neuropsychiatric Services of Greater Washington, Inc. 8404-P Seven Corners Place Falls Church, VA 22044 USA	5077IL/0013:0024 5077IL/0013:0024	D-B Comp O-L E	1.117/1, 1.148/1, 1.306/1 1.262/1	1.398/1 1.442/274	CANDA CT Report
Darcourt, Prof. G. Clinique de Psychiatrie et de Psychologie Medicale C.H.U. Hopital Pasteur 30 Avenue de la Voie Romaine BP 69 06002 Nice Cedex FRANCE	5077IL/0005: UK-0003 204636/0008:0005 (5077US/0001) 5077IL/0012:0030 5077IL/0012:0030	O-L pilot D-B Comp D-B Comp O-L E	1.254/1 1.137/1, 1.303/1, 1.225/1, 1.350/1 1.262/1	1.439/272 1.389/1 1.423/1 1.442/274	CANDA CANDA CANDA CT Report
Daubenton, Dr. F. Medical School University of Capetown Ronderbosch SOUTH AFRICA Valkenberg Hospital Private Bag X1 Observatory 7935 SOUTH AFRICA	204636/0007:0038 5077IL/0014:0047 5077IL/0014:0047	D-B Comp D-B Comp O-L E	1.217/1, 1.348/1 1.243/1, 1.354/1 1.262/1	1.415/1 1.431/1 1.442/274	CANDA CANDA CT Report

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	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT FORMS*
Daumer, Dr. J. C.H.S. Charcot Secteur Adulte 2W 56854 Cuadan FRANCE	50771L/0012:0039	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0039	O-L E	1.262/1	1.442/274	CT Report
Davidson, M., MD Psychiatry Service 116A VA Medical Center 130 West Kingsbridge Road Bronx, NY 10468 USA	50771L/0005: US-0004 (APS 0-991-1)	O-L pilot	1.254/1	1.439/272	CANDA
de Beaurepaire, Dr. R. C.H.S. du Bon Sauveur Pavillon Pere Jamet 93 Rue Caponiere 14032 Caen FRANCE	50771L/0012:0044	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0044	O-L E	1.262/1	1.442/274	CT Report
De Bieker, Dr. E. Psychiatrisch Ziekenhuis St. Lucia Ankerstraat 91 9100 Sint Niklaas BELGIUM	50771L/0014:0010	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	50771L/0014:0010 ¹³	O-L E	1.262/1	1.442/274	CT Report
Debuick, Dr. R. Service de Psychiatrie Hopital Brugmann Place A Van Gehuchten 4 1020 Bruxelles BELGIUM	50771L/0014:0066	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	50771L/0014:0066 ¹³	O-L E	1.262/1	1.442/274	CT Report
DeCherney, G. Stephen, MD Medical Research Institute of Delaware 4755 Ogleton-Stanton Road Newark, DE 19718 USA	50771L/0007:0007	Clin Pharm	1.97/1	1.378/328	NA
DeNayer, Dr. A.R. Service de Psychiatrie Hopital Ste-Therese Rue Trieu Kaisin 134 6061 Montignies Sur Sambre BELGIUM	50771L/0014:0067	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	50771L/0014:0067	O-L E	1.262/1	1.442/274	CT Report
DeSilva, Dr. M.S.L. Department of Mental Health Heatherwood Hospital London Road Ascot Berkshire SI5 8AA UNITED KINGDOM	204636/0008:0009 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.384/1	CANDA

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Diamond, Bruce, PhD Psychiatry Service 116A Augusta VA Medical Center One Freedom Way Augusta, GA 30911 USA	5077IL/0006:0008 ³ (APS 0-A31-1/0008)	D-B Comp	1.132/1, 1.301/1	1.384/1	CANDA
Dickson, Ruth, MD Clinical Pharmacology Unit Medical Research Department ZENECA Pharmaceuticals Mereside, Alderley Park Macclesfield, Cheshire SK10 4TG UNITED KINGDOM	5077IL/0013:0023 2	O-L E	1.262/1	1.442/274	CT Report
Didi, Dr. R. C.H.S. La Chartreuse 1 Bd Chanoine Kir 21033 Dijon Cedex FRANCE	5077IL/0012:0004 5077IL/0012:0004	D-B Comp O-L E	1.225/1, 1.350/1 1.262/1	1.423/1 1.442/274	CANDA CT Report
Dierick, Dr. G. Ziekenhuis Reigerlo Reigerlo 10 8730 Beernem BELGIUM	5077IL/0012:0024 5077IL/0012:0024	D-B Comp O-L E	1.225/1, 1.350/1 1.262/1	1.423/1 1.442/274	CANDA CT Report
Dierick, Dr. M. St. Camillus Institute Beukenlaan 20 9051 Sint Denijs-Westrem BELGIUM	5077IL/0005: UK-0018 204636/0007:0009	O-L pilot D-B Comp	1.254/1 1.217/1 1.348/1	1.439/272 1.415/1	CANDA CANDA
Dietzel, Dr. M. Psychiatrische Universitätsklinik Währingergürtel 18-20 A-1090 Wien AUSTRIA	204636/0008:0012 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.384/1	CANDA
Doane, Joseph C. Bessler Clinical Research Unit 900 Osceola Drive West Palm Beach, FL 33409 USA	5077IL/0018:0001	Clin Pharm	1.98/1	1.379/1	NA

NAME/ADDRESS	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Donovan, A. J. G., MA, MB, BChir, DA Clinical Pharmacology Unit ZENECA Pharmaceuticals Mereside, Adderly Park Macclesfield, Cheshire SK10 4TG UNITED KINGDOM	50771L/0025:0001 ²⁵	Clin Pharm	1.96/1	1.378/208	NA
Dott, Sharon G., MD University of Texas Medical Branch Department of Psychiatry and Behavioral Sciences 1014 Texas Avenue Galveston, TX 77555-0428 USA	50771L/0013:0017	D-B Comp	1.117/1, 1.148/1, 1.308/1	1.398/1	CANDA
	50771L/0013:0017	O-L E	1.262/1	1.442/274	CT Report
	50771L/0015:0005	D-B Comp	1.171/1, 1.314/1	1.408/1	CANDA
	50771L/0015:0005 50771L/0031:0004	O-L E D-B Comp	1.262/1 1.261/333	1.442/274 1.442/273	CT Report CANDA
Dries, Dr. P.J.T. Delta Ziekenhuis der Gemeente Rotterdam Albrandswaardsedijk 74 3172 AA Poortugaal NETHERLANDS	50771L/0014:0031	D-B Comp	1.243/1, 1.354/1	1.442/273	CANDA
	50771L/0014:0031	O-L E	1.262/1	1.442/274	CT Report
Dubinsky, Richard M., MD Associate Professor of Neurology University of Kansas Medical Center 3901 Rainbow Boulevard Kansas City, KS 66160-7314 USA	50771L/0024:0001 ⁶	Clin Pharm	1.129/377	1.383/169	NA
	(Part B) 50771L/0024:0001 ⁹	O-L E	1.262/1	1.442/274	CT Report
Duboc, Dr. G.E. C.H.S. de Navarre Rue de Conches 27022 Evereux Cedex FRANCE	50771L/0012:0042	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0042	O-L E	1.262/1	1.442/274	CT Report
Ebert, Dr. D. Psychiatrische Klinik und Poliklinik Schwabachanlage 6 91054 Erlangen GERMANY	50771L/0012:0056	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0056	O-L E	1.262/1	1.442/274	CT Report
Eccleston, Prof. D. Department of Psychiatry Royal Victoria Infirmary Queen Victoria Road Newcastle-upon-Tyne NE1 4LP UNITED KINGDOM	50771L/0005: UK-0006	O-L pilot	1.254/1	1.439/272	CANDA
Eichelman, Burr S., MD, PhD Department of Psychiatry Temple University School of Medicine 3401 Broad Street Philadelphia, PA 19140 USA	5077US/0001:0004 ¹⁰ (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA

NAME/ADDRESS	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Emsley, Prof. R.A. Department of Psychiatry Faculty of Medicine University of Stellenbosch PO Box 19063 Tygerberg 7505 SOUTH AFRICA	204636/0007:0037	D-B Comp	1.217/1, 1.348/1	1.415/1	CANDA
	5077IL/0014:0050	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0050 ¹³	O-L E	1.262/1	1.442/274	CT Report
Ereshefsky, Larry, PharmD University of Texas Health Science Center at San Antonio San Antonio State Hospital Clinical Pharmacy Programs 7703 Floyd Curl Drive San Antonio, TX 78284 USA	5077US/0001:0009 ¹¹ (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0017:0005	Clin Pharm	1.100/1	1.379/231	CANDA
	5077IL/0017:0005	O-L E	1.262/1	1.442/274	CT Report
Eriksson, Dr. L. Psyk Kliniken Lillhagens Sjukhus Box 3005 S 42203 Hisings Backa SWEDEN	5077IL/0014:0065	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0065 ¹³	O-L E	1.262/1	1.442/274	CT Report
Erkwoh, Dr. R. Psychiatrische Klinik der RWTH Pauluelstrasse 30 52057 Aachen GERMANY	5077IL/0012:0016	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
Ermentini, Prof. A. Universita de Brescia Ospedale Civile Piazza Spedali Civile 25123 Brescia ITALY	5077IL/0012:0068	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0068	O-L E	1.262/1	1.442/274	CT Report
Fabre, Louis F., Jr., MD, PhD Research Testing, Inc. 5503 Crawford Street Houston, TX 77004 USA Fabre Research Clinics, Inc. 5503 Crawford Street Houston, TX 77004 USA	5077US/0002:0001	Clin Pharm	1.103/1	1.380/1	NA
	5077IL/0004 (APS 9-396-1)	Clin Pharm	1.83/1, 1.130/1, 1.300/1 1.254/1	1.375/1	NA
	5077IL/0005: US-0001 (APS 0-396-2)	O-L pilot		1.439/272	CANDA
	5077IL/0008:0001	Clin Pharm	1.82/1	1.374/1	NA
	5077IL/0015:0007	D-B Comp	1.171/1, 1.314/1 1.262/1	1.406/1	CANDA
	5077IL/0015:0007 ²⁷	O-L E	1.79/89	1.442/274	CT Report
	5077IL/0016:0001	Clin Pharm	1.104/1	1.372/1	CANDA
5077IL/0020:0001	Clin Pharm	1.90/1	1.380/104	NA	
5077IL/0044:0003	Clin Pharm		1.377/1	NA	
Faltus, Mudr. F. Psychiatricka Klinika Ke Karlovu 11 128 21 Praha 2 CZECH REPUBLIC	204636/0008:0015 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0014:0015	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0015	O-L E	1.262/1	1.442/274	CT Report

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Farmer, Mildred, MD Clinical Studies, Florida 780 94th Avenue North, Suite 102 St. Petersburg, FL 33702 USA	50771L/0048:0011	O-L	1.258/1	1.442/272	CANDA
Faustman, William O., PhD Stanford VA Mental Health Clinical Research Center, Unit 4C2 and 4B2 DVA Medical Center 3801 Miranda Avenue Palo Alto, CA 94304 USA	5077US/0001:0014 ¹² (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Fenton, Prof. G.W. Department of Psychiatry University of Dundee Ninewells Hospital Dundee DD1 9SY UNITED KINGDOM	50771L/0012:0014 50771L/0012:0014	D-B Comp O-L E	1.225/1, 1.350/1 1.262/1	1.423/1 1.442/274	CANDA CT Report
Ferguson, Dr. B.G. Department of Psychiatry Mapperley Hospital Porchester Road Nottingham NG6 6AA UNITED KINGDOM	204636/0007:0004 50771L/0012:0003 50771L/0012:0003	D-B Comp D-B Comp O-L E	1.217/1, 1.348/1 1.225/1, 1.350/1 1.262/1	1.415/1 1.423/1 1.442/274	CANDA CANDA CT Report
Ferguson, James M., MD Pharmacology Research Corporation Suite 350 448 East 6400 South Salt Lake City, UT 84107 USA	50771L/0013:0018 50771L/0013:0018 50771L/0015:0008 50771L/0015:0008 50771L/0031:0021 50771L/0048:0003	D-B Comp O-L E D-B Comp O-L E D-B Comp O-L	1.117/1, 1.148/1, 1.308/1 1.262/1 1.171/1, 1.314/1 1.262/1 1.261/333 1.258/1	1.398/1 1.442/274 1.406/1 1.442/274 1.442/273 1.442/272	CANDA CT Report CANDA CT Report CANDA CANDA
Ferreira, Dr. L.M. Hospital Magalhaes Lemos Servico Povoá Vila do Conda Estrada da Circumvalacao 4100 Porta PORTUGAL	50771L/0012:0082 50771L/0012:0082	D-B Comp O-L E	1.225/1, 1.350/1 1.262/1	1.423/1 1.442/274	CANDA CT Report
Ferrey, Dr. C.H. Emile Roux rue de Docteur Roux 95600 Eaubonne FRANCE	204636/0007:0028	D-B Comp	1.217/1, 1.348/1	1.415/1	CANDA
Fleischhacker, Prof. W.W. Biological Psychiatry Research Unit Department of Psychiatry Innsbruck University Clinic Anichstrasse 35 A-6020 Innsbruck AUSTRIA	204636/0008:0011 (5077US/0001) 50771L/0012:0027	D-B Comp D-B Comp	1.137/1, 1.303/1 1.225/1, 1.350/1	1.389/1 1.423/1	CANDA CANDA

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Franks, S., Dr. Department of Psychiatry Gordon Hospital 126 Vauxhall Road London SW1 UK	204636/0008:0001 ¹⁸ (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Fujii, Dr. Yasuo Yamanashi Prefectural Northern Hospital 3314-13 Kamijomimamiwari Asahi-cho Nirasaki-shi Yamanashi JAPAN	H-15-21:5 H-15-22:32 H-15-23:32	O-L O-L O-L	1.282/377 1.282/402 1.282/435	1.442/275 1.442/276 1.442/277	CANDA CANDA NA
Fukui, Dr. Yoshihisa Sankokai Second Kitayama Hospital 161 Iwakurakamigura-tyo Sakyou-ku Kyoto-shi Kyoto JAPAN	H-15-21:12 H-15-22:38 H-15-23:38	O-L O-L O-L	1.282/377 1.282/402 1.282/435	1.442/275 1.442/276 1.442/277	CANDA CANDA NA
Fukushima, Prof. Yutaka Hirosaki University School of Medicine 53 Honamathi Hirosaki-shi Aomori JAPAN	H-15-22:6 H-15-23 ¹³	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
Gzornitz, William F., Jr., MD, PhD Department of Psychiatry University of Kansas Medical Center 3901 Rainbow Boulevard Kansas City, KS 66160-7314 USA	5077IL/0024:0001 ⁹ (Part B) 5077IL/0024:0001 ⁹	Clin Pharm O-L E	1.129/373 1.262/1	1.383/169 1.442/274	NA CT Report
Gagiano, Prof. C.A. Department of Psychiatry University of Orange Free State PO Box 339 Bloemfontein 9300 SOUTH AFRICA	5077IL/0005: UK-0011 204636/0007:0017 5077IL/0014:0046 5077IL/0014:0046	O-L pilot D-B Comp D-B Comp O-L E	1.254/1 1.217/1, 1.348/1 1.243/1, 1.354/1 1.262/1	1.439/272 1.415/1 1.431/1 1.442/274	CANDA CANDA CANDA CT Report
Gaussares, Dr. C. C.H.S. Charles Perrons 121 Rue de la Bechade 33076 Bordeaux Cedex FRANCE	5077IL/0012:0038 5077IL/0012:0038	D-B Comp O-L E	1.225/1, 1.350/1 1.262/1	1.423/1 1.442/274	CANDA CT Report

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Geretsegger, Dr. C. Landes-Nervenklinik Salzburg Ignaz-Harrer Strasse-79 5020 Salzburg AUSTRIA	5077IL/0012:0028	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0028	O-L E	1.262/1	1.442/274	CT Report
Gerlach, Dr. J. Sankt Hans Hospital 4000 Roskilde DENMARK	5077IL0014:0019	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
Gerner, Robert H., MD 11500 West Olympic Boulevard Suite 635 Los Angeles, CA 90068 USA	5077IL/0015:0008	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0008 ²⁷	O-L E	1.262/1	1.442/274	CT Report
Gewirtz, George, MD Department of Psychiatry Columbia University School of Medicine NY State Psychiatric Institute 722 West 168th Street New York, NY 10032 USA	5077IL/0006:0009	D-B Comp	1.132/1, 1.301/1	1.384/1	CANDA
	(APS 0-A31-1/009) 5077IL/0013:0003 ¹⁴	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0003 ¹⁴	O-L E	1.262/1	1.442/274	CT Report
Gladson, Michael, MD DeKalb Medical Center 2701 North Decatur Road Decatur, GA 30033 USA	5077US/0001:0017	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	(204638/0008) ¹⁵				
Grace, Jeffrey, MD Buffalo Psychiatric Center 400 Forest Avenue Buffalo, NY 14213 USA	5077IL/0013:0014	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0014	O-L E	1.262/1	1.442/274	CT Report
Gross, Lawrence S., MD Los Angeles County USC Medical Center Adult Psychiatric Outpatient Clinic 1937 Hospital Place Los Angeles, CA 90033 USA	5077IL/0015:0009	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0009 ²⁷	O-L E	1.262/1	1.442/274	CT Report
Guimon, Dr. Hospital Cival de Basurto Servicio de Psiquiatria Avenida de Montevideo Bilbao SPAIN	204638/0007:0015	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Gutiérrez, Dr. M. Servicio de Psiquiatria Hospital Santiago C/Olaguibel S/N Vitoria SPAIN	5077IL/0012:0087	D-B Comp	1.225/1	1.423/1	CANDA
	5077IL/0012:0087	O-L E	1.350/1 1.262/1	1.442/274	CT Report
Hallstrom, C., Dr. Department of Psychiatry Charing Cross Hospital London UK	204636/0008:0001 ¹⁸ (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Hamner, Mark B., MD VA Medical Center, 116A Inpatient Psychiatry 5BN 109 Bee Street Charleston, SC 29401-5799 USA	5077IL/0006:0010 (APS 0-A31-A/010)	D-B Comp	1.132/1, 1.301/1	1.384/1	CANDA
	5077IL/0013:0004	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0004	O-L E	1.262/1,	1.442/274	CT Report
	5077IL/0015:0010	D-B Comp	1.171/1 1.314/1	1.406/1	CANDA
	5077IL/0015:0010 ²⁷ 5077IL/0031:0005	O-L E D-B Comp	1.262/1 1.261/333	1.442/274 1.442/273	CT Report CANDA
Hanada, Prof. Masanori Kinki University School of Medicine 377-2 Onohigashi Osakasayama-shi Osaka JAPAN	H-15-22:46	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Hansen, J. Psykatr hospital i Dianalund DE Saliserj 35 Dianalund Z5 DENMARK	5077IL/0014:0022	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
Hart, Prof. G.A. Department of Psychiatry University of Witwaterstrand 7 York Road Parktown 2193 Johannesburg SOUTH AFRICA	204636/0007:0016	D-B Comp	1.217/1, 1.348/1,	1.423/1	CANDA
	5077IL/0014:0045	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0045	O-L E	1.262/1	1.442/274	CT Report
Hasegawa, Dr. Youichi Keiyukai Sankei Hospital 3-29-1 Aoba-cho Higashimurayama-shi Tokyo JAPAN	H-15-22:23	O-L	1.282/402	1.442/276	CANDA
	H-15-23:23	O-L	1.282/435	1.442/277	NA
Hashimoto, Dr. Atsutaka Eiwakai Kaizuka Sanatorium 497 Mori Kaizuka-shi Osaka JAPAN	H-15-22:50	O-L	1.282/402	1.442/276	CANDA
	H-15-23:50	O-L	1.282/435	1.442/277	NA

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Hauge, Dr. L. Psykiatrisk Avdeling Innerred Sykeus 7600 Levanger NORWAY	5077IL/0014:0041	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0041	O-L E	1.262/1	1.442/274	CT Report
Hayano, Dr. Taizo Wakayama Prefecture Goryo Hospital 31 Syo Oaza Kibi-tyo Arita-gun Wakayama JAPAN	H-15-21:18	O-L	1.282/377	1.442/275	CANDA
	H-15-22:56	O-L	1.282/402	1.442/276	CANDA
	H-15-23:56	O-L	1.282/435	1.442/277	NA
Hellebuyck, Dr. H. Psych Centrum Heilig Hart Poperingseweg 16 8900 Ieper BELGIUM	5077IL/0014:0011	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0011	O-L E	1.262/1	1.442/274	CT Report
Hertzman, Marc, MD North Arundel Hospital Dept of Psychiatry 301 Hospital Drive Glen Burnie, MD 21061-5803 USA	5077IL/0013:0011	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0011	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0048:0004	O-L	1.258/1	1.442/272	CANDA
Herz, Marvin I., MD University of Rochester Strong Ties Annex Department of Psychiatry 1650 Elmwood Avenue Rochester, NY 14620 USA Rochester Psychiatric Center 1111 Elmwood Avenue Rochester, NY 14620 USA	5077IL/0013:0005	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0005	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0015:0011	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0011 5077IL/0031:0024	O-L E D-B Comp	1.262/1 1.261/333	1.442/274 1.442/273	CT Report CANDA
Hikichi, Dr. Akiyoshi Social Security Hiroshima Citizen's Hospital 7-33 Moto-mati Naka-ku Hiroshima-shi Hiroshima JAPAN	H-15-22:51	O-L	1.282/402	1.442/275	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Hippius, Prof. H. Psychiatrische Klinik der Universitat Munchen Nubaumstrasse GERMANY	5077IL/0005: UK-0021	O-L pilot	1.254/1	1.439/272	CANDA

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Hirakawa, Dr. Hiroyuki Koseikai Harakawa Hospital 1076 Miyama-cho Hachiohji-shi Tokyo JAPAN	H-15-22:21	O-L	1.282/402	1.442/276	CANDA
	H-15-23:21	O-L	1.282/435	1.442/277	NA
Hirano, Dr. Takashi Aomori Prefecture Central Hospital 33-2 Aza-isono Ohaza-tsukurimithi Aomori-shi Aomori JAPAN	H-15-22:8	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Hirsch, Prof. S.R., BA, MPhil, MD, FRCP, FRCPsych Department of Psychiatry Charing Cross Hospital Fulham Palace Road London W6 8RF UNITED KINGDOM	50771L/0005: UK-0001	O-L pilot	1.254/1	1.439/272	CANDA
	204636/0008:0001 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	50771L/0012:0001	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0001	O-L E	1.282/1	1.442/274	CT Report
Hirschfeld, Robert, MD Department of Psychiatry and Behavioral Sciences University of Texas Medical Branch 1014 Texas Avenue Galveston, TX 77550 USA	50771L/0008:0005 (APS 0-A31-1/0005)	D-B Comp	1.132/1, 1.301/1	1.384/1	CANDA
Holsboer, Prof. F. Max Planck Institute Munchen GERMANY	50771L/0005: UK-0019	O-L pilot	1.254/1	1.439/272	CANDA
Holt, P., MRCP, Dip Pharm Med Dip Pharm Med Leicester Clinical Research Centre 72 Hospital Close Leicester LE 5 4WW UNITED KINGDOM	50771L/0026	D-B bio- equivalence	1.94/1	1.378/1	NA
Igarashi, Dr. Yoshio Zenwakai Chichibu Central Hospital 1404 Ohaza-terao Thithibu-shi Saitama JAPAN	H-15-21:2	O-L	1.282/377	1.442/275	CANDA
	H-15-22:28	O-L	1.282/402	1.442/276	CANDA
	H-15-23:28	O-L	1.282/435	1.442/277	NA
Ikawa, Prof. Genro Nara Medical University 840 Shijyo-tyo Kashihara-shi Nara JAPAN	H-15-22:34	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Ikegami, Dr. Mamoru Sanjyokai Sogo Hospital Higashikori Hospital 1-24-34 Higashikori Hirakat-shi Osaka JAPAN	H-15-21:14	O-L	1.282/377	1.442/275	CANDA
	H-15-22:44	O-L	1.282/402	1.442/276	CANDA
	H-15-23:44	O-L	1.282/435	1.442/277	NA
Invernizzi, Prof. G. Universita Degla Studi di Milano Ospedale Maggiore Policlinico Via F Sforza 35-20122 Milano ITALY	5077IL/0012:0075	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0075	O-L E	1.262/1	1.442/274	CT Report
Ishii, Dr. Toshiki Kora Hospital 107 Kora Hikami-tyo Hikami-gun Hyogo JAPAN	H-15-22:13	O-L	1.282/402	1.442/276	CANDA
	H-15-23:13	O-L	1.282/435	1.442/277	NA
Iwama, Dr. Hisayuki Kiyose Hospital 3-10-5 Takeoka Kiyose-shi Tokyo JAPAN	H-15-22:16	O-L	1.282/402	1.442/276	CANDA
	H-15-23:13	O-L	1.282/435	1.442/277	NA
Iwamura, Dr. Hisashi Geisei Hospital 4268 Washokukou Geisei-mura Aki-gun Kochi JAPAN	H-15-22:64	O-L	1.282/402	1.442/276	CANDA
	H-15-23:64	O-L	1.282/435	1.442/277	NA
Iwao, Dr. Yoshiro Iwaokai Tokyo Kaido Hospital 1-4-5 Suehiro-chu Ohme-shi Tokyo JAPAN	H-15-22:13	O-L	1.282/402	1.442/276	CANDA
	H-15-23:13	O-L	1.282/435	1.442/277	NA
Izquierdo de la Torre, Dr. J. Servicio de Psiquiatria Hospital Clinico de Salamanca Paseo de San Vicente 108 Salamanca SPAIN	5077IL/0012:0088	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0088	O-L E	1.262/1	1.442/274	CT Report

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	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Jacobson, Dr. O: Kas Glostrup NDR Ringven 2600 Glostrup DENMARK	5077IL/0014:0020	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
Janka, Dr. Z. Department of Psychiatry Szentgyorgi Albert Medical University, PF 397 H-6701 Szeged HUNGARY	5077IL/0014:0037	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0037	O-L E	1.262/1	1.442/274	CT Report
Jaskiw, George, MD Director, Geriatric Psychiatry Division of Psychiatry 116A(B), VA-Medical Center 10000 Brecksville Road Brecksville OH 44141 USA	5077IL/0017:0002	Clin Pharm	1.100/1	1.379/231	CANDA
	5077IL/0017:0002	O-L E	1.262/1	1.442/274	CT Report
Javitt, Daniel, MD, PhD Bronx Psychiatric Center Ward 19 - Research 1500 Waters Place Bronx, NY 10461 USA	5077IL/0031:0006	D-B Comp	1.261/333	1.442/273	CANDA
Jolley, A., Dr. Department of Psychiatry St Bernards Wing Ealing hospital Uxbridge Road Southall Middlesex UB1 3EU UK	204636/0008:0001 ¹⁶ (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Jones, Barry, MD Psychopharmacology Research Training Center Hamilton Psychiatric Hospital 100 West 5th Street Hamilton, Ontario L9C 3N6 CANADA	5077IL/0031:0007 ⁵	D-B Comp	1.261/333	1.442/273	CANDA
	5077IL/0015:0027 ²⁶	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0027 ²⁶	O-L E	1.262/1	1.442.274	CT Report
Karson, Craig N., MD VA Medical Center North Little Rock Division 116A/NLR Department of Psychiatry 2200 Fort Roots Drive North Little Rock, AR 72114-1706 USA Arkansas State Hospital 4313 North Markham Street Little Rock, AR 72205 USA	5077US/0001:0012 ¹⁷ (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Kasper, Prof. A. Psychiatrische Universitätsklinik Währinger Gurtel 18-20 Wien AUSTRIA	5077IL/0014:0006	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0006	O-L E	1.262/1	1.442/274	CT Report
Kato, Dr. Akira Meiwakai Biwako Hospital 1-8-5 Sakamotohonmami Otu-shi Shiga JAPAN	H-15-21:13	O-L	1.282/377	1.442/275	CANDA
	H-15-22:36	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Katsura, Dr. Kunio Hoseikai Ozone Hospital 2-6-4 Hounan-tyo Higasi Toyonaka-shi Osaka JAPAN	H-15-22:41	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Keck, Paul E. Jr., MD University of Cincinnati College of Medicine Biological Psychiatry Center 231 Bethesda Avenue, ML 559 Cincinnati, OH 45267-0559 USA	5077US/0001:0015 (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0013:0012	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0012	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0031:0020	D-B Comp	1.261/333	1.442/273	CANDA
Kerwin, Dr. R. Institute of Psychiatry De Crespigny Park Denmark Hill London SE5 8AF UNITED KINGDOM	204636/0007:0001	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA
Keys, Michael A., MD Older Adult Center for Clinical Research University of Cincinnati College of Medicine 231 Bethesda Avenue, ML 559 Cincinnati, OH 45267-0559 USA	5077IL/0017:0003 ¹⁸	Clin Pharm	1.100/1	1.379/231	CANDA
	5077IL/0017:0003 ¹⁸	O-L E	1.262/1	1.442/274	CT Report
Kidoue, Dr. Yoichi Shin Awaji Hospital 43 Kamikamo Sumoto-shi Hyogo JAPAN	H-15-22:13	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442.277	NA

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
King, Dr. D.J. Department of Therapeutics and Pharmacology Queen's University of Belfast 97 Lisburn Road Belfast BT9 7BL UNITED KINGDOM	50771L/0012:0002	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0002	O-L E	1.262/1	1.442/274	CT Report
Kissling, Dr. W. Psychiatrische Klinik der TU Munchen Ismaninger Strasse 22 81675 Munchen GERMANY	50771L/0012:0011	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0011	O-L E	1.262/1	1.442/274	CT Report
Klieser, Dr. E. Psychiatrische Klinik der Universitat Dusseldorf Bergische Landstrasse 2 4000 Dusseldorf 12 GERMANY	204636/0008:0025 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Knesevich, John W., MD 109 Ponemah Road, #9, Unit F Amherst, NH 03031 USA	50771L/0015:0033	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	50771L/0015:0033	O-L E	1.262/1	1.442/274	CT Report
	50771L/0048:0006	O-L	1.258/1	1.442/272	CANDA
Knesevich, Mary Ann, MD Terrell State Hospital, Ward L1 1200 East Brin Terrell, TX 75160 USA St. Paul Medical Center 5959 Harry Hines Boulevard PO Box 1, Suite 924 Dallas, TX 75235 USA	5077US/0001:0010 (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	50771L/0013:0007	D-B Comp	1.117/1, 1.148/1, 1.308/1	1.398/1	CANDA
	50771L/0013:0007	O-L E	1.262/1	1.442/274	CT Report
	50771L/0015:0012	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	50771L/0015:0012	O-L E	1.262/1	1.442/274	CT Report
Kolin, Irving S., MD Psychiatric Unit Sand Lake Hospital 9400 Turkey Lake Road Orlando, FL 32819 USA 1065 West Morse Boulevard Suite 202 Winter Park, FL 32789 USA	5077US/0001:0018 (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Koponen, Dr. H. Moision Hospital 50 520 Mikkeli FINLAND	50771L/0014:0027	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	50771L/0014:0027	O-L E	1.262/1	1.442/274	CT Report

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Koyama, Prof. Tsukasa Hokkaido University School of Medicine Nishi-5 Kita 14-jo Kita-ku Sapporo-shi Hokkaido JAPAN	H-15-22:1	O-L	1.282/402	1.442/276	CANDA
	H-15-23:1	O-L	1.282/435	1.442/277	NA
Krausz, Dr. M. Psychiatrische und Nervenlinik Poliklinik der Universitat Hamburg Martinistrasse 52 20251 Hamburg GERMANY	5077IL/0012:0052	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0052	O-L E	1.262/1	1.442/274	CT Report
Krystal, John, MD West Haven VAMC Psychiatric Services (116 A) West Haven, CT 06516 USA	5077IL/0031:0023	D-B Comp	1.261/333	1.442/273	CANDA
Kuroda, Prof. Shigetoshi Okayama University Medical School 2-5-1 Sikata-tyo Okayama-shi Okayama JAPAN	H-15-22:57	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Kutcher, Dr. S.P. Department of Psychiatry Sunnybrook Health Sciences Center 2075 Bayview Avenue Toronto Ontario M4N 3M5 CANADA	5077IL/0012:0049	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0049	O-L E	1.262/1	1.442/274	CT Report
Labelle, Alain, MD Royal Ottawa Hospital 1145 Carling Avenue Ottawa, Ontario K1Z 7K4 CANADA	5077IL/0015:0027 ²⁸	D-B Comp	1.171/1, 1.314/1	1.408/1	CANDA
	5077IL/0015:0027	O-L E	1.262/1	1.442/274	CT Report
Laddomada, Dr. P. Primario Servizio Psichiatrico Ospedale Sirai 09013 Carbonia CA ITALY	5077IL/0012:0073	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0073	O-L E	1.262/1	1.442/274	CT Report
Lambert, Dr. T. Sir Charles Gairdner Hospital Perth AUSTRALIA	5077IL/0014:0004	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0004	O-L E	1.262/1	1.442/274	CT Report

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			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Langstrom, B. Prof., Director Uppsala University PET Centre 5-78185 Uppsala SWEDEN	5077IL/0029	Clin Pharm	1.116/1, 1.129/1	1.382/146	CANDA
	5077IL/0033	Clin Pharm	1.116/358, 1.129/358	1.383/1	CANDA
Lawson, William, MD, PhD John L. McClellan VAMC Department of Psychiatry 2200 For: Roots Drive North Little Rock, AR 72114 USA	5077IL/0031:0008	D-B Comp	1.261/333	1.442/273	CANDA
Lindenmayer, J.P., MD Nathan Kline Institute Rockland Psychiatric Center 140 Old Orangeburg Road Building 37 Orangeburg, NY 10962 USA	5077US/0001:0013 (204638/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0031:0018	D-B Comp	1.261/333	1.442/273	CANDA
Manhattan Psychiatric Center Psychopharmacology Reseach Unit Dunlop 14A, Ward's Island New York, NY 10035 USA					
Lindqvist, Dr. L. Psyk Kliniken Centrallasarettet 961 85 Boden SWEDEN	5077IL/0014:0059	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0059	O-L E	1.262/1	1.442/274	CT Report
Lindstrom, Prof. L. Psihiatriskaforskning Senneten Uppsala Universitet Centrallasarettet 72189 Vasteras SWEDEN	5077IL/0014:0081 ¹	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0029	Clin Pharm	1.116/1, 1.128/1	1.382/146	CANDA
	5077IL/0029	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0033:0001	Clin Pharm	1.116/358 1.129/358	1.383/1	CANDA
Uppsala Universitet 5 - 751 85 Uppsala SWEDEN					
Lipinski, J.F., Jr., MD Chief, Clinical Research Section McLean Hospital Mailman Research Center 115 Mill Street Belmont, MA 02178 USA	5077IL/0005: US-0003 (APS 0-848-1)	O-L pilot	1.254/1	1.439/272	CANDA

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Lohr, James, MD VA Medical Center Hospital Department of Psychiatry, 116A 3350 La Jolla Village Drive San Diego, CA 92161-2002 USA	5077US/0001:0008 (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0031:0010	D-B Comp	1.261/333	1.442/273	CANDA
	5077IL/0048:0005	O-L	1.258/1	1.442/272	CANDA
Longoni, Dr. R. Unita Operativa Psichiatria Ospedale Civile 20070 Vizzolo Predabissi Milano ITALY	5077IL/0012:0076	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0076	O-L E	1.262/1	1.442/274	CT Report
Lopez-Ibor, Prof. J. Hospital Ramon y Cajal Servicio de Psiquiatria Carretera de Calernar KM9100 Madrid SPAIN	204636/0007:0012	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA
	5077IL/0014:0051	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
Lynch, Dr. J. St. Lukes' Hospital Clonmel County Tipperary EIRE Department of Psychiatry St. Michaels' Hospital Clonmel County Tipperary EIRE	204636/0008:0024 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0012:0006	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0006	O-L E	1.262/1	1.442/274	CT Report
MacEwan, Gordon W., MD St Vincent's Hospital 749 West 33rd Avenue Vancouver, BC V5Z 2K4 CANADA	5077IL/0013:0020	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0020	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0031:0028 ²⁷	D-B Comp	1.261/333	1.442/273	CANDA

NAME/ADDRESS	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
MacFarlane, Dr. D.J. Department of Psychiatry Downshire Hospital Ardglass Road Downpatrick County Down Northern Ireland BT30 6RA UNITED KINGDOM	204636/0007:0024	D-B Comp	1.217/1, 1.348/1	1.415/1	CANDA
	50771L/0012:0008	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0008	O-L E	1.262/1	1.442/274	CT Report
Ards Hospital Newtownards County Down Northern Ireland BT23 4AS UNITED KINGDOM					
Machiyama, Prof. Yukiteru Gunma University School of Medicine 3-39-15 Showa-cho Maebashi-shi Gunma JAPAN	H-15-22:12	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Mahapatra, Dr. S.B. Department of Psychiatry The General Hospital Hartlepool Cleveland TS24 9AH UNITED KINGDOM	204636/0008:0020 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	50771L/0012:0007	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0007	O-L E	1.262/1	1.442/274	CT Report
Manunn, Roderick, PhD San Antonio State Hospital Clinical Research Unit MC-4 6711 South New Braunfels Avenue San Antonio, TX 78223 USA	50771L/0031:0022 ¹⁸	D-B Comp	1.261/333	1.442/273	CANDA
Malanowski, Dr. J. Psychiatric Clinic C.H. 7408 CAZ15 SWITZERLAND	50771L/0012:0048	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
Malinen, Dr. H. Kuopio University Julkula Hospital 70 200 Kuopio FINLAND	50771L/0014:0029	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	50771L/0014:0029	O-L E	1.262/1	1.442/274	CT Report
Malla, Dr. A. Department of Psychiatry Victoria Hospital Corporation 375 South Street London Ontario N6G 4G5 CANADA	50771L/0012:0061	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0061	O-L E	1.262/1	1.442/274	CT Report

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	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Mallya, Gopinath, MD McLean Hospital 115 Mill Street Belmont, MA 02178 USA	5077IL/0015:0036 ²⁷	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0036 ²⁷	O-L E	1.262/1	1.442/274	CT Report
Manchanda, Dr. R. Department of Psychiatry University Hospital 339 Windermere Road London Ontario N6A 5A5 CANADA	5077IL/0012:0060	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0060	O-L E	1.262/1	1.442/274	CT Report
Marbury, C. Thomas, MD Orlando Clinical Research Center 4401 South Orange Avenue, Suite 108 Orlando, FL 32806 USA	5077IL/0019:0001	Clin Pharm	1.99/1	1.379/112	NA
Marie-Cardine, Dr. M. C.H.S. Le Vinatier 95 Boulevard Pinel 69677 Bron Cedex FRANCE	5077IL/0012:0036	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0036	O-L E	1.262/1	1.442/274	CT Report
Martens, Dr. J.M. Sint Lucaskliniek Laar 140 2180 Ekeren BELGIUM	5077IL/0012:0022	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0022	O-L E	1.262/1	1.442/274	CT Report
Martin, Dr. Service de Psychiatrie C.H. Victor Duprey 69 rue de Lieutenant Colonel Prudhon 95107 Argenteuil FRANCE	204836/0007:0029	D-B Comp	1.217/1 1.348/1	1.423/1	CANDA
Matsubara, Dr. Shigenro Tokachi National Medical Hospital 2 Suzuranmotomathi Otofuke-cho Katoh-gun Hokkaido JAPAN	H-15-22:2	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Matsumoto, Dr. Sumitaka Koseikai Mitinoo Hospital 2-1 Nijigaoka-tyo Nagasaki-shi Nagasaki JAPAN	H-15-21:21	O-L	1.282/377	1.442/275	CANDA
	H-15-22:69	O-L	1.282/402	1.442/276	CANDA
	H-15-23:69	O-L	1.282/277	1.442/277	NA

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	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Mauas, Dr. L. Department A Shalvata Mental Health Center Hod-Hasharon ISRAEL	5077IL/0012:0097	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0097	O-L E	1.262/1	1.442/274	CT Report
McEvoy, Joseph, MD John Umstead Hospital 12th Street Butner, NC 27509 USA	5077IL/0006:0001 (APS 0-A31-1/0001)	D-B Comp	1.132/1, 1.301/1	1.384/1	CANDA
	5077IL/0031:0019	D-B Comp	1.261/333	1.442/273	CANDA
McGrath, Dr. J. Wolston Park Hospital Brisbane AUSTRALIA	5077IL/0014:0003	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0003	O-L E	1.262/1	1.442/274	CT Report
McManus, Dennis, MD Southern Illinois University School of Medicine Department of Neurology RC402 800 North Rutledge, Room C411 Springfield, IL 62794 USA	5077IL/0048:0007	O-L	1.258/1	1.442/272	CANDA
Meats, Dr. P.S. Department of Psychiatry Millbrook Kings Mill Hospital Sutton in Ashfield Notts NG17 4NL UNITED KINGDOM	5077IL/0012:0013	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
Mehtonen, Dr. O.P. Pitkaniemen Sairaala PL 2000 33521 Tampere FINLAND	5077IL/0014:0028	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0028	O-L E	1.262/1	1.442/274	CT Report
Meltzer, H., MD Department of Psychiatry Case Western Reserve University School of Medicine 2040 Abington Road Cleveland, OH 44106 USA	5077IL/0005: US-0002 (APS 0-754-1)	O-L pilot	1.254/1	1.439/272	CANDA
Mendlewicz, Prof. J. Hopital Erasme Route de Lennik 808 1070 Bruxelles BELGIUM	5077IL/0005: UK-0010	O-L pilot	1.254/1	1.439/272	CANDA
	204636/0007:0010	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA
Merideth, Charles H., MD Affiliated Research Institute 7676 Hazard Center Drive, #1320 San Diego, CA 92108 USA	5077IL/0013:0026	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0026	O-L E	1.262/1	1.442/274	CT Report

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			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Mesotten, Dr. F. Medisch Centrum St. Jozef Abdijstraat 2 3740 Munsterbilzen BELGIUM	5077IL/0012:0021	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0021	O-L E	1.262/1	1.442/274	CT Report
Michaelis, Prof. R. Krankenhaus Itzehoe Abt. Psychiatrie Robert-Koch Strasse 2 25524 Itzehoe GERMANY	5077IL/0012:0051	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0051	O-L E	1.262/1	1.442/274	CT Report
Miller, Alexander, MD University of Texas Health Science Center at San Antonio San Antonio State Hospital Clinical Pharmacy Programs 7703 Floyd Curl Drive San Antonio, TX 78284-7792 USA	5077US/0001:0009 ¹¹ (204636/0006)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0013:0006 ²²	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0006 ²²	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0015:0013 ⁶	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0013 ⁶	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0031:0022	D-B Comp	1.261/333	1.442/273	CANDA
Miller, Marvin J., MD Larue D. Carter Memorial Hospital Department of Psychiatry 1315 West 10th Street Indianapolis, IN 46202 USA	5077IL/0015:0014	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0014	O-L E	1.262/1	1.442/274	CT Report
Millson, D. S., BSc, MB, BChir, PhD, MD, MFPM Clinical Pharmacology Unit ZENECA Pharmaceuticals Mereside, Macclesfield SK10 4TG UNITED KINGDOM	5077IL/0025:0001 ²⁵	Clin Pharm	1.96/1	1.378/208	NA
Minami, Dr. Yoshitake Toyokai Kijima Hospital 892 Mori Kaizuka-shi Osaka JAPAN	H-15-22:49	O-L	1.282/402	1.442/276	CANDA
	H-15-23:49	O-L	1.282/435	1.442/277	NA
Miyano, Dr. Satoru Kuchan Kousei Hospital Higashi 1-2 Kita 4-jo Kuchan Abuta-gun Hokkaido JAPAN	H-15-22:3	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA

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			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Mori, Dr. Shigeo Darumakai Higashi Kakogawa Hospital 1197-3 Shinzaike Hiraoka-tyo Kakogawa-shi Hyogo JAPAN	H-15-22:51 H-15-23:51	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
Mortimer, Dr. A. St. Lukes Hospital Crosland Moor Huddersfield Yorkshire UNITED KINGDOM	204636/0007:0003	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA
Mukherjee, Sukdeb, MD Creedmoor Psychiatric Center Research Division, Building 74 80-45 Winchester Boulevard Queens Village, NY 11427 USA	50771L/0006:0006 (APS 0-A31-1/006)	D-B Comp	1.132/1, 1.301/1	1.384/1	CANDA
Murakami, Dr. Atsushi Fuyokai Samraku Hospital 76-1 Aza-satomi Yotsuishi Aomori-shi Aomori JAPAN	H-15-22:7 H-15-23:7	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
Murasaki, Prof. Mitsukuni Kitasato University East Hospital 2-1-1 Asamizodai Sagamihara-shi Kanagawa JAPAN	H-15-11/12 H-15-13 H-15-21:8 H-15-22 ¹³ H-15-23 ¹³	Clin Pharm Clin Pharm O-L O-L O-L	1.79/1 1.79/34 1.282/377 1.282/402 1.282/435	1.371/205 1.371/207 1.442/275 1.442/276 1.442/277	NA NA CANDA CANDA NA
Murray, G H., MB, Mch, MA Medical Research Department ICI Pharmaceuticals Mereside, Alderley Park Macclesfield, Cheshire SK 10 4TF UNITED KINGDOM	204636/0001	D-B Comp	1.77/1	1.371/1	NA
Murray, Prof. R. Institute of Psychiatry De Crespigny Park Denmark Hill London SE5 8AF UNITED KINGDOM	50771L/0005: UK-0004	O-L pilot	1.254/1	1.439/272	CANDA
Nagao, Dr. Kihachiro Nagaokai Neyagawa Sanatorium 1-24-34 Neya Neyagawa-shi Osaka JAPAN	H-15-21:19 H-15-22:45 H-15-23:45	O-L O-L O-L	1.282/377 1.282/402 1.282/435	1.442/275 1.442/276 1.442/277	CANDA CANDA NA

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			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Nair, Vasavan N.P., DPM, MD Douglas Hospital Research Centre 6875 La Salle Boulevard Verdun, Quebec H4H 1R3 CANADA	5077IL/0013:0021	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0021 5077IL/0031:0011	O-L E D-B Comp	1.262/1 1.261/333	1.442/274 1.442/273	CT Report CANDA
Nakajima, Dr. Akira Fukushimakai-Jobu Hospital 5-6-1 Kojima Honjo-shi Saitama JAPAN	H-15-22:29	O-L	1.282/402	1.442/276	CANDA
	H-15-23:29	O-L	1.282/435	1.442/277	NA
Nakajima, Prof. Temo Kyoto Prefectural University of Medicine 466 Kajimati Hirokouji-agaru Kawaramatitoori Jyoukyou-ku Kyoto-shi Kyoto JAPAN	H-15-21:11	O-L	1.282/377	1.442/275	CANDA
	H-15-22 ¹³	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Nakane, Prof. Yoshitomi Nagasaki University School of Medicine 1-7-1 Sakamoto Nagasaki-shi Nagasaki JAPAN	H-15-21:13	O-L	1.282/377	1.442/275	CANDA
	H-15-22:68	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Nasrallah, Henry A., MD Department of Psychiatry Ohio State University College of Medicine 473 West 12th Avenue Columbus, OH 43210 USA	5077IL/0008:0012 (APS-0-A31-1/012)	D-B Comp	1.132/1, 1.301/1	1.384/1	CANDA
Nemeroff, Charles, MD Wesley Woods Geriatric Center 1841 Clifton Road Atlanta, GA 30329 USA	5077IL/0048:000820	O-L	1.258/1	1.442/272	CANDA
Newcomer, John W., MD Washington University School of Medicine Department of Psychiatry 4940 Children's Place, Box 8134 St. Louis, MO 63110 USA	5077IL/0013:0013	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0013	O-L E	1.262/1	1.442/274	CT Report

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Nikaido, Dr. Matsumo Takikawa City Hospital 2-2-34 Ohmathi Takikawa-shi Hokkaido JAPAN	H-15-22:4 H-15-23:4	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
Nimeus, Dr. A. Psyk Kliniken Box 638 St Lars-omr 2200 06 Lund SWEDEN	5077IL/0014:0056	D-B Comp	1.243/1 1.354/1	1.431/1	CANDA
Nomura, Prof. Junichi Faculty of Medicine, Mie University 2-174 Edohashi Tu-shi Mie JAPAN	H-15-22:35 H-15-23 ¹³	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
Nordahl, Thomas, MD, PhD University of California Davis Medical Center Department of Psychiatry 4430 V Street Sacramento, CA 95817 USA	5077IL/0015:0015 5077IL/0015:0015	D-B Comp O-L E	1.171/1, 1.314/1 1.262/1	1.406/1 1.442/274	CANDA CT Report
Nugent, Dr. D. Department of Psychiatry Gransha Hospital Clooney Road Londonderry Northern Ireland BT47 1TF UNITED KINGDOM	204636/0007:0021	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA
Nyholm, Dr. R. Tammiharjun Hospital 10 600 Tammisaari FINLAND	5077IL/0014:0026 5077IL/0014:0026	D-B Comp O-L E	1.243/1, 1.354/1 1.262/1	1.431/1 1.442/274	CANDA CT Report
O'Brien, Charles P., MD, PhD VA Medical Center, 116A University and Woodland Avenues Philadelphia, PA 19104 USA	5077US/0001:0003 (204636/0008)	D-B Comp	1.171/1, 1.303/1	1.389/1	CANDA
Ohhara, Dr. Sohichiro Hitachi Nagisakai Ohhara Mental Hospital 1-13-18 Ohmika-cho Hitachi-shi ibaragi JAPAN	H-15-22:11 H-15-23:11	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA

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	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Ohno, Dr. Tsuneyuki Rokusankai Osaka Sayama Hospital 3-216-1 Iwamuro Osakasayama-shi Osaka JAPAN	H-15-22:47	O-L	1.282/402	1.442/276	CANDA
	H-15-23:47	O-L	1.282/435	1.442/277	NA
Ohtaka, Dr. Tadashi Tochigi Prefecture Okamoto Hospital 2162 Aza-shimookamoto Kawachi-gun Tothigi JAPAN	H-15-22:10	O-L	1.282/402	1.442/276	CANDA
	H-15-23:10	O-L	1.282/435	1.442/277	NA
Oka, Dr. Saori Keiseikai Hospital Higashi 20 Kita 27-jo Higashi-ku Sapporo-shi Hokkaido JAPAN	H-15-22:5	O-L	1.282/402	1.442/276	CANDA
	H-15-23:5	O-L	1.282/435	1.442/277	NA
Okamura, Dr. Tadabiko Kowakai Uenoshiba Hospital 4-5-16 Uenoshiba-tyo Sakai-shi Osaka JAPAN	H-15-22:48	O-L	1.282/402	1.442/276	CANDA
	H-15-23:48	O-L	1.282/435	1.442/277	NA
Ostorharics, Dr. H.G. Department of Psychiatry Petz A Hospital Gyor, Vas Vari P U 2 H-9002 HUNGARY	5077IL/0012:0093	D-B Comp	1.255/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0093	O-L E	1.262/1	1.442/274	CT Report
Owen, Richard, MD John L. McClellan VA Medical Center North Little Rock Division 116A/NLR Department of Psychiatry 2200 Fort Roots Drive North Little Rock, AR 72114-1706 USA Arkansas State Hospital 4313 North Markham Street Little Rock, AR 72205 USA	5077US/0001:0012 ¹⁷ (204636/0008)	D-B Comp	1.131/1, 1.303/1	1.389/1	CANDA
	5077IL/0015:0016	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0016	O-L E	1.262/1	1.442/274	CT Report

NAME/ADDRESS	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Oxenkrug, Gregory F., MD, PhD Psychiatry Services, 116A VA Medical Center 830 Chalkstone Avenue Providence, RI 02908 USA	5077IL/0006:0011 (APS 0-A31-1/011)	D-B Comp	1.132/1, 1.301/1	1.384/1	CANDA
	5077IL/0013:0008	D-B Comp	1.117/1, 1.148/1	1.398/1	CANDA
	5077IL/0013:0008	O-L E	1.306/1 1.262/1	1.442/274	CT Report
St. Elizabeth's Medical Center SEMC/Department of Psychiatry 736 Cambridge Street Boston, MA 02135 USA					
Ozsvath, Prof. Dr. K. Department of Psychiatry University Medical School of Pecs RET utea 2 H-7623 Pecs HUNGARY	204636/0008:0018 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0014:0036	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0036	O-L E	1.262/1	1.442/274	CT Report
Pailles, Verdeau, Dr. Hospital de Santa Maria Clinique de la Cite 12 rue do Jardin Beaumetz BP no 191 1104 Carcassonne Cedex France	204636/0007:0030	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA
Paes de Sousa, Dr. M.J. Servicio de Psiquiatria Avenida Prof. Egas Moniz 1600 Lisboa PORTUGAL	5077IL/0012:0081	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0081	O-L E	1.262/1	1.442/274	CT Report
Palha, Prof. A.P. Casa de Saude de Bom Jesus Nogueiro 4719 Braga PORTUGAL	5077IL/0012:0080	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0080	O-L E	1.262/1	1.442/274	CT Report
Palomo, Dr. T. Servicio de Psiquiatria Hospital 12 de Octubre Ctra Andalucia KM 5400 Madrid SPAIN	5077IL/0012:0085	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0085	O-L E	1.262/1	1.442/274	CT Report
Pancheri, Prof. P. Universita di Roma Viale dell'Universita 30-00185 Roma ITALY	5077IL/0012:0072	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0072	O-L E	1.262/1	1.442/274	CT Report

NAME/ADDRESS	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Parashos, Dr. A.- Aristotelian University of Thessaloniki Konstantinoupoleos 36 Stavroupoli 564 29 Thessaloniki GREECE	5077IL/0012:0064	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0064	O-L E	1.262/1	1.442/274	CT Report
Patel, Dr. A.G. Department of Mental Services Fairfield Hospital Stotfold Near Hitchin Hertfordshire SG5 4AA UNITED KINGDOM	204636/0008:0010 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Patis, Prof. M. Hopital Central C.H.U. Clinique Psychiatre 1 Place de L'Hopital BP 426 67091 Strasbourg Cedex FRANCE	204636/0008:0008 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0012:0031	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0031	O-L E	1.262/1	1.442/274	CT Report
Patterson, William M., MD Birmingham Research Group, Inc. 2120 Lynngate Drive Birmingham, AL 35216 USA Hillcrest Hospital 6869 Fifth Avenue South Birmingham, AL 35212 USA	5077US/0001:0016 (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0013:0025 ²¹	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0025 ²¹	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0015:0017	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
5077IL/0015:0017	O-L E	1.262/1	1.442/274	CT Report	
Pavan, Prof. L. Universita di Padova Via Giustiniani 2-30538 Padova ITALY	5077IL/0012:0069	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0069	O-L E	1.262/1	1.442/274	CT Report
Pears, J. S., MB, ChB, MRCP, MD Clinical Pharmacology Unit ZENECA Pharmaceuticals Mereside, Adderly Park Macclesfield, Cheshire SK10 4TG UNITED KINGDOM	5077IL/0025:0001 ²⁵	Clin Pharm	1.96/1	1.378/208	NA
Peters, Prof. U.H. Med Einrichtung der Universitat Kohn Fachabteilung Psychiatrie Josef-Stelzmann Strasse 9 50931 Kohn GERMANY	5077IL/0012:0055	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0055	O-L E	1.262/1	1.442/274	CT Report

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Peuskens, Prof. J. University Psychiatric Centre St. Jozef Kliniek Leuvensesteenweg 517 3070 Kortenberg BELGIUM	5077IL/0005: UK-0009	O-L pilot	1.254/1	1.439/272	CANDA
	204636/0007:0007	D-B Comp	1.217/1, 1.348/1	1.415/1	CANDA
	5077IL/0014:0008	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0008	O-L E	1.262/1	1.442/274	CT Report
Pfefferbaum, Adolf, MD Stanford VA Mental Health Clinical Research Center, Unit 4C2 and 4B2 DVA Medical Center 3801 Miranda Avenue Palo Alto, CA 94304 USA	5077US/0001:0014 ¹² (204636/0008)	D-B Comp	1.137/1 1.303/1	1.389/1	CANDA
Pitts, Wesley M., MD VA Medical Center 1500 East Woodrow Wilson Avenue Jackson, MS 39216-5199 USA University of Mississippi Medical Center 2500 North State Street Jackson, MS 39216 USA	5077US/0001:0006 ⁸ (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0013:0002	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0002	O-L E	1.262/1	1.442/274	CT Report
Poirier, Dr. C.H. Sainte Anne 1 rue Cabanis 75674 Paris Cedex 14 FRANCE	204636/0007:0025	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA
Pomara, Nunzio, MD Nathan Kline Institute 140 Old Orangeburg Road Orangeburg, NY 10962 USA	5077IL/0048:0009	O-L	1.258/1	1.442/272	CANDA
Potkin, Steven G., MD, PhD UCI Medical Center Department of Psychiatry and Human Behavior 101 City Drive South, Route 88 Orange, CA 92668 USA	5077IL/0015:0018	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0018	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0024:0002 (Part A)	Clin Pharm	1.123/1	1.383/2	NA
	5077IL/0024:0002 ¹³	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0027:0001	Clin Pharm	1.111/1, 1.126/1	1.381/230	NA
	5077IL/0031:0012	D-B Comp	1.261/333	1.442/273	CANDA
	5077IL/0035:0001	Clin Pharm	1.85/1	1.376/1	CANDA
	5077IL/0035:0001	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0044:0002	Clin Pharm	1.90/1	1.377/1	NA
5077IL/0046:0001	Clin Pharm	1.114/1	1.382/1	NA	
5077IL/0046:0001	O-L E	1.262/1	1.442/274	CT Report	

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	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Pretorius, Dr. H.W. Department of Psychiatry University of Pretoria PO Box 667 Pretoria 0001 SOUTH AFRICA	5077IL/0014:0049	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0049	O-L E	1.262/1	1.442/274	CT Report
Priest, Prof. R. Department of Psychiatry St. Mary's Hospital Medical School Praed Street London W2 1NY UNITED KINGDOM	5077IL/0012:0020	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0020	O-L E	1.262/1	1.442/274	CT Report
Puystjens, Dr. M. OLV Kliniek Koning Albertlaan 8 8200 Brugge BELGIUM	5077IL/0014:0009	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0009	O-L E	1.262/1	1.442/274	CT Report
Ramirez, Luis F., MD Cleveland VA Medical Center Department of Psychiatry, Room 116A 10000 Brecksville Road Brecksville, OH 44141 USA	5077IL/0015:0037	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0037 ²⁷	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0031:0013	D-B Comp	1.261/333	1.442/273	CANDA
Rapisarda, Prof. V. Universita di Catania Ospedale Policlin Viale Andrea Doria 6 95125 Catania ITALY	5077IL/0012:0078	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0078	O-L E	1.262/1	1.442/274	CT Report
Ravizza, Prof. L. Universita di Torino Ospedale Molinette Via Cherasco 15-10126 Torino ITALY	5077IL/0012:0066	D-B Comp	1.225/1, 1.350/1,	1.423/1	CANDA
	5077IL/0012:0066	O-L E	1.262/1	1.442/274	CT Report
Reiman, Eric, MD Good Samaritan Regional Medical Center 925 East McDowell Road, 4th Floor Phoenix, AZ 85006 USA	5077IL/0031:0026	D-B Comp	1.261/333	1.442/273	CANDA

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			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Remington, Gary J., MD, PhD Clarke Institute of Psychiatry 250 College Street Toronto, Ontario M5T 1R8 CANADA	5077IL/0015:0028	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0028	O-L E	1.262/1	1.442/274	CT Report
Riccio, M., Dr. Consultant Psychiatrist St Mary Abbots Hospital Marloes Road Kensington London W8 5LQ UK	204636/0008:0001 ¹⁸ (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Riesenberg, Robert A., MD DeKalb Medical Center 2701 North Decatur Road Decatur, GA 30033 USA Biobehavioral Research Center 825 DeKalb Industrial Way Decatur, GA 30033 USA	5077US/0001:0017 (204636/0008) ¹⁵	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0015:0019	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0019	O-L E	1.262/1	1.442/274	CT Report
Rinaldi, Prof. F. Universita di Napoli Via Pansini 5 80131 Napoli ITALY	5077IL/0012:0079	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0079	O-L E	1.262/1	1.442/274	CT Report
Robotti, Dr. C.A. Il Servizio di Psichiatria Ospedale Maggiore di Borgotrento Piazzale Stefani 1-37126 Verona ITALY	5077IL/0012:0070	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0070	O-L E	1.262/1	1.442/274	CT Report
Roche-Rabreau, Dr. Hopital de Lagny 31 Avenue de General Leclerc 77405 Lagny Cedex FRANCE	204636/0007:0039	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA
Roland, Dr. A. Psykiatrisk Acedling Sentraljokehuset 1 Moere OG Romsdal 6026 Alesund NORWAY	5077IL/0014:0038	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0038	O-L E	1.262/1	1.442/274	CT Report
Ropert, Dr. Pavillion H. Michaud C.H.S. Sainte Anne 1 rue Cabanis 75674 Paris Cedex 14 FRANCE	204636/0007:0036	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA

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			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Rosenthal, Murray H., DO Behavioral Medicine Resources 9449 Balboa Avenue, Suite 205 San Diego, CA 92123 USA	5077IL/0015:0020	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0020	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0048:0010	O-L	1.258/1	1.442/272	CANDA
Rotrosen, John, MD Department of Veterans Affairs New York VA Medical Center 423 East 23rd Street New York, NY 10010 USA	5077US/0001:0011 (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0013:0015	D-B Comp	1.117/1, 1.148/1, 1.308/1	1.398/1	CANDA
	5077IL/0013:0015	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0015:0021	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0021	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0031:0014	D-B Comp	1.281/333	1.442/273	CANDA
Rudolf, Prof. G.A. Klinik und Poliklinik Fur Psychiatrie der Wilhelms Universitat Muenster Albert Schweizer Strasse 11 48149 Muenster GERMANY	5077IL/0012:0057	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0057	O-L E	1.262/1	1.442/274	CT Report
Rushton, A., MB, ChB, MRCP, DMS Medical Research Department ICI Pharmaceuticals Mereside, Alderley Park Macclesfield, Cheshire SK10 4TF UNITED KINGDOM	5077IL/0025:0001 ²⁵ 204636/0001	Clin Pharm Clin Pharm	1.96/1 1.77/1	1.378/208 1.371/1	NA NA
Ruther, Prof. E. Psychiatrische Klinik der Gottingen Universitat Von Siebold Strasse 5 37075 Gottingen GERMANY	5077IL/0012:0053	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0053	O-L E	1.262/1	1.442/274	CT Report
Ruyer, Dr. F. C.H.S. d'Evereux 62 Rue des Conches 27022 Evereux Cedex FRANCE	5077IL/0012:0034	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0034	O-L E	1.262/1	1.442/274	CT Report
Ryan, William, MD University Hospital Jefferson Towers, North Wing University of Alabama at Birmingham School of Medicine 819 South 19th Street Birmingham, AL 35233 USA VAB Clinical Research 2nd Floor 920 18th St. South Birmingham, AL 95233 USA	5077IL/0006:0003 ²² (APS-A31-1/003)	D-B Comp	1.132/1, 1.301/1	1.384/1	CANDA

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	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Saarijarvi, Dr. S. Psykiatrian Klinikka Kunnallissairaalan tie 20 Rak. 9 20 700 Turku FINLAND	50771L/0014:0025	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	50771L/0014:0025	O-L E	1.262/1	1.442/274	CT Report
Saito, Dr. Masaharu Inogashira Hospital 4-14-1 Kamirenjaku Mitaka-shi Tokyo JAPAN	H-15-21:3	O-L	1.282/377	1.442/275	CANDA
	H-15-22:18	O-L	1.282/402	1.442/276	CANDA
	H-15-23:18	O-L	1.282/435	1.442/277	NA
Saitoh, Prof. Masami Kansai Medical University 1 Fumizono-tyo Moriguti-shi Osaka JAPAN	H-15-22:43	O-L	1.282/402	1.442/276	CANDA
	H-15-23:43	O-L	1.282/435	1.442/277	NA
Sakai, Prof. Toshiaki Osaka Medical College 2-7 Daigaku-tyo Takatuki-shi Osaka JAPAN	H-15-22:39	O-L	1.282/402	1.442/276	CANDA
	H-15-23:39	O-L	1.282/435	1.442/277	NA
Sakamura, Dr. Yu National Psychiatric Institute of Shimolusa 578 Hennda-cho Midori-ku Chiba-shi Chiba JAPAN	H-15-22:25	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Salorio, Dr. B. Servicio de Psiquiatria Hospital General Intendente Jorge Palacios I Murcia SPAIN	50771L/0014:0055	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
Salzman, Carl, MD Psychopharmacology Research Corp. 74 Fenwood Road Boston, MA 02115 USA	50771L/0048:0012	O-L	1.258/1	1.442/272	CANDA

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	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Sasaki, Dr. Toshiki Ishigoka Hospital 915 Hamano-cho Chuo-ku Chiba-shi Chiba JAPAN	H-15-22:24 H-15-23:24	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
Sasaki, Dr. Yunoshin Keiaikai Fukuma Hospital 2310 Fukuma-tyo Munakata-gun Fukuoka JAPAN	H-15-22:13 H-15-23:13	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
Satlin, Andrew, MD Director of Geriatrics McLean Hospital 115 Mill Street Belmont, MA 02178 USA	5077IL/0017:0004	Clin Pharm	1.100/1	1.379/231	CANDA
Satori, Dr. Joji Fukukokai Soba Hospital 3-3-1 Ichiba Funabashi-shi Chiba JAPAN	H-15-22:26 H-15-23:13	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
Saxena, Bishan, PhD Psychopharmacology Research Training Center Hamilton Psychiatric Hospital 100 West 5th Street Hamilton, Ontario L9C 3N6 CANADA	5077IL/0015:0029 5077IL/0015:0029 5077IL/0031:0007 ⁶	D-B Comp O-L E D-B Comp	1.171/1, 1.314/1 1.262/1 1.261/333	1.406/1 1.442/274 1.442/273	CANDA CT Report CANDA
Schaerf, Frederick, MD Medical Studies, Florida 12645 New Brittany Boulevard Building 15 Fort Myers, FL 33907 USA	5077IL/0048:0017	O-L	1.258/1	1.442/272	CANDA
Schneider, Lon, MD 2011 Zonal Avenue Hoffman Building, Room 101 Los Angeles, CA 90033 USA	5077IL/0048:0013	O-L	1.258/1	1.442/272	CANDA

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Schroeder, Nitra, PhD Western Psychiatric Institute and Clinic 3811 O'Hara Street Pittsburgh, PA 15213 USA Special Studies Center South 2, Ward 4B 1601 Mayview Road Bridgeville, PA 15107 USA	5077IL/0031:0009 ³¹	D-B Comp	1.261/333	1.442/273	CANDA
Schroeder, Dr. Y. Psychiatrische Universitaetklinik Voss Strasse 9 69115 Heidelberg GERMANY	5077IL/0012:0025 5077IL/0012:0025	D-B Comp O-L E	1.225/1, 1.350/1 1.262/1	1.423/1 1.442/274	CANDA CT Report
Schweitzer, Prof. I. Academic Unit Nemps PO Box 101 Bundoora, Victoria 3083 AUSTRALIA	5077IL/0014:0002 5077IL/0014:0002	D-B Comp O-L E	1.243/1, 1.354/1 1.262/1	1.431/1 1.442/274	CANDA CT Report
Seifertova, Mudr. D. Psychocentrum Praha Ustavani 91 CS-181 03 Praha 8-Bohnice CZECH REPUBLIC	204636/0008:0013 (5077US/0001) 5077IL/0014:0014 5077IL/0014:0014	D-B Comp D-B Comp O-L E	1.137/1, 1.303/1 1.243/1, 1.354/1 1.262/1	1.389/1 1.431/1 1.442/274	CANDA CANDA CT Report
Sensky, T., Dr. Department of Psychiatry West Middlesex Hospital Isleworth Middlesex TW7 6AF UK	204636/0008:0001 ¹⁸ (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Seva, Dr. A. Servicio de Psiquiatria Hospital Clinico Avenida San Juan Bosco 15 50009 Zaragoz SPAIN	5077IL/0014:0052	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
Sharif, Zafar A., MD Creedmoor Psychiatric Center 80-45 Winchester Boulevard Building 40, 11th Floor, SRU Queens Village, NY 11427 USA	5077IL/0013:0003 ¹⁴ 5077IL/0013:0003 ¹⁴ 5077IL/0031:0017	D-B Comp O-L E D-B Comp	1.117/1, 1.148/1, 1.306/1 1.262/1 1.261/333	1.398/1 1.442/274 1.442/273	CANDA CT Report CANDA

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Shaw, Dr. S.H. Department of Psychiatry Stanley Royd Hospital Aberford Road Wakefield West Yorkshire WF1 4DQ UNITED KINGDOM	204636/0008:0019 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0012:0012	D-B Comp	1.225/1 1.350/1	1.423/1	CANDA
	5077IL/0012:0012	O-L E	1.262/1	1.442/274	CT Report
Sneht, G. Michael, MD Birmingham Research Group, Inc 2120 Lynngate Drive Birmingham, AL 35216 USA	5077IL/0013:0025 ²¹	D-B Comp	1.117/1, 1.148/1	1.398/1	CANDA
	5077IL/0013:0025 ²¹	O-L E	1.262/1	1.442/274	CT Report
Srinikal, Dr. Noritoshi Narimasu Kousei Hospital 1-19-1 Misono Itabashi-ku Tokyo JAPAN	H-15-22:17	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Shriqui, Christian L., MD, MSc Hospital Robert-Giffard 2601 Chemin de la Canardiere Beauport, Quebec G1J 2G3 CANADA	5077IL/0013:0022	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0022	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0031:0027	D-B Comp	1.261/333	1.442/273	CANDA
Siddiqui, Dr. V.A. Princess Royal Hospital Lewes Road Haywards Heath West Sussex, RH16 4EX UNITED KINGDOM	5077IL/0012:0010 ⁷	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
Silver, Dr. H. Mazra Psychiatric Hospital Akko ISRAEL	5077IL/0012:0098	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0098	O-L E	1.262/1	1.442.274	CT Report
Silverstone, Dr. P. Department of Psychiatry University of Alberta Hospital 8440-112 Street Edmonton Alberta T6G 2B7 CANADA	5077IL/0012:0063	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0063	O-L E	1.262/1	1.442/274	CT Report
Simpson, George M., MD Medical College of Pennsylvania (EPPI) Department of Clinical Psychopharmacy 3200 Henry Avenue Philadelphia, PA 19129 USA	5077IL/0015:0032	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0032	O-L E	1.262/1	1.442/274	CT Report

NAME/ADDRESS	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Sirota, Dr. P. Department 6A Abarbanel Mental Health Center Bat-Yam ISRAEL	5077IL/0012:0083	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0083	O-L E	1.262/1	1.442/274	CT Report
Small, Gary, MD UCLA Neuropsychiatric Institute 760 Westwood Plaza, 37-432 Los Angeles, CA 90033 USA	5077IL/0048:0014 ²⁷	O-L	1.258/1	1.442/272	CANDA
Small, Joyce, MD Department of Psychiatry Larue D. Carter Memorial Hospital 1315 West 10th Street Indianapolis, IN 46202 USA	5077US/0001:0001 (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0013:0009	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0009	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0031:0015	D-B Comp	1.261/333	1.442/273	CANDA
Smeraldi, Prof. E. DSNP Ospedale S Raffaele Via Prinetti 29-20127 Milano ITALY	5077IL/0012:0065	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0065	O-L E	1.262/1	1.442/274	CT Report
Smith, Nathan, MD University Hospital Jefferson Towers, North Wing University of Alabama at Birmingham School of Medicine 619 South 19th Street Birmingham, AL 35233 USA University of Alabama Clinical Research 2nd Floor 920 18th Street South Birmingham, AL 35233 USA	5077IL/0006:0003 ²² (APS 0-031-1/003)	D-B Comp	1.132/1, 1.301/1	1.384/1	CANDA
	5077IL/0006:003 ²² (APS 0-031-1/003)	O-L E	1.262/1	1.442/274	CT Report
Soni, Dr. S. Department of Psychiatry Hope Hospital Eccles Old Road Salford, Manchester M6 8HD UNITED KINGDOM	204636/0007:0002	D-B Comp	1.217/1, 1.348/1	1.415/1	CANDA
Sorita, Dr. Katsuhiko Hamazono Hospital 2968 Wada-cho Kohfu-shi Yamanashi JAPAN	H-15-21:9	O-L	1.282/377	1.442/275	CANDA
	H-15-22:34	O-L	1.282/402	1.442/276	CANDA
	H-15-23:34	O-L	1.282/435	1.442/277	NA

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Steinbook, Richard, MD University of Miami Jackson Memorial Medical Center Department of Psychiatry, D-29 Mental Health Institute, Room 112B 1611 NW 12th Avenue Miami, FL 33136 USA	5077US/0001:0004 ¹⁰ (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
	5077IL/0013:0010	D-B Comp	1.117/1, 1.148/1, 1.306/1	1.398/1	CANDA
	5077IL/0013:0010	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0015:0022 ⁴	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0022 ⁴	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0031:0016	D-B Comp	1.261/333	1.442/273	CANDA
Stip, Dr. E. Centre de Recherche Fernard-Seguin 7331 rue Hochelaga Montreal Quebec H1N 3V2 CANADA	5077IL/0012:0059	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0059	O-L E	1.262/1	1.442/274	CT Report
Stoessl, Dr. J. Psychiatrisches Krankenhaus der Stadt Wien VII Psychiatrische Abteilung Baumgartner Hohe 1 1145 Wien AUSTRIA	5077IL/0012:0029	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0029	O-L E	1.262/1	1.442/274	CT Report
Strakowski, Stephen M., MD Biological Psychiatry Program University of Cincinnati College of Medicine 231 Bethesda Avenue, Suite ML-0559 Cincinnati, OH 45267-0559 USA	5077IL/0015:0023	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
	5077IL/0015:0023	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0047:0001	Clin Pharm	1.106/1	1.380/254	CANDA
	5077IL/0047:0001	O-L E	1.262/1	1.442/274	CT Report
Sumiyoshi, Dr. Akitsugu Tokiwa Hospital 3439-2 Tokiwa-cho Machida-shi Tokyo JAPAN	H-15-21:7	O-L	1.282/377	1.442/275	CANDA
Sundararajan, Dr. K. Department of Psychiatry Halifax General Hospital Halifax West Yorkshire UNITED KINGDOM	204636/0008:0022 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Suzuki, Dr. Toru Seikoika Komakino Hospital 274 Uratakao-chu Hachiohji-shi Tokyo JAPAN	H-15-21:4	O-L	1.282/377	1.442/275	CANDA
	H-15-22:19	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Svetska, Prof. Mudr. J. Psychiatricka Klinika Lekarska Fakulta Masarykovy University 657 15 Brno Bohnice CZECH REPUBLIC	5077IL/0014:0016	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	5077IL/0014:0016	O-L E	1.262/1	1.442/274	CT Report
Szulecka, Dr. T.K. Department of Psychiatry Bassetlaw District General Hospital Blythe Road Worksop Nottingham UNITED KINGDOM	204636/0008:0021 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Doncaster Royal Infirmary Armthorpe Road Doncaster DN2 5LT UNITED KINGDOM	5077IL/0012:0005	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0005	O-L E	1.262/1	1.442/274	CT Report
Takahashi, Dr. Katsuro National Nagasaki Central Hospital 2-1001-1 Hisahara Omura-shi Nagasaki JAPAN	H-15-21:22	O-L	1.282/377	1.442/275	CANDA
	H-15-22:70	O-L	1.282/402	1.442/276	CANDA
	H-15-23:70	O-L	1.282/435	1.442/277	NA
Takahashi, Dr. Yukihiko Seifukai Ibaraki Hospital 1-4-1 Soujji Ibaraki-shi Osaka JAPAN	H-15-21:15	O-L	1.282/377	1.442/275	CANDA
	H-15-22 ¹³	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Takamatsu, Dr. Isao Jikokai Wakahisa Hospital 5-3-1 Wakahisa Minami-ku Fukuoka-shi Fukuoka JAPAN	H-15-22:66	O-L	1.282/402	1.442/276	CANDA
	H-15-23:66	O-L	1.282/435	1.442/277	NA
Tamminga, Carol A., MD Maryland Psychiatric Research Center Inpatient Unit, PO Box 21247 White Building Spring Grove Hospital Grounds Baltimore, MD 21228 USA	5077IL/0006:0007 (APS 0-A31-1/0007)	D-B Comp	1.132/1 1.301/1	1.384/1	CANDA

NAME/ADDRESS	LOCATION IN APPLICATION				
	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Tandon, Rajiv, MD University of Michigan Medical Center Department of Psychiatry, Unit 8D 1500 East Medical Center Drive Ann Arbor, MI 48109-0116 USA	5077IL/0013:0016	D-B Comp	1.117/1, 1.148/1 1.306/1	1.398/1	CANDA
	5077IL/0013:0016	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0015:0025	D-B Comp	1.171/1, 1.314/1	1.406/1	CANDA
Targum, Steven D., MD Crozer-Chester Medical Center One Medical Center Boulevard Old Main Upland, PA 19013 USA Delaware Valley Clinical Studies 1015 Chestnut Street Suite 1303 Philadelphia, PA 19107 USA	5077IL/0015:0024	O-L E	1.262/1	1.442/274	CT Report
	5077IL/0048:0018	O-L	1.258/1	1.442/272	CANDA
Tariot, Pierre, MD Monroe Community Hospital Psychiatric Unit 435 East Henrietta Road Rochester, NY 14620 USA	5077IL/0048:0015	O-L	1.258/1	1.442/272	CANDA
Tashiro, Prof. Nobutada Faculty of Medicine Kyushu University 3-1-1 Maidashi Higashi-ku Fukuoka-shi Fukuoka JAPAN	H-15-22:65	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	US
Thienhaus, Ole J., MD Older Adult Center for Clinical Research University of Cincinnati College of Medicine 231 Bethesda Avenue, ML 559 Cincinnati, OH 45267-0559 USA	5077IL/0017:0003 ¹⁸	Clin Pharm	1.100/1	1.379/231	NA
	5077IL/0017:0003 ¹⁸	O-L E	1.262/1	1.442/274	CT Report
Thomas, Dr. C.S. Department of Psychiatry University Hospital of South Manchester Manchester M20 UNITED KINGDOM	5077IL/0012:0019	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0019	O-L E	1.262/1	1.442/274	CT Report
Tignol, Prof. J. C.H.S. Charles Perrens 121 Rue de la Bechade 33076 Bordeaux Cedex FRANCE	5077IL/0012:0035	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	5077IL/0012:0035	O-L E	1.262/1	1.442/274	CT Report

NAME/ADDRESS	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Toone, Dr. B.K. Department of Psychiatry King's College Hospital Denmark Hill London SE5 9RS UNITED KINGDOM	50771L/0005: UK-0002	O-L pilot	1.254/1	1.439/272	CANDA
Toru, Prof. Michio Tokyo Medical and Dental University School of Medicine 1-5-45 Yushima Bunkyo-ku Tokyo JAPAN	H-15-22 ¹³ H-15-23 ¹³	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
True, Janet E., MD San Antonio State Hospital Clinical Research Unit-MC-4 6711 South New Braunfels Avenue San Antonio, TX 78223 USA	50771L/0013:0006 ²³ 50771L/0013:0006 ²³ 50771L/0031:0022 ¹⁹	D-B Comp O-L E D-B Comp	1.117/1, 1.148/1, 1.308/1 1.262/1 1.261/333	1.398/1 1.442/274 1.442/273	CANDA CT Report CANDA
Tsutsumi, Dr. Shigetoshi Osaka Psychiatry Research Institute Shinabuyama Hospital 4-10-1 Usahara Takatuki-shi Osaka JAPAN	H-15-21:16 H-15-22:40 H-15-23:40	O-L O-L O-L	1.282/377 1.282/402 1.282/435	1.442/275 1.442/276 1.442/277	CANDA CANDA NA
Tsutsumi, Dr. Yurichiro Ongata Hospital 105 Nishitarakata-cho Hachiohji-hi Tokyo JAPAN	H-15-22 ¹³ H-15-23 ¹³	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
Tune, Larry, MD Wesley Woods Geriatric Center 1841 Clifton Road Atlanta, GA 30329 USA	50771L/0048:0006 ²³	O-L	1.258/1	1.244/272	CANDA
Tuninger, Dr. E. Psykiatriska Ingang S2 Allmänna Sjukhuset S 214 01 Malmö SWEDEN	50771L/0014:0068 50771L/0014:0068	D-B Comp O-L E	1.243/1, 1.354/1 1.262/1	1.431/1 1.442/274	CANDA CT Report

NAME/ADDRESS	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Uchida, Dr. Shigeru Mannari Hospital 1-6-5 Tanimannari Okayama-shi Okayama JAPAN	H-15-22:58 H-15-23:58	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
Udelman, Harold D., MD Biomedical Stress Research Foundation, Ltd. 45 East Osborn Road Phoenix, AZ 85012 USA	5077IL/0015:0035 5077IL/0015:0035	D-B Comp O-L E	1.171/1, 1.314/1 1.262/1	1.406/1 1.442/274	CANDA CT Report
Uebelhack, Prof. R. Humboldt-Universitat Berlin Abteilung Psychiatrie Schumannstrasse 20-21 10115 Berlin GERMANY	5077IL/0012:0054 5077IL/0012:0054	D-B Comp O-L E	1.225/1, 1.350/1 1.262/1	1.423/1 1.442/274	CANDA CT Report
Oshijima, Prof. Sadanobu The Jikei University School of Medicine 3-19-18 Nishishinbashi Minato-ku Tokyo JAPAN	H-15-22:14 H-15-23 ¹³	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
Vaadal, Dr. J.M. Psykiatrisk Avdeling Fylkessjukehuset 1 Molde 6450 Hjelset NORWAY	5077IL/0014:0044 5077IL/0014:0044	D-B Comp O-L E	1.243/1, 1.354/1 1.262/1	1.431/1 1.442/274	CANDA CT Report
Vallejo, Dr. J. Hospital Principes de Espana Servicio de Psiquiatria Feixa Llarga S/N 08709 Hospitalet de Llobregat Barcelona SPAIN	204636/0007:0013 5077IL/0014:0053	D-B Comp D-B Comp	1.217/1, 1.348/1 1.243/1 1.354/1	1.415/1 1.431/1	CANDA CANDA
Van Moffaert, Prof. M. UZ Gent De Pintelaan 185 9000 Gent BELGIUM	5077IL/0014:0012 5077IL/0014:0012	D-B Comp O-L E	1.243/1, 1.354/1 1.262/1	1.431/1 1.442/274	CANDA CT Report
Varenius, Dr. A. S:TA Maria Sjukhus Psykos S 251 88 Helsingborg SWEDEN	5077IL/0014:0069 5077IL/0014:0069	D-B Comp O-L E	1.243/1, 1.354/1 1.262/1	1.431/1 1.442/274	CANDA CT Report

NAME/ADDRESS	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Vaz Serra, Prof. A. Hospitais de Universidade de Coimbra, Servicio de Psiquiatria Alameda Dr Armando Goncalves 3000 Coimbra PORTUGAL	50771L/0012:0089	D-B Comp	1.225/1, 1.350/1	1.423/1	CANDA
	50771L/0012:0089	O-L E	1.262/1	1.442/274	CT Report
	50771L/0014:0030	D-B Comp	1.243/1, 1.354/1	1.431/1	CANDA
	50771L/0014:0030	O-L E	1.262/1	1.442/274	CT Report
veiligan, Dawn, PhD San Antonio State Hospital Clinical Research Unit-MC-4 6711 South New Braunfels San Antonio, TX 78223 USA	50771L/0013:0006 ²³	D-B Comp	1.117/1, 1.148/1, 1.308/1	1.398/1	CANDA
	50771L/0013:0006 ²³	O-L E	1.262/1	1.442/274	CT Report
Verdeau-Pailles, Dr. Clinique de la Cite 12 rue du Jardin Beaumetz BP no 191 11004 Carcassonne Cedex FRANCE	204636/0007:0030	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA
Vereecken, Dr. St. Jan Hospital of Psychiatry 9900 Eeklo BELGIUM	204636/0007:0034	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA
Vidon, Dr. Centre C.H.S. Esquirol 57 rue du Mazrechal Leclerc 94229 Saint Maurice Cedex FRANCE	204636/0007:0033	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA
Vinar, Dr. O. Institute of Psychiatric Research Ustavni 91 CS-18103 Praha 8-Bohnice CZECH REPUBLIC	204636/0008:0014 (5077US/0001)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Vinogradov, Sophia, MD San Francisco VA Medical Center 4150 Clement Street, 118C San Francisco, CA 94121 USA	50771L/0015:0026	D-B Comp	1.117/1, 1.314/1	1.406/1	CANDA
	50771L/0015:0026	O-L E	1.262/1	1.442/274	CT Report
	50771L/0048:0016	O-L	1.258/1	1.442/272	CANDA

NAME/ADDRESS	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Wagner, Richard L., MD Institute of Mental Health Louis Pasteur Building, 4th floor Howard Avenue Cranston, RI 02920 USA	5077US/0001:0005 (204636/0008)	D-B Comp	1.137/1, 1.303/1	1.389/1	CANDA
Waki, Dr. Akira Ryofukai Takahashi Hospital 2200 Abe Otiai-tyo Takahashi-shi Okayama JAPAN	H-15-22 ¹³ H-15-23 ¹³	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
Watanabe, Prof. Shosuke Kawasaki Medical School 577 Matubara Kurashiki-shi Okayama JAPAN	H-15-22:59 H-15-23:59	O-L O-L	1.282/402 1.282/435	1.442/276 1.442/277	CANDA NA
Weizman, Prof. A. Psychiatric Department Geha Psychiatric Hospital PO Box 102 Petach Tikva 49100 ISRAEL	5077IL/0012:0047 5077IL/0012:0047	D-B Comp O-L E	1.225/1, 1.350/1 1.282/1	1.423/1 1.442/274	CANDA CT Report
Wiesel, Prof. F.A. Insitutionen for Psykiatei Ulleraker Akademisruta Sjuthuset 73017 Uppsala SWEDEN	5077IL/0033:0002 ²⁴	Clin Pharm	1.116/358 1.129/358	1.383/1	CANDA
Williams, A. J., MB, ChB, BSc, PhD, MFFM, FRCP Clinical Pharmacology Unit Medical Research Department ZENECA Pharmaceuticals Mereside, Alderley Park Macclesfield, Cheshire SK10 4TG UNITED KINGDOM	5077IL/0025:0001 ²⁵	Clin Pharm	1.98/1	1.378/208	NA
Williams, Richard, MD Calgary General Hospital Department of Psychiatry 841 Centre Avenue East Calgary, Alberta T2E 0A1 CANADA	5077IL/0013:0023 5077IL/0013:0023	D-B Comp O-L E	1.117/1, 1.148/1 1.308/1 1.282/1	1.398/1 1.442/274	CANDA CT Report
Wilmotte, Dr. Hopital Van Gogh Charleroi BELGIUM	204636/0007:0008	D-B Comp	1.217/1 1.348/1	1.415/1	CANDA

NAME/ADDRESS	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Wvstedt, Dr. B.L. Psyk Kliniken Danderyds Sjukhus 182 88 Danderyd SWEDEN	5077IL/0014:0062	D-B Comp	1.243/1	1.431/1	CANDA
	5077IL/0014:0062 ¹³	O-L E	1.354/1 1.262/1	1.442/274	CT Report
Yagi, Prof. Gohei School of Medicine, Keio University 35 Shinanomachi Shinjuku-ku Tokyo JAPAN	H-15-22:13	O-L	1.282/402	1.442/276	CANDA
	H-15-23:13	O-L	1.282/435	1.442/277	NA
Yamauchi, Prof. Toshiro Saitama Medical School 38 Ohaza-morohongo Moroyama-cho Iruma-gun Saitama JAPAN	H-15-21:1	O-L	1.282/377	1.442/275	CANDA
	H-15-22:27	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Yamawaki, Prof. Shigeto Hiroshima University School of Medicine 1-2-3 Kasumi Minami-ku Hiroshima-shi Hiroshima JAPAN	H-15-22 ¹³	O-L	1.282/402	1.442/276	CANDA
	H-15-23:61	O-L	1.282.435	1.442/277	CANDA NA
Yamazumi, Dr. Shun Yamazumi Hospital 1-6-10 Misaku Kohfu-shi Yamanashi JAPAN	H-15-21:8	O-L	1.282/377	1.442/275	CANDA
	H-15-22:33	O-L	1.282/402	1.442/276	NA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	
Yano, Dr. Tetsuo Yoshida Hospital 3666 Yoshida Yoshida-tyo Takada-gun Hiroshima JAPAN	H-15-22:15	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Yates, R. A., MA, MB, ChB, PhD, MRCP, MFPM Medical Research Department ICI Pharmaceuticals Mereside, Alderley Park Macclesfield, Cheshire SK10 4TF UNITED KINGDOM	204636/0002:0001	D-B Comp	1.77/164	1.371/36	NA
	204636/0003:0001	D-B Comp	1.78/1	1.371/92	CANDA
	5077IL/0025:0001 ²⁵	Clin Pharm	1.96/1	1.378/208	NA

NAME/ADDRESS	TRIAL NUMBER/ CENTER	TYPE OF TRIAL	LOCATION IN APPLICATION		
			TRIAL REPORT vol/pg	CRF TABULATION vol/pg	CASE REPORT F- ORMS*
Yoshimasu, Prof. Fumio Wakayama Prefectural Medical University 17 ban-tyo Wakayama-shi Wakayama JAPAN	H-15-21:17	O-L	1.282/377	1.442/275	CANDA
	H-15-22 ¹³	O-L	1.282/402	1.442/276	CANDA
	H-15-23 ¹³	O-L	1.282/435	1.442/277	NA
Yoshimoto, Dr. Wataru Shinwakai Hatano Hospital 131 Sanya Hatano-shi Kanagawa JAPAN	H-15-21:10	O-L	1.282/377	1.442/275	CANDA
	H-15-22:31	O-L	1.282/402	1.442/276	CANDA
	H-15-23:31	O-L	1.282/435	1.442/277	NA
Yoshiura, Dr. Kazunari Nagasaki Prefecture Ohmura Hospital 1575-2 Nishibe-tyo Omura-shi Nagasaki JAPAN	H-15-22:71	O-L	1.282/402	1.442/276	CANDA
	H-15-23:71	O-L	1.282/435	1.442/277	NA

*Request for waiver of paper case report form requirement was granted July 25, 1995 (FDA Serial No. 95-127).

CANDA = CRFs on CANDA

NA = No CRFs on CANDA

**Type of trial:

D-B Comp = Double-Blind Comparison

O-L = Open-Label

Clin Pharm = Clinical Pharmacology

O-L E = Open-Label Extension

***Trial number/center:

If more than one number exists for a trial, the primary number is listed first followed by the alternate number in parentheses.

ed drug for trial 50771L/0014, but he is not included in the

- ¹ Prof. L. Lindstrom is included in this list because he received trial report because he did not enroll subjects in this trial.
- ² Nina Schooler and Robert Baker were coinvestigators on this trial.
- ³ Bruce Diamond and Richard Borison were coinvestigators on this trial.
- ⁴ Richard Steinbook and Ramon Boza were coinvestigators on this trial.
- ⁵ Barry Jones, Erhard Busse, and Bishan Saxena were coinvestigators on this trial.
- ⁶ Alexander Miller and John Chiles were coinvestigators on this trial.
- ⁷ Dr. V.A. Siddiqui was the subject of a fraud investigation and, therefore, his results were not included in the report for Trial 50771L/0012.
- ⁸ Wesley Pitts and Brian Crabtree were coinvestigators on this trial.
- ⁹ Richard Dubinsky and William Gabrielli were coinvestigators on this trial.
- ¹⁰ Dr. Eichelman did not conduct the trial although drug was sent to his site, and Center 4 was reassigned to Dr. Steinbook.
- ¹¹ Alexander Miller, Larry Ereshefsky, and Cheryl Anderson were coinvestigators on this trial.
- ¹² Adolf Pfefferbaum and William Faustman were coinvestigators on this trial.
- ¹³ This investigator received a drug shipment but had enrolled no subjects as of the primary data cutoff date (1 June 1995). For Japanese sites, center numbers were not assigned until a subject was enrolled.
- ¹⁴ This site was taken over by Dr. Z. A. Sharif upon Dr. Gewirtz's death.
- ¹⁵ Robert Riesenbergl and Michael Gladson were coinvestigators on this trial.
- ¹⁶ Dr. T.R.E. Barnes, Dr. T. Sensky, Dr. M. Riccio, Dr. S. Franks, Dr. A. Jolley, and Dr. C. Hallstrom were coinvestigators on this trial.
- ¹⁷ Richard Owen and Craig Karson were coinvestigators on this trial.
- ¹⁸ Michael A. Keys, MD began the trial, but it was completed by Ole J. Thienhaus, MD.
- ¹⁹ Janet True and Roderick Mahurin were coinvestigators on this trial.
- ²⁰ Larry Tune and Charles Nemeroff were coinvestigators on this trial.
- ²¹ Michael Shehi and William Patterson were coinvestigators on this trial.
- ²² Nathan Smith and William Ryan were coinvestigators on this trial.
- ²³ Janet True and Dawn Velligan were coinvestigators on this trial. True and Velligan were replaced by Alexander Miller on 30-Jun-95.
- ²⁴ Prof. F.A. Wiesel was inadvertently not included in the ongoing trial report for Trial 50771L/0033. He did contribute two subjects to the trial before the data cut-off date of 1 June 1995.
- ²⁵ Dr. A.J. Williams, Dr. D.S. Millson, Dr. J.S. Pears, Dr. A. Rushton, and Dr. R.A. Yates were coinvestigators on this trial.
- ²⁶ Barry Jones and Alan LaBelle were coinvestigators on this trial.
- ²⁷ This investigator received a drug shipment but did not participate in the open-label extension trial; no subjects enrolled.
- ²⁸ Ruth Dickson replaced Richard Williams as the principal investigator at this center before the secondary data cutoff date (1 March 1996).

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA 20-639

Sponsor: Zeneca Pharmaceuticals

Clock Date: July 29, 1996

Drug Name

Generic Name: Quetiapine fumarate

Trade Name: Seroquel

Drug Characterization

Pharmacologic Category: Serotonin and Dopamine Antagonist

**Proposed Indication: Management of the Manifestations of Psychotic
Disorders**

NDA Classification: 1S

Dosage Forms: Oral tablets; 25, 100, and 200 mg

Reviewer Information

Clinical Reviewer: Andrew D. Mosholder, M.D.

Review Completion Date: June 13, 1997

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1.0 Material Utilized in Review

1.1 Materials from NDA/IND

This NDA was submitted partly in hard copy and partly in electronic format. Case report forms were available only in electronic format, while certain study reports were available only in hard copy. Additionally, electronic datasets were provided for a variety of demographic, safety and efficacy parameters, both for individual studies and for selected pools of studies. Specific analyses or searches performed using these data sets are noted in this review.

The following documents were among those most frequently consulted, often in electronic format using the sponsor's CANDAs, in preparing this review:

Integrated summary of efficacy
Integrated summary of safety
Study reports for trials 0006, 0008, 0012, 0013, and 0015
Four month safety update report 11/27/96
Literature summary (volume 283, hard copy only)
Report on thyroid data (4/14/97)

Information on Zeneca's commercial INDs for quetiapine

The following case report forms were examined: all deaths, and patients 0001/0014/1406, 0012/0091/9143, 0012/0019/1903, and 0012OLE/0002/0203.

1.2 Related Reviews, Consults, etc.

Consults have been received from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products, regarding the risk of cataracts with quetiapine treatment; from the Division of Gastrointestinal and Coagulation Drug Products, regarding white blood cell abnormalities with quetiapine treatment; and from the Division of Metabolic and Endocrine Drug Products, regarding the risk of hypothyroidism with quetiapine exposure.

1.3 Other Resources

Grateful acknowledgement is made to Drs Roberta Glass and Greg Burkhart, of the FDA's Division of Neuropharmacologic Drug Products, for their assistance with aspects of this review.

2.0 Background

2.1 Indication

There are currently over a dozen marketed antipsychotic compounds in the U.S. By convention, the efficacy of these drugs has been shown primarily in acutely psychotic schizophrenic patients, on the basis that drugs shown to be effective in such patients also are effective in other forms of psychosis such as mania, psychotic depression and the like. Only one marketed neuroleptic, clozapine, has been shown to be effective in patients refractory to other neuroleptic compounds. Use of clozapine is restricted to such refractory patients, however, because of the risk of agranulocytosis associated with clozapine therapy.

Traditional neuroleptics such as phenothiazines all block dopamine D2 receptors, and are associated with troublesome extrapyramidal side effects (EPS) and tardive dyskinesia. Recent interest in the field of antipsychotic drug development has focused on the so called serotonin-dopamine antagonists, sometimes designated SDA drugs. There is optimism in the field, as yet incompletely validated by clinical trial data, that such compounds will have certain desirable properties including lack of extrapyramidal side effects, improved activity against the so called "negative" symptoms of schizophrenia, and freedom from tardive dyskinesia. The first such compound to be marketed domestically was risperidone; more recently, olanzepine was approved. Other serotonin dopamine antagonist drugs in late stages of development are ziprasidone and sertindole, the latter having significant cardiovascular toxicity due to prolongation of the QT interval. Quetiapine (Seroquel) is also a serotonin-dopamine antagonist, developed with the same rationale outlined above.

2.2 Important Information from Related INDs and NDAs and from Pharmacologically Related Agents

There is no specific information from related INDs or NDAs that is particularly relevant for the clinical review of quetiapine. There have been no INDs for the compound other than Zeneca's.

2.3 Administrative History

The original commercial IND for quetiapine.

Early in the development program, there was concern about preclinical findings of ophthalmological toxicity, and consequently ophthalmologic assessments were included in the safety monitoring of subjects. In October 1991, FDA permitted women of child bearing potential in clinical trials.

In February 1993, the sponsor and FDA held an End of Phase II meeting. In the latter part of 1993, Zeneca sought and obtained agency recommendations for a quetiapine study in treatment resistant schizophrenic patients (study 0031). In June 1995, Zeneca met with staff from FDA Biopharmaceutics to discuss aspects of the development program, and in the same month the sponsor and FDA held a pre-NDA meeting. At the pre-NDA meeting, it was agreed that efficacy analyses would include the Schedule for Assessment of Negative Symptoms (SANS) total score, and the standard 4 item psychosis cluster from the Brief Psychiatric Rating Scale (BPRS). Agreement was also reached on which clinical trials would be included in the primary integrated safety database.

FDA granted Zeneca a waiver for submission of hard copies of case report forms. In July 1995, Zeneca met with the agency to discuss the CANDAs format.

2.4 Proposed Directions for Use

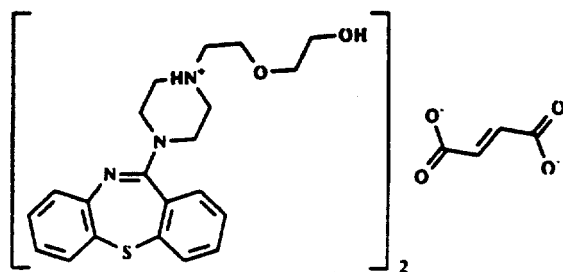
The draft labeling recommends the following: The starting dose should be 25 mg BID, with titration to a target dose of 300 mg/day over 4 days. The drug may be given on a TID schedule if desired. The maximum recommended dose is 800 mg/day; doses designated as effective in the clinical trials are as 150-750 mg/day, with maximal effect seen at 300 mg/day. The elderly, and patients with hepatic disease, should have slower titration and lower dosages. Some general guidance for re-initiation of treatment and for switching from other neuroleptics to Seroquel is provided.

2.5 Foreign Marketing

Quetiapine is not marketed anywhere in the world.

3.0 Chemistry

The chemical structure of quetiapine fumarate is shown below.



Quetiapine fumarate

I am not aware of any unresolved chemistry, manufacturing and controls issues that would preclude marketing approval.

4.0 Animal Pharmacology

Quetiapine is a serotonin and dopamine antagonist. The sponsor's table below displays the activity of the compound for various receptors, in terms of IC₅₀.

TABLE: Quetiapine affinity for multiple neurotransmitter receptors

	5-HT _{1A}	5-HT ₂	D ₁	D ₂	H ₁	α ₁	α ₂	Muscarinic	Benzodiazepine
IC ₅₀ (nM)	717	148	1268	329	30	94	271	> 10000	> 5000

From this, it will be seen that the compound has activity at a number of receptors, particularly 5HT₂, D₂, H₁, and alpha-1.

Quetiapine is active in a number of animal models deemed predictive of antipsychotic effects, but shows less effects than standard neuroleptics in tests predictive for the development of EPS, such as catalepsy induction. The drug is proconvulsant in mice. In dogs, quetiapine did not appreciably alter the electrocardiogram. Prolactin elevations were observed, especially in rats.

Chronic toxicity studies were notable for development of cataracts in dogs, an effect the sponsor attributed to impairment of cholesterol biosynthesis. A number of thyroid gland abnormalities; e.g., thyroid follicular cell hypertrophy, were observed in various species. Hepatocyte hypertrophy was found in three species, attributed to hepatic enzyme induction. Carcinogenicity testing produced thyroid follicular cell adenomas in mice and mammary adenocarcinomas in rats.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program (Primary Source Data)

5.1.1 Study Type and Design/Patient Enumeration

Appendix table 5.1.1.1 displays the numbers of patients in the Integrated Primary Database for the quetiapine development program, as of the 3/1/96 cutoff date for the first NDA safety update. A total of 2,635 subjects and patients were exposed to quetiapine in the Phase I, II, or III clinical trials which Zeneca considered suitable for the primary integrated safety database. Of these, 343 subjects received quetiapine in Phase I trials and 2,387 patients received quetiapine in Phase II-III clinical trials; 95 of the latter group had prior exposure to quetiapine in Phase I studies.

Zeneca imposed a cutoff date of 6/1/95 for all safety data in the original NDA Integrated Primary Database, with a later cutoff date for serious adverse events. The 4 month safety update, however, provided comprehensive adverse event data through 3/1/96. Thus the primary integrated database available for this safety review included all adverse event data through 3/1/96.

Out of a total of 44 clinical trials, 5 phase I trials and 4 phase II-III trials were excluded from the primary integrated database, as will be described below.

Out of the 2387 quetiapine treated subjects in the Phase II-III primary database, 1711 were exposed in controlled clinical trials.

5.1.2 Demographics

Appendix Table 5.1.2.1 displays the demographic profile for the Phase I studies. As seen, Phase I studies involved primarily younger white males.

Appendix Table 5.1.2.2 shows the demographic characteristics for the Phase II-III integrated primary database. The subjects in the Phase II and III clinical trials were mostly white, predominantly male, and mostly younger than 40 years.

5.1.3 Extent of Exposure (dose/duration)

Appendix table 5.1.3.1 shows the duration of exposure by mean dose during Phase I studies, in terms of numbers of subjects exposed for a specific dose and duration. As expected for clinical pharmacology studies, the exposure was primarily at lower doses and at shorter durations.

Appendix table 5.1.3.2 displays the same matrix for the Phase II-III primary integrated database.

Of particular interest in the above table is the number of patients who received quetiapine in the recommended dose range. The draft labeling suggests a target dose of 300 mg/day, and it will be seen that there were a total of 1245 patients who received doses in the range of 150-450 mg. With respect to duration of exposure, over 500 patients received the drug for approximately 6 months (i.e., 184 days) or more.

Appendix table 5.1.3.3 displays the overall exposure for quetiapine and control treatments in the primary integrated database, in terms of patient years (defined as the total days on therapy divided by 365).

5.2 Secondary Source Data

5.2.1 Non-IND and Excluded Studies

Zeneca chose to exclude certain clinical trials from the primary database, as discussed at the Pre-NDA meeting with the agency. Narrative summaries for deaths, withdrawals and serious adverse events were nonetheless provided for these studies in the Integrated Summary of Safety. The following is a list of the excluded studies. All the Japanese studies (those below whose study number starts with the letter H), phase I studies involving doses too small to be clinically relevant, and ongoing studies were excluded.

PHASE I STUDIES

SINGLE-DOSE TRIALS

204636/0001 (N = 9)

204636/0002 (N = 9)

H-15-11/12 (N = 17)

MULTIPLE-DOSE TRIALS

204636/0003 (N = 7)

H-15-13 (N = 8)

PHASE II-III STUDIES

5077IL/0031 (N = 18); STILL BLINDED/ONGOING

H-15-21 (N = 54) (OPEN LABEL)

H-15-22 (N = 165) (OPEN LABEL)

H-15-23 (N = 75) (OPEN LABEL)

Including these trials listed below, a total of 2,714 patients were known to have received quetiapine in the all completed and ongoing clinical studies, as of the 6/1/95 primary cutoff date for the ISS. The corresponding number of patients having received quetiapine in any integrated or nonintegrated trial as of the 3/1/96 cutoff date for the safety update was not specified.

Quetiapine is not marketed anywhere in the world. Zeneca has sponsored all clinical trials with quetiapine to date, and Zeneca has chosen not to make quetiapine available for compassionate use, so that the clinical data reported by Zeneca should represent all clinical experience with quetiapine.

5.2.2 Postmarketing Experience

Quetiapine is not marketed in any country.

5.2.3 Literature

As stated, all clinical trials with quetiapine have been conducted with Zeneca's sponsorship, and quetiapine has not been available for compassionate use; thus, no reports in the literature should involve additional clinical data beyond what Zeneca has already presented.

The sponsor submitted a preclinical and clinical bibliography, with reprints of the clinical references included (NDA volume 283). The cutoff date for the literature search was 4/16/96. The clinical bibliography comprised roughly 60 publications from U.S. and foreign journals. My own review of these publications did not disclose any new findings of significance. Additionally, Dr. Lisa Arvanitis, Zeneca's project physician for quetiapine, reported that she had reviewed the

literature and that it contained no unsuspected adverse safety findings.

5.3 Comment on Adequacy of Clinical Experience

In my judgement, the sponsor's clinical development program provides an adequate clinical data base for review of the NDA. The total numbers of patients exposed and the duration of exposure are comparable to the databases for antipsychotic compounds approved recently. Efficacy data is provided by more than one adequate and well controlled clinical study. No pediatric clinical data was provided; there was open label safety data provided for geriatric patients in study 0048.

5.4 Comment on Data Quality and Completeness

On balance, the data supplied in the NDA was judged to be of a sufficient quality to permit review. One exception to this involved individual patient data for some patients having serious adverse events; in a number of cases, the sponsor failed to provide sufficient clinical details or follow up information. Such cases will be described in the review of systems. Another data quality issue involved allegations of misconduct on the part of one of the clinical investigators, Dr. Borison. Zeneca performed a reanalysis of their clinical data minus the data from Dr. Borison's site, and found that data from his site had little influence on the overall efficacy findings or the adverse event incidences. These re-analyses will be described.

6.0 Human Pharmacokinetic Considerations

Please refer to the biopharmaceutics review for complete details. Note that because healthy volunteers did not tolerate more than very low doses of the compound, much of the pharmacokinetic studies were performed with volunteer schizophrenic patients.

Quetiapine is rapidly and extensively absorbed after oral administration, and displays linear pharmacokinetics. The compound is primarily cleared by hepatic metabolism and is a cytochrome P450 3A4 substrate, with excretion mainly in urine and very little drug excreted unchanged. The major metabolites found in plasma are not very pharmacologically active. Terminal half life was determined to be roughly 7 hours; volume of distribution was 681 L. The sponsor states that plasma concentrations corresponding to clinical doses range from 200-3000 ng/ml. There is considerable interindividual variability in pharmacokinetics.

Quetiapine C_{max} and AUC increased 25% and 15%, respectively, with feeding. The drug is moderately protein bound in plasma (83%).

With respect to special populations, mean clearance decreased up to 50% in elderly patients. Gender and race do not appear to have an effect on quetiapine pharmacokinetics. Severe renal insufficiency and hepatic disease were both observed to reduce clearance roughly 25%. Specific studies in special population subgroups are noted below.

Study 0016 was a pharmacokinetic study in schizophrenic men and women, treated with quetiapine titrated to 250 mg/d for 15 days. The sponsor reported no significant differences in pharmacokinetics or adverse events between males and females in this study; however, the sample was small (13 men and 15 women).

Study 0018 was a pharmacokinetic study in 8 nonpsychotic patients with cirrhosis and normal controls, administered a single 25 mg dose. Two of the eight patients had much lower clearance of quetiapine than observed in the normal control subjects. There were no unusual adverse

events among the patients with liver disease; however, this sample is very small.

Study 0019 was a pharmacokinetic study of a single 25 mg quetiapine dose administered to 8 renal patients and 8 normal controls. Zeneca concluded that there were no unique adverse events reported in renal patients given a single dose of quetiapine. Again, the sample size was very small.

Regarding drug interactions, the sponsor has concluded that quetiapine or its metabolites will not produce clinically meaningful inhibition of cytochromes P450 1A2, 2C9, 2C19, 2D6, or 3A4. Concomitant phenytoin resulted in a substantial increase in quetiapine clearance, possibly through induction of CYP 3A4; concomitant cimetidine had little effect on quetiapine pharmacokinetics. Coadministration of quetiapine did not effect the pharmacokinetics of antipyrine, lithium or lorazepam.

After the NDA was submitted, the sponsor submitted a brief report on the results of two other in vivo interaction studies, 0063 involving coadministration of fluoxetine and imipramine (n=26), and 0064 involving coadministration of haloperidol, risperidone and thioridazine (n=36). The sponsor concluded that quetiapine pharmacokinetics was not significantly affected by fluoxetine, imipramine, haloperidol or risperidone, while thioridazine appeared to induce metabolism of quetiapine with a corresponding reduction in AUC of 41%. The only adverse event of note during these studies was a conduction delay attributed to imipramine in one patient. These data have not yet been reviewed by the Biopharmaceutics reviewer.

7.0 Efficacy

7.1 Background

Zeneca has completed a total of 8 controlled clinical trials of quetiapine in the treatment of psychosis (please refer to the appendix table of all studies). Of these 8 studies, 4 can be considered capable by design of providing meaningful data on the efficacy of quetiapine in acutely ill schizophrenic patients. These studies provide the focus for the review of efficacy data; all were randomized, double blind, parallel group, multicenter 6 week trials, and all involved schizophrenic patients:

Study 0006, n= 109 total, comparing quetiapine 75-750 mg/day and placebo

Study 0008, n=266 total, comparing quetiapine \leq 250 mg/day, quetiapine \leq 750 mg/day, and placebo

Study 0013, n=361 total, a fixed dose study comparing quetiapine 75, 150, 300 mg, 600 mg, and 750 mg daily with haloperidol 12 mg/day and placebo

Study 0012, n=618 total, comparing quetiapine 225 mg BID, 150 mg TID, and 25 mg BID

Note that for studies 0006, 0008, and 0013, all quetiapine dosing was TID, while in study 0012 one group received TID dosing and the other two groups BID dosing.

The remaining 4 controlled trials will not be considered in detail in this review. One was a small pilot trial, Study 0004, which produced statistically significant results favoring quetiapine over placebo in the amelioration of psychotic symptoms, despite having an enrollment of only 12 subjects.

Study 0015, a relapse prevention trial one year in length, lacked a placebo control group and failed to show a difference in relapse rates among treatment groups. Thus it did not generate meaningful efficacy data.

The remaining 2 controlled trials (0007 and 0014) were 6 week long multicenter active controlled trials that failed to show a difference between quetiapine and the comparator drug (chlorpromazine in study 0007 and haloperidol in study 0014). In fact, the CGI results favored haloperidol over quetiapine in study 0014 (but there was no difference between treatments on the PANSS).

7.2 Review of individual studies

7.2.1 Study 0006

Investigator(s)/Location

The investigators and sites for this study are listed in Appendix table 7.2.1.1. This was a 12 site, U.S. study.

Study Plan

Objective(s)/Rationale

The objective of this study was to evaluate the safety and efficacy of quetiapine compared to placebo, in the treatment of hospitalized patients with acute exacerbations of chronic or subchronic schizophrenia.

Population

Patients were males and females incapable of becoming pregnant, aged 18-60 years. (The original protocol was amended to permit women of child bearing potential who were using contraception). Patients were required to be hospitalized and have a DSM III-R diagnosis of subchronic or chronic schizophrenia with acute exacerbation. Patients were required to be in general good physical health, with hypertension, substance abuse, other DSM Axis I disorders, mental retardation, epilepsy, suicidality, and allergies as reasons for exclusion. In addition, patients were required to have a minimum score of 45 on the Brief Psychiatric Rating Scale (BPRS), a score of at least 4 on the Clinical Global Impression (CGI) of severity, and a score of at least 4 on the core psychosis items of the BPRS (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content).

Design

Patients were to have discontinued all psychotropic medications at the beginning of the study, and were then to be treated with single blind placebo for at least 2 days. Patients who met the entry criteria at the end of the single blind placebo period were randomized to receive either quetiapine or placebo. Dosing was to start at 25 mg tid for the first one or two days. Beyond this, the protocol was not very specific regarding titration but did allow the investigator to increase the dose by 1 or 2 25 or 50 mg tablets up to 3 times per day. Dose increases up to 500 mg daily, and temporarily above 500 mg (to a maximum of 750 mg daily) for no more than 14 days, were permissible. Concomitant chloral hydrate, benzotropine, and diphenhydramine were allowable. A subsequent amendment to the protocol permitted use of pm lorazepam.

Scheduled screening assessments consisted of history and physical examinations, ophthalmologic (slit lamp) examinations, vital signs, ECGs, clinical laboratories, and thyroid function tests. Weekly assessments included BPRS, CGI, Schedule for Negative Symptoms (SANS), Simpson rating scale for EPS, and Abnormal Involuntary Movement Scale (AIMS). Safety monitoring included vital signs, clinical laboratories, ECGs, and thyroid function tests. Treatment was for 6 weeks, and a protocol amendment specified that patients were to remain hospitalized the entire time.

Analysis Plan

The primary outcome measure was defined a priori as the Brief Psychiatric Rating Scale (BPRS) total score, measured at endpoint (i.e., the last visit for which there is data). Analysis of covariance with baseline value, treatment and center, was designated in the protocol as the analytic method.

Study Conduct/Outcome

Patient Disposition

A total of 146 patients entered the screening phase of the trial, and of these, 109 completed the screening phase and were randomized. Of the 37 patients not randomized, the majority did not meet safety entry criteria, as shown in the table below, adapted from the sponsor's study report.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TABLE Screen failures - Trial 0006

Reasons for screen failure	n (%)
Intercurrent medical event	3
Refused to continue/lost to follow-up	1
Subject withdrew consent	4
Other	29
Clinically significant lab	6
Abnormal ophthalmologic exam	14
Hypertensive/hypertensive med	1
Clinically significant abnormal ECG	4
Alcohol/drug dependence	1
All criteria met	8
Total	37 (100)

The following table, reproduced from the sponsor's study report, displays the disposition of the patients randomized in the study. It will be seen that there were more discontinuations for treatment failure in the placebo group than the quetiapine group.

Study 0006: Numbers of patients and reasons for withdrawal

	Quetiapine (n = 54)	Placebo (n = 55)
Treatment failure	16	27
Protocol violation	1	0
Adverse clinical or laboratory experience	2	2
Withdrawal of consent	5	3
Other	2	1
Total number of patients withdrawn	26	33

Appendix table 7.1.2.3 presents the numbers of patients completing each week of the study, by treatment group. There were proportionately more patients in the placebo group dropping out during the later weeks of the study. At week 4, less than 70% of patients remained in either treatment group.

Demographics/Group Comparability

Appendix table 7.2.1.2 displays the demographic characteristics for subjects in this trial. The patients were primarily white males; the quetiapine and placebo groups were comparable with respect to demographic composition.

With respect to baseline comparability, there was not a statistically significant difference between groups for the total BPRS scores (quetiapine mean 55.8 versus placebo mean 54.1, $p=0.19$), but there was for the CGI severity scores (quetiapine mean 4.96 versus placebo mean 4.64,

p=0.03). No statistical testing was performed for baseline comparisons of SANS and BPRS psychosis cluster scores.

Dosing Information

Appendix table 7.2.1.4 presents the mean quetiapine dosage for patients remaining in the study at each week. The mean dose for completers remained around 400 mg/day for the final weeks of the study.

Concomitant Medications

The table below lists the use of selected concomitant medications by treatment group.

Selected concomitant medication use(adapted from electronic version of study report)

	Quetiapine n = 54	Placebo n = 55
Chloral Hydrate		
Number of patients	38	44
Benzotropine mesylate		
Number of patients	5	6
Diphenhydramine HCl		
Number of patients	2	3
Lorazepam		
Number of patients	17	15

Overall the treatment groups were similar with respect to numbers of patients receiving these concomitant medications.

Efficacy Results

Appendix tables present the efficacy data for the important outcome measures (total BPRS score, CGI severity, BPRS psychosis cluster items, and SANS total score), by week, for each treatment group. Both the last observation carried forward (LOCF) analysis and the completers analysis are shown. In general, the quetiapine group was superior to the placebo group at several timepoints during the trial, but only by the last observation carried forward analysis. At the final week, the drug group was not superior to the placebo group at a 5% level of statistical significance on any measure, although several earlier weeks showed significance for the drug group on the BPRS total score, CGI severity, BPRS psychosis cluster, and SANS total score, especially in the LOCF analyses.

Miscellaneous Issues

Although there was imbalance at baseline with respect to CGI severity scores between the groups, analysis of covariance should have served to correct for this imbalance.

No plasma drug concentrations were obtained during the study.

Because of allegations of misconduct at one site (Center 008, where Dr. Borison was the principal investigator), Zeneca provided a reanalysis of the efficacy data for the BPRS total score and CGI severity score, omitting data from Center 008. This procedure had negligible impact on the results for these two variables, and there was generally no loss of statistical significance (in fact, some p-values were actually smaller without Center 008 data).

Conclusions

On balance, this study provides marginal support for antipsychotic efficacy of quetiapine, when titrated to a wide dose range. Strictly speaking, however, the data fall short of meeting the customary level of statistical proof, particularly for the observed cases analyses.

7.2.2 Study 0008

Investigator(s)/Location

Appendix 7.2.2.1 lists the investigators and sites for this study, which was conducted in the U.S. and abroad.

Study Plan

Objective(s)/Rationale

This study was intended to determine the safety and efficacy of quetiapine, administered with low and high dosage regimens, versus placebo, for the treatment of hospitalized patients with an acute exacerbation of schizophrenia.

Population

Eligible subjects were male and female adults, aged 18-65 years; females of child bearing potential were permitted by a protocol amendment, provided they were using contraception. Patients had to meet DSM-III-R criteria for subchronic or chronic schizophrenia with acute exacerbation. Additionally, they were required to have a BPRS score of at least 27, a score of at least 4 on the CGI severity scale, and a score of at least 3 on 2 of the BPRS psychosis cluster items. The following were grounds for exclusion: use of antihypertensive medication, unstable medical conditions, substance abuse, suicidality, epilepsy, allergies, other DSM-III-R Axis I disorders. The protocol specified a target enrollment of 165 patients from the U.S. and overseas.

Design

This was a multicenter, double blind, randomized, parallel group, placebo controlled trial. Note that there were two separate protocols for this study, one for domestic sites and one for foreign sites. The two protocols were similar but not identical. Patients were required to be hospitalized for at least the first 4 weeks (later shortened to 3 weeks). There was no single blind placebo lead in period for this trial at foreign sites, although in the U.S. the study protocol specified a single blind placebo treatment of 2-14 days. Patients were to be randomized to either placebo, quetiapine 250 mg/d maximum or quetiapine 750 mg/d maximum. Medication was to be given QID at foreign sites and TID in the U.S., titrated according to clinical response, up to the randomly assigned maximum dose, for a duration of 6 weeks. The initial dose was to be 75 mg/d; beyond this, no specific titration schedule was set forth in the U.S. protocol. In the European protocol, the suggested maximum dosing schedule was as follows: Day 1, 75 mg; Day 2, 150 mg; Day 3, 250 mg; day 4, 350 mg; day 5, 500 mg; day 6, 600 mg; day 7, 750 mg. Patients were not to receive more than 500 mg daily for more than 2 weeks, however. Chloral hydrate, benzotropine and diphenhydramine were allowable as concomitant psychotropic medications. Scheduled screening assessments included physical examinations, ophthalmologic examinations, ECGs, clinical laboratories, BPRS, CGI, Comprehensive Psychiatric Rating Scale

(CPRS), and PANSS. Assessments were scheduled weekly.

Analysis Plan

The primary outcome measures were defined as the BPRS and CGI scales, mean change from baseline.

Study Conduct/Outcome

Patient Disposition

In Europe, 117 patients entered the study and were randomized to double blind treatment. In the U.S., where patients first entered a single blind placebo period, 196 patients received single blind placebo, and a total of 169 were then randomized to double blind treatment. The majority of those not randomized failed to meet safety entry criteria. In addition, one patient in the U.K. apparently withdrew from the trial after receiving low dose quetiapine and re-enrolled in the high dose quetiapine group (with patient numbers UK-001/00019 and UK-001/00022, respectively). This patient was excluded from the analysis. Also, patient UK-001/00801 was excluded because of a diagnosis of schizophreniform disorder rather than schizophrenia: although this was permitted by a protocol amendment, this was the only non-schizophrenic patient in the study.

Overall, a total of 286 patients (117 European and 169 U.S.) were randomized to double blind treatment. Ninety six were assigned to high dose quetiapine, 94 to low dose quetiapine and 96 to placebo. This was considerably more than the planned number of patients (165 planned total), which Zeneca attributed to an increase in recruitment late in the trial. Apparently the sponsor believed that some of the European sites might not pass data quality audits, and to compensate the recruitment at other sites was boosted. As it turned out, no sites had to be excluded because of data quality concerns, and the end result was excess enrollment (see Zeneca's correspondence for details).

The table below displays the disposition of patients and the reasons for premature discontinuation by treatment group.

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TABLE Numbers of patients and reasons for withdrawal, Study 0008 (adapted from sponsor's electronic version of study report)

	Quetiapine		Placebo (n = 96)
	High dose (n = 96)	Low dose (n = 94)	
Treatment failure	25	34	42
Protocol violation	1	1	0
Adverse clinical or laboratory experience	7	7	3
Death during randomised treatment	0	0	0
Withdrawal of consent	10	4	8
Intercurrent medical event	1	1	0
Other	4	7	4
Total number of patients withdrawn	48	54	57

Not surprisingly, the placebo group had the highest dropout rate for treatment failure, and in fact had the highest dropout rate overall by a slight margin.

Appendix table 7.2.2.2 shows the numbers of patients remaining in each treatment group by week.

Demographics/Group Comparability

The patients in this study were primarily male caucasians, with a mean age in the late thirties. Appendix table 7.2.2.1 shows the demographic characteristics by treatment group. There was no obvious imbalance between treatment groups with respect to demographic characteristics.

Regarding baseline comparability, the Kruskal Wallace test for a difference among the three groups was marginally significant ($p=0.06$) for baseline BPRS scores, with the high dose group having a mean score roughly 3 points higher than the placebo group, as seen in the appendix tables. Differences between treatment groups on the CGI severity and SANS were not as statistically significant.

Dosing Information

Appendix table 7.2.2.3 lists the mean daily dose for patients in both quetiapine groups completing each week of the study. After titration the low dose group generally had mean doses close to 250 mg/d, and the high dose group had mean doses around 500 mg/d. Thus, dosing was close to the maximum on average for the low dose but well below the maximum on average for the high dose group. This likely reflected the prohibition on dosing above 500 mg for more than 2 weeks.

Concomitant Medications

The study report provided information on concomitant medications for agitation, insomnia and EPS. Anti-EPS medications were administered to 7 of 96 (7%) high dose quetiapine patients, 3 of 94 (3%) low dose patients, and 10 of 96 (10%) placebo patients. Chloral hydrate was given to 51 of 96 high dose patients (53%), 49 of 94 (52%) low dose patients, and 49 of 96 (51%) placebo patients. Some type of benzodiazepine was administered to 36 of the 96 (38%) high dose patients, 48 of 94 (51%) low dose patients, and 38 of 96 (40%) placebo patients. Thus there was not a large imbalance with respect to use of concomitant medications in the three treatment

groups. The use of anti-EPs medication was actually highest in the placebo group.

Efficacy Results

Appendix tables display the results for the primary efficacy measures. On the BPRS total score, the high dose quetiapine group showed a statistically significant improvement relative to placebo with both the LOCF analysis and the observed cases analysis. This was not the case for the low dose group, however. The same pattern of results was obtained with the CGI severity scores, the BPRS psychosis cluster scores, and the SANS total scores (the latter administered only in the U.S.). The PANSS, on the other hand, was administered only in Europe, and the negative PANSS scale generally did not show statistical superiority for either active drug group over placebo; however, the sample size may have been inadequate for statistical power, since results were consistently numerically superior for the high dose group.

Miscellaneous Issues

It is not likely that the baseline imbalance with respect to BPRS scores biased the results in favor of the high dose group. Analysis of covariance should have accounted for this imbalance.

There was a substantial over enrollment of patients in this trial relative to the protocol specified target. However, this did not appear to be a result of an interim analysis suggesting a need for more patients to be enrolled, as the sponsor affirmed that no interim data analysis was performed. Furthermore, an analysis by the Biometrics reviewer, Dr. David Hoberman, showed that even if enrollment had been stopped after the first 165 patients, as originally planned, the results would still have shown superiority for quetiapine; please refer to Dr. Hoberman's review for details.

In the U.S. plasma concentration data was obtained. The median plasma concentration of quetiapine at week 6 was 42 ng/ml for the 250 mg dose group and 68 ng/ml for the 750 mg/d dose group. No statistical correlation between plasma concentration and improvement on efficacy measurements was found.

Conclusions

On balance, this study provides statistical evidence that quetiapine administered at a high dose (i.e., roughly 500 mg daily) is effective in the treatment of psychosis associated with schizophrenia. Improvement was found in both positive and negative symptomatology. Efficacy of the lower dose, roughly 250 mg on average, was not supported.

7.2.3 Study 0013

Investigator(s)/Location

The investigators and sites for study 0013 are listed in appendix 7.2.3. Sites were in the U.S. and Canada.

Study Plan

Objective(s)/Rationale

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The primary objective of this study was to determine the dose-response relationship for quetiapine in the treatment patients with acute exacerbation of schizophrenia.

Population

Targeted enrollment was a total of 350 patients (50 per treatment arm). Eligible patients were those aged 18 to 65 with chronic or subchronic DSM-III-R schizophrenia, in acute exacerbation. Mental retardation, organic mental disorder, substance abuse, seizures, pregnancy, breast feeding, leukopenia, unstable medical illness, history of clozapine related agranulocytosis, or abnormal ECG were all grounds for exclusion. Patients were to have a minimum score of 27 on the BPRS, a minimum score of 4 on the CGI severity rating, and a minimum score of 3 on the four item psychosis cluster of the BPRS. Also, patients were not to have demonstrated a more than 20% improvement in the BPRS, or an improvement of more than 1 point on the CGI, during the one week screening period.

Design

Patients were to be hospitalized for at least the first 4 weeks of double blind treatment. The study began with a 3-7 day single blind placebo lead in period, after which patients were to be randomly assigned to one of the following seven double blind treatments: haloperidol 12 mg/d, placebo, quetiapine 75 mg/d, quetiapine 150 mg/d, quetiapine 300 mg/d, quetiapine 600 mg/d, quetiapine 750 mg/d. Dosing of study medication was to be TID, and the medication dose was to be titrated during the first 1-2 weeks of double blind treatment and remain constant during the final 4 weeks. The recommended titration schedule was as follows for the 750 mg dose: Day 1, 75 mg; day 2, 150 mg; day 3, 250 mg; day 4, 300 mg; day 5, 400 mg; day 6, 600 mg; day 7, 750 mg. Scheduled screening procedures included history and physical examination, BPRS, CGI, hematology laboratories, liver function tests, thyroid function tests, pregnancy testing, ECGs, and prolactin levels. Baseline assessments were scheduled at the end of the single blind placebo wash out period, and patients were to be assessed weekly during double blind treatment. Efficacy measures included BPRS, CGI and SANS, and safety assessments included vital signs, clinical laboratories, and EPS rating scales. Chloral hydrate, lorazepam, and benztropine could be provided as needed, and medication for stable medical conditions was allowed. Open label treatment was permissible for patients who had completed at least 2 weeks of double blind treatment.

Analysis Plan

The BPRS total score and the CGI severity score, considered at endpoint, were the designated primary outcome measures. The primary method of analysis was designated as a dose-response model, rather than pairwise comparisons to placebo.

Study Conduct/Outcome

Patient Disposition

A total of 402 patients entered the single blind phase of the trial; 41 of these discontinued before randomization (chiefly because of withdrawal of consent). Thus, 361 patients were randomized to double blind treatment, with roughly 50 patients entering each of the 7 treatment arms. The percentage of patients completing each week of the study is shown in the appendix table by treatment group. Less than half the patients in the trial completed the study, although retention in some groups was higher than others.

The overall disposition of patients in each treatment group is shown in table 7.2.3.1 below.

TABLE 7.2.3.1 Numbers (%) of patients and reasons for withdrawal (adapted from the sponsor's electronic study report)

Treatment Group:	Quetiapine					Haloperidol (n = 52)	Placebo (n = 51)
	75 mg (n = 53)	150 mg (n = 48)	300 mg (n = 52)	600 mg (n = 51)	750 mg (n = 54)		
Total number of patients withdrawn	36 (68)	27 (56)	28 (54)	24 (47)	28 (52)	34 (65)	35 (69)
Reason for withdrawal							
Lack of efficacy	27	23	22	16	19	17	30
Refusal to continue/ failed to return	8	4	5	7	6	13	3
Adverse experience/ intercurrent illness	0	0	0	0	1	4	2
Protocol noncompliance	1	0	1	1	2	0	0

In all treatment groups, discontinuations for lack of effect outnumbered discontinuations for adverse experiences.

The appendix table 7.2.3.2 displays the completion rate for each week of the study by treatment group.

Demographics/Group Comparability

Appendix table 7.2.3.1 shows the demographic characteristics of the patient population in this study. In all treatment groups, patients were chiefly white males; the mean age in all groups was in the late thirties. Paranoid schizophrenia was the most common diagnosis.

With respect to baseline comparability, Zeneca stated in the study report that there were no statistically significant differences at baseline between treatment groups, but I was unable to locate a supporting analysis in the study report.

Dosing Information

This was a fixed dose study.

Concomitant Medications

In the quetiapine groups, use of concomitant benzotropine ranged from 8-12% of patients. The majority of patients in all groups received chloral hydrate, and roughly half of patients in most treatment groups received lorazepam. The table below displays the use of these three medications by treatment group.

TABLE 7.2.3.2 Selected concurrent medication use (adapted from sponsor's electronic study report)

Medication	Treatment group						Haloperidol (n = 52)	Placebo (n = 51)
	SEROQUEL							
	75 mg (n = 53)	150 mg (n = 48)	300 mg (n = 52)	600 mg (n = 51)	750 mg (n = 54)			
Chloral hydrate								
Number of patients (%)	36 (68)	29 (60)	34 (65)	31 (61)	33 (61)	41 (79)	40 (78)	
Lorazepam								
Number of patients (%)	33 (62)	23 (48)	26 (50)	22 (43)	26 (48)	32 (62)	25 (49)	
Benztropine mesylate								
Number of patients (%)	6 (11)	5 (10)	4 (8)	6 (12)	6 (11)	25 (48)	7 (14)	

Efficacy Results

Appendix tables show the results for the primary outcome measures. With respect to the BPRS total score, the CGI severity scores, and the BPRS psychosis cluster, efficacy results by LOCF showed statistically significant results relative to placebo for all doses except 75 mg/d. The findings on the observed cases analysis were not as robust, particularly towards the later weeks in the trial, but this is not unusual for antipsychotic clinical trials with large numbers of dropouts. The haloperidol 12 mg group showed statistical superiority on all three of the above measures as well, and generally performed better in the observed cases analysis than any of the quetiapine groups. Other than the observation that the lowest dose (75 mg/d) of quetiapine was the only dose which did not show an effect, there appeared to be little evidence for a dose response effect, as the size of the mean changes from baseline was fairly consistent across dose groups.

For negative symptoms, the quetiapine 300 mg and the haloperidol groups showed statistical superiority to placebo on both LOCF and OC analyses. The quetiapine 600 mg/d group also demonstrated some efficacy versus placebo, although not as consistently as the 300 mg and haloperidol groups.

Miscellaneous Issues

No statistical correlation was found for plasma drug concentration and outcome on efficacy measurements. Plasma drug concentrations for patients completing week 6 are shown below.

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Table: Plasma drug concentrations at week 6 by dose, study 0013:

DOSE (MG/D)	MEAN (SD) TROUGH QUETIAPINE CONCENTRATION (NG/ML)
75	14 (11)
150	28 (16)
300	44 (34)
600	91 (59)
750	94 (72)

Because of allegations of misconduct at Dr. Borison's center, Center 001, Zeneca reanalyzed the efficacy results minus data from Center 001 (submission of 9/24/96). The results for BPRS total score and CGI severity score changed only slightly when data from Center 001 was omitted, and statistical comparisons to placebo were essentially unchanged.

Conclusions

This trial provides statistical evidence that quetiapine is active in the treatment of psychotic schizophrenic patients, at doses of 150 mg/d and above. The 75 mg/d dose did not demonstrate efficacy, however. For the other quetiapine dose groups and the haloperidol active control, primary efficacy results were comparable, and no dose response relationship for doses above 75 mg/d was evident. There was evidence for reduction in negative symptoms, as measured by the SANS, for the haloperidol group and the quetiapine 300 mg group. The improvement seen for negative symptoms with haloperidol treatment is of interest, since many experts believe that traditional antipsychotic drugs are not as capable of ameliorating negative schizophrenic symptoms as are newer medications.

7.2.4 Study 0012

Investigator(s)/Location

A total of 89 centers in various foreign countries participated in this trial; no domestic sites participated. The investigators and sites for this study are listed in appendix 7.2.4. Note that Center 10 was omitted from the analysis after Zeneca learned that the investigator had allegedly committed fraud during a previous clinical investigation.

Study Plan

Objective(s)/Rationale

The purpose of this study was to compare the efficacy and safety of quetiapine administered 225 mg BID, 150 mg TID, and 25 mg BID, in the treatment of patients with an acute exacerbation of chronic or subchronic schizophrenia. The goal was to provide support for dosing quetiapine BID rather than TID, with the expectation that a BID dose regimen will improve compliance.

Population

Subjects were to be inpatients with an acute exacerbation of subchronic or chronic schizophrenia (as per DSM-III-R). The goal was to recruit 510 subjects. Adult males or females, aged 18-65, were eligible, but females were to have a negative pregnancy test if of child bearing age, and were not to be breast feeding. Subjects were to have a minimum CGI Severity score of 4, and a minimum BPRS total score of 27, with a score of at least 3 on two or more of the BPRS psychosis cluster items. Exclusion criteria encompassed substance abuse, organic mental disorder, mental retardation, previous exposure to quetiapine, history of clozapine related agranulocytosis, seizures, and presence of risk factors for blood borne infections such as HIV or hepatitis.

Design

The study design included three phases. The initial phase was a no medication washout period, followed by a 6 week, 3 arm, randomized, double blind, parallel group treatment period employing doses of quetiapine 25 mg BID, 225 mg BID, and 150 mg TID. Dosage was to be titrated upwards during the 7 days. The third and final phase was open label extension treatment for patients who had completed at least 2 weeks of double blind treatment. Subjects were to be hospitalized for at least 2 weeks of double blind treatment. Screening was to be performed 3 to 7 days before randomization, and all psychotropic medication was to be stopped at least 2 days before the baseline assessments (performed at the time of randomization). Final determination of eligibility was to be made using the baseline assessment. Screening assessments included history and physical examinations, clinical laboratories, thyroid function tests, ECGs, pregnancy testing, and serum prolactin levels. Efficacy measures included the BPRS, SANS, and CGI. Safety monitoring included vital signs, clinical laboratories and EPS rating scales. Patients were to be seen weekly during the double blind period, and less often for open label treatment. Medication for stable conditions was permissible; the only permissible psychotropic medications were benzodiazepines and anti-EPS medication.

Analysis Plan

The protocol defined the primary efficacy measures as change from baseline in BPRS total score and CGI severity score at 6 weeks. Analysis of covariance was designated as the analytic method.

Protocol Amendments

The protocol was amended more than a dozen times. Many protocol amendments were specific to individual countries. Amendments concerned issues such as entry of women of child bearing potential, pharmacokinetic sampling, ophthalmology assessments, length of inpatient treatment, length of open label treatment, and various safety assessments. Additionally, there was a separate protocol for Canadian sites, although I was unable to discern any important differences between the two versions of the protocol.

Study Conduct/Outcome

Patient Disposition

A total of 678 patients enrolled in the study; 4 of these were enrolled at the site that was eventually excluded because of past allegations of research misconduct, leaving 674 patients.

Fifty six patients did not proceed to double blind treatment after the initial baseline period; of these, 25 withdrew consent and 31 failed to meet entry criteria. Thus, 618 patients were randomized to double blind treatment. Of these, 597 had at least one assessment after receiving study drug, and thereby constituted the intent to treat group (195 patients for quetiapine 225 mg BID, 204 for quetiapine 150 mg TID, and 198 for quetiapine 25 mg BID).

The table below presents the overall disposition of patients in the study. These figures refer to the set of all randomized patients, and it was not clear from the sponsor's presentation if these numbers were the same for the intent to treat group.

TABLE Number of patients and reasons for withdrawal (adapted from sponsor's electronic study report)

Reason for withdrawal	SEROQUEL	SEROQUEL	SEROQUEL
	450 mg (bid)	450 mg (tid)	50 mg (bid)
	n	n	n
Lack of efficacy	60	64	80
Protocol non-compliance	7	6	6
Adverse event or intercurrent illness	12	7	7
Refused to continue or lost to follow-up	19	20	26
Total number of patients withdrawn	98	97	119

In this study, 47% of the quetiapine 225 mg BID group, 44% of the quetiapine 150 mg TID group, and 53% of the quetiapine 25 mg BID group withdrew prematurely. The rate of completion by week in the study is shown for each group in appendix table 7.2.4.2.

Demographics/Group Comparability

Appendix table 7.2.4.1 presents the demographic characteristics for patients in this study. Note that the sponsor provided these data for the set of all randomized patients, rather than the intent-to-treat sample, but in all likelihood the demographic profiles should be similar for the two patient sets. The patients in this study were overwhelmingly caucasian, with a mean age in the thirties. The treatment groups appeared to be similar demographically. Baseline total BPRS mean scores were close to 42 for all three groups.

Dosing Information

This was a fixed dose study.

Concomitant Medications

Zeneca presented information on concomitant use of benzodiazepines and anti-EPS drugs. These data are presented in the table below.

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Concomitant Benzodiazepine and anti-eps medication (adapted from sponsor's electronic study report)

	quetiapine 450 mg (bid) (n = 200)	quetiapine 450 mg (tid) (n = 209)	quetiapine 50 mg (bid) (n = 209)
Number of patients receiving benzodiazepines (%)	112 (56)	119 (57)	124 (59)
Number of patients receiving medication for EPS (%)	18 (9)	12 (6)	14 (7)

The proportion of patients receiving these types of medications was similar in all 3 treatment groups. Analysis of data on other concomitant medications was not provided.

Efficacy Results

Appendix tables present the results for the outcome measures of interest. For the mean BPRS total score, both the 225 mg BID and the 150 mg TID groups were superior at a statistically significant level to the 25 mg BID by the LOCF analysis. By the observed cases analysis, results were in favor of the 225 mg BID group, but 150 mg TID showed no statistically significant differences versus 25 mg BID.

On the CGI severity score analysis of covariance, data were not normally distributed, as evidenced by non-random residuals. Consequently, the sponsor opted for a categorical analysis approach, in which some categories were collapsed, using the Cochran Mantel Haenzel method. These results are displayed in an appendix table. The 225 mg BID group showed statistical superiority to the low dose group on this variable, but the 150 mg TID group did not.

On the BPRS psychosis cluster scores, the 225 mg BID group showed statistical superiority to the 25 mg BID group consistently on the LOCF analysis, and somewhat less consistently on the observed cases analysis. However, the 150 mg TID group was not superior to the 25 mg BID group at a statistically significant level for this measure.

For negative symptoms, results on the LOCF analysis favored the 225 mg BID group over the low dose by a statistically significant margin in the final weeks. Results were less consistent on the observed case analysis.

Miscellaneous Issues

Center 10 was excluded from the analysis after the sponsor learned that the investigator had been struck off the medical register in the U.K. because of allegations of misconduct during a previous study. This site had enrolled only 4 patients.

Trough plasma drug concentrations were to be obtained weekly; however, only 4 subjects in each group actually had such levels drawn, making conclusions about pharmacokinetic differences between the regimens problematic. In fact, the mean plasma concentration obtained from this small sample of patients was at times higher for the 50 mg/day group than for the high dose groups, a reflection of the wide individual variability in plasma drug concentrations.

Conclusions

This study supports efficacy of quetiapine 225 mg BID over 25 mg BID in the treatment of actively psychotic schizophrenic patients. The data provide marginal support for the efficacy of 150 mg TID over the low dose. One could speculate that patients in the BID dose group may have been more compliant than the subjects taking the TID doses; however, adequate plasma drug concentration data is lacking to evaluate this. With respect to negative symptoms, the efficacy of the higher dose treatment groups was not as consistently shown. On balance, this trial may be interpreted as supporting the efficacy of a BID dosing regimen, at least for a total dose of 450 mg.

7.2.5 Other Studies

Trial 0004 was a single center pilot study which, although small in sample size, demonstrated superiority of quetiapine over placebo. This was a randomized, double blind, placebo controlled study in which 12 schizophrenic inpatients participated. Eight received quetiapine and 4 received placebo; duration of treatment was 3 weeks and the median quetiapine dose was 200 mg. At endpoint, the mean BPRS score for the quetiapine group had decreased by 21 points, a statistically significant effect compared to placebo. This effect size was considerably larger than those seen in the pivotal studies.

Study 0015 was a one year, multicenter, randomized trial of relapse prevention, which compared haloperidol 12 mg/d to quetiapine 75 mg/d, 300 mg/d and 600 mg/d. Three hundred and one stable schizophrenic outpatients participated. Although the hypothesis was that a dose effect would be found, no treatment differences in rate of relapse were observed. Without a placebo group for determination of assay sensitivity, results from this trial are inconclusive.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

To examine the possibility that demographic characteristics influenced response, the sponsor provided no formal treatment by age, gender or race interaction analyses for the efficacy data. The sponsor did, however, display efficacy data separately by age category (over versus under age 40), by race and by gender, using BPRS and CGI data from trials 0013, 0006 and 0008. By inspection, there were no major differences in the efficacy results when subdivided in this fashion for race or gender. With respect to age, the effect size for drug relative to placebo appeared to be greater in the under 40 age group, particularly for trial 0006. The clinical implications of this observation are unclear, however. Please refer to the discussion of demographic influences in DR. Hoberman's statistical review.

7.3.2 Choice of dose

In study 0013, all daily doses above 75 mg (i.e., 150, 300, 600 and 750 mg) showed efficacy relative to placebo with comparable effect sizes. However, in study 0008, the quetiapine high dose group, with a mean dose of around 500 mg/d, performed better than the low dose group having a mean dose of roughly 250 mg/d. In the proposed labeling, the sponsor indicates that the target dose should be 300 mg/d based on the above. In reaching this conclusion the sponsor seems to be giving more weight to study 0013 than to study 0008. However, study 0013 was the only adequate and well controlled study to use fixed doses.

7.3.3 Duration of Treatment

The efficacy of quetiapine was demonstrated in 6 week long controlled clinical trials. The long term relapse prevention trial, study 0015, failed to demonstrate efficacy for either quetiapine or the active control relative to the low dose quetiapine group. Thus, there is no data on efficacy beyond a treatment duration of 6 weeks.

7.4 Conclusions regarding efficacy data

Data from more than one adequate and well controlled study has shown quetiapine to be effective in the acute treatment of psychotic patients with schizophrenia. Data on long term relapse prevention are lacking. When the data are pooled according to age groups, the effect of the drug appears to be more robust in the subset of patients below 40 years of age.

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8.0 Integrated Review of Safety

8.1 Background and Methodology for Safety Review

Both the original NDA submission integrated phase II-III primary database and data from the NDA four month safety update were available for the safety review. Additionally, the sponsor provided safety data in manipulable electronic SAS format, for both the initial primary database and the 4 month safety update database. Additional information from certain foreign studies that were not part of the primary integrated database was considered, especially with respect to serious adverse events. The safety review focused on the phase II-III clinical experience as being the most relevant to the intended population for quetiapine treatment. Short term placebo controlled trials were the focus for evaluation of more common adverse events, since this data set provided a comparator group. The entire database of quetiapine exposures was searched for less common but more medically significant adverse events when appropriate. The sponsor's one year relapse prevention study, although lacking a placebo group, did include a haloperidol comparison group and also afforded an ability to examine dose effects during long term treatment, since three fixed doses of quetiapine were employed. In the discussion that follows, the convention for identifying individual patients will be to list their trial number, followed by their center number and individual patient number. Thus the designation 5077IL/0048;US-0010/1011 refers to a patient in study 5077IL/0048 (sometimes listed simply as 0048 for convenience), at U.S. center number 0010 with subject number 1011. Open label extension treatment is designated by the abbreviation OLE.

The NDA primary integrated database for Phase II-III studies included 2162 quetiapine treated patients, and the safety update submission included an additional 225 quetiapine patients, for a total of 2387 patients.

8.1.1 Deaths

Appendix table 8.1.1.1 lists all deaths associated with quetiapine treatment as of the cutoff date for the safety update (3/1/96). In my opinion, none of these deaths can be attributed exclusively to the effects of quetiapine. Specific cases and the possible influence of quetiapine on certain disease states are discussed under the relevant body system, in the review of systems that follows. Whether more aggressive medical management might have benefitted patient 0012/0045/4502, whose angina worsened over several days prior to his death from cardiac arrest, or patient 0012/0091/9103, who died with a progressive basilar artery thrombus and was apparently not transferred to a neurology service for 2 weeks after his initial neurological symptoms, is difficult to say.

Appendix table 8.1.1a lists certain other deaths reported outside the NDA or NDA safety update, for which only limited information is available (from IND safety reports, the IND annual report, and an interim IND safety summary that Zeneca submitted 9/20/96)

Table 8.1.1.2 in the appendices shows the overall mortality in the Phase II-III integrated quetiapine database. There is no suggestion of excessive mortality associated with quetiapine treatment from these data.

8.1.2 Other Serious Adverse Events

Zeneca provides the following definition of serious adverse event in the Integrated Summary of Safety: "any event that suggests a significant hazard, contraindication, side effect, or precaution."

This category is broader than the more explicit FDA definition of a serious adverse experience (as one that meets any of the following descriptions: fatal; life threatening; permanently disabling; leading to hospitalization; cancer; overdose; or congenital anomaly). However, it would presumably include all events meeting the more specific FDA definition.

Designation of a clinical trial event as serious was a judgement of the Zeneca physician monitor early in the development program, but subsequent to the End of Phase II meeting with FDA the sponsor permitted the clinical investigator to make this determination.

Zeneca states in the Integrated Summary of Safety that certain events were automatically considered serious: those involving the COSTART terms convulsion, grand mal convulsion, myoclonus (if used for investigators' terms of tonic and/or clonic convulsions), syncope, suicide attempt, overdose, neuroleptic malignant syndrome, and agranulocytosis.

Among the 343 quetiapine treated subjects in the Phase I studies in the primary integrated database, the sponsor reported that 11 (3.2%) had serious adverse events. Among the 2,387 quetiapine treated patients in the Phase II-III primary integrated database, there were 180 (7.5%) with serious adverse events (subjects and patients could have more than one serious adverse event). Specific serious adverse events will be discussed under the Review of Systems.

8.1.3 Dropouts

8.1.3.1 Overall Profile of Dropouts

Overall, in the initial NDA primary integrated database, 80% of quetiapine treated patients (1731 out of 2162) in Phase II-III trials discontinued treatment prematurely. The comparable figure for Phase I studies was 14% (42 out of 300 subjects). (The sponsor did not provide data on the overall pattern of dropouts for the safety update database.) The table below displays the reasons for premature discontinuation from studies in the Phase II-III integrated database, not including the safety update data.

TABLE Number of subjects withdrawn and reason for withdrawal in Phase II-III trials (adapted from sponsor's electronic submission)

Reasons for withdrawal	Number of subjects withdrawn (%)		
	Quetiapine (n = 2162)	Comparison drugs (n = 420)	Placebo (n = 206)
Total number of subjects withdrawn	1731 (80.1)	177 (42.1)	126 (61.2)
Lack of efficacy	1033 (47.8)	68 (16.2)	100 (48.5)
Subject refused to continue or was lost to follow-up	398 (18.4)	47 (11.2)	14 (6.8)
Adverse event or intercurrent illness	154 (7.1)	45 (10.7)	7 (3.4)
Subject withdrew consent	4 (0.2)	8 (1.9)	0
Protocol noncompliance	118 (5.5)	5 (1.2)	0
Other*	24 (1.1)	4 (0.9)	5 (2.4)

* Zeneca reports that 2 of the 24 patients listed as other acutely dropped out for adverse experiences (eye disturbance and postural hypotension).

The majority of patients withdrawn discontinued for lack of efficacy. The group most relevant for the safety review is, of course, the 154 patients who discontinued quetiapine because of medical problems, either intercurrent illness or adverse events. Note that investigators were required to indicate if an adverse event was a reason for premature discontinuation; more than

one adverse event could be so designated (per telecon with sponsor 12/2/96).

It may be more informative to consider dropouts from a pool of short term trials, since the data above combines double blind and open label treatment. The sponsor provided the following table of reasons for withdrawal from short term placebo controlled trials (studies 0004, 0006, 0008, 0013).

Table Reasons for withdrawal from short term placebo controlled trials (adapted from sponsor's ISS)

Reasons for withdrawal	Number of subjects withdrawn (%)	
	Quetiapine (n = 510)	Placebo (n = 208)
Total number of subjects withdrawn	271 (53.1)	126 (61.2)
Lack of efficacy	182 (35.7)	100 (48.5)
Subject refused to continue or was lost to follow-up	49 (9.6)	14 (6.8)
Adverse event or intercurrent illness	19 (3.7)	7 (3.4)
Protocol noncompliance	8 (1.6)	0
Other	13 (2.5)	5 (2.4)

Note that withdrawal for lack of efficacy was more common among placebo patients, while withdrawal for adverse events was roughly equivalent between the two groups.

8.1.3.2 Adverse Events Associated with Dropout

Overall, a total of 176 out of 2387 (7.4%) patients treated with quetiapine in the integrated primary database withdrew prematurely because of adverse events.

To examine the adverse events commonly cited as reasons for discontinuation, it may be useful to focus on the pool of controlled clinical trials, since this subset of data includes comparator groups with roughly comparable exposure. This would not be the case if one considers the entire quetiapine exposure database, which includes much exposure in uncontrolled open label treatment, making comparisons to control groups problematic. The table below displays the more common adverse events reported as reasons for premature discontinuation among quetiapine treated patients in controlled studies.

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TABLE

Adverse events leading to withdrawal of 3 or more subjects from treatment with quetiapine in controlled Phase II-III trials (adapted from sponsor's electronic ISS) Control groups are included for comparison. Data is from studies 0004, 0006, 0007, 0008, 0012, 0013, 0014, and 0015.

COSTART term	Number of subjects withdrawn (%)		
	Quetiapine (n = 1710)	Active Controls (n = 420)	Placebo (n = 206)
Total number of subjects withdrawn because of adverse events*	86 (5.0)	45 (10.7)	6 (2.9)
Somnolence	24 (1.4)	4 (1.0)	0
Postural hypotension	7 (0.4)	0	0
SGPT increased	6 (0.4)	1 (0.2)	1 (0.5)
SGOT increased	5 (0.3)	0	1 (0.5)
Hypotension	5 (0.3)	0	0
Depression	5 (0.3)	4 (1.0)	0
Leukopenia	4 (0.2)	0	0
Dizziness	4 (0.2)	0	0
Suicide attempt	3 (0.2)	2 (0.5)	0
Tachycardia	3 (0.2)	2 (0.5)	1 (0.5)
Gamma glutamyl transpeptidase increased	3 (0.2)	0	0
Alkaline phosphatase increased	3 (0.2)	0	0
Agitation	3 (0.2)	2 (0.5)	0

*Subjects may have had more than one adverse event leading to withdrawal.

Specific adverse experiences associated with dropout will be described under the review of systems.

8.1.4 Other Search Strategies

Zeneca analyzed the incidence of particular adverse events and sets of adverse events in terms of subject years of exposure for quetiapine and control treatments. The following table shows the results of the sponsor's analysis of these selected events. Exposures for quetiapine are shown with and without data from the safety update. Specific events of concern are discussed later in the review of systems.

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TABLE Incidence of important groups of selected adverse events (adapted from sponsor's electronic ISS)

Adverse event group**	Quetiapine (n = 2162) SY = 585.1		Quetiapine with safety update (n = 2387) SY = 865.3		Haloperidol (n = 320) SY = 42.3		Chlorpromazine (n = 100) SY = 9.2		Placebo (n = 206) SY = 14.6	
	k (%)*	ER	k (%)*	ER	k (%)*	ER	k (%)*	ER	k (%)*	ER
Syncope	21 (1.0)	3.7	28 (1.1)	3.0	1 (0.3)	2.4	1 (1.0)	10.9	0	0
Convulsion	9 (0.4)	1.5	18 (0.8)	2.1	2 (0.6)	4.7	2 (2.0)	21.8	1 (0.5)	6.9
Neuroleptic malignant syndrome	2 (0.1)	0.3	2 (0.1)	0.2	0	0	0	0	0	0
Suicidality	34 (1.6)	5.8	40 (1.5)	4.6	6 (1.9)	14.2	0	0	2 (1.0)	13.7
Depression	38 (1.8)	6.5	43 (1.8)	5.0	5 (1.6)	11.8	0	0	4 (1.9)	27.5
Cataract	15 (0.7)	2.6	16 (0.7)	1.8	1 (0.3)	2.4	0	0	0	0
Thyroid disorder	10 (0.5)	1.7	15 (0.6)	1.7	0	0	0	0	0	0
Rash and allergic phenomena	81 (3.7)	13.8	96 (4.0)	11.1	13 (4.0)	30.7	5 (5.0)	54.5	9 (4.4)	61.8
Edema	27 (1.2)	4.6	44 (1.8)	5.1	1 (0.3)	2.4	0	0	1 (0.5)	6.9
Leukopenia	43 (2.0)	7.3	48 (2.0)	5.5	0	0	1 (1.0)	10.9	0	0
Leukocytosis	11 (0.5)	1.9	13 (0.5)	1.5	0	0	1 (1.0)	10.9	5 (2.4)	34.3
Eosinophilia	6 (0.3)	1.0	8 (0.3)	0.9	1 (0.3)	2.4	0	0	0	0
Thrombocytopenia	2 (0.1)	0.3	2 (0.1)	0.2	1 (0.3)	2.4	0	0	0	0
Increased liver function tests	71 (3.2)	12	76 (3.2)	8.8	0	0	4 (4.0)	43.6	4 (1.9)	27.5

*Number of subjects with adverse events (%).

SY = Subject years of follow up

ER = Event rate per 100 subject-years exposure

**Costart terms used in search, if more than the term listed:

depression: depression, depression for investigators' terms that do not indicate suicidal ideation, depression psychotic

suicidality: suicidality, depression for investigators' terms that indicate suicidal ideation, suicide attempt, overdose, intentional injury

syncope: syncope, syncope for investigators terms that do not indicate seizure

convulsion: convulsion, grand mal convulsion, myoclonus for investigators' terms of tonic convulsion or clonic convulsion, syncope for investigators terms that indicate seizure

increased liver function tests: increased liver enzyme tests, SGOT increased, SGPT increased, alkaline phosphatase increase, gamma glutamyl transpeptidase increased, bilirubinemia

leukopenia: leukopenia, agranulocytosis

thyroid disorder: thyroid disorder, hypothyroidism, hormone level altered

rash: rash, maculopapular rash, vesiculobullous rash, allergic reaction, pruritus, angioedema

edema: edema edema facial, edema generalized, edema peripheral, edema larynx, lymphedema

cataract: cataract, cataract specified, eye disorder for investigators' terms that indicate cataract

8.1.5 Adverse Event Incidence Tables

8.1.5.1 Approach to Eliciting Adverse Events in the Development Program

In the integrated summary of safety, Zeneca states that an adverse event was considered as any pathologic or unintended change in structure, function, or chemistry of the body associated with use of the drug. Zeneca employed an adverse event thesaurus based upon the standard COSTART dictionary of adverse events. I found no indication that adverse event questionnaires were used in the clinical trials, thus I presume that all adverse events reported were spontaneously volunteered. The exception was use of rating scales for documentation of extrapyramidal symptoms (EPS). In a schizophrenic population, reliance on spontaneously volunteered complaints may result in underreporting, as has been observed in clinical trials which used both spontaneously volunteered reports and reports elicited by an adverse event checklist.

8.1.5.2 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

From the sponsor's electronic CANDAs version of the primary integrated database, I was able to create a spreadsheet showing the investigator's adverse event terms alongside the COSTART

terms to which they were coded. A random audit of these revealed no obvious systematic misclassification of adverse event terms. On occasion, cases that were individually reviewed were reclassified (e.g., certain serious adverse events described under review of systems).

8.1.5.3 Selecting the Key Adverse Event Tables for Characterizing the Adverse Event Profile

One approach to evaluating the more common adverse events is to pool data from all the short term placebo controlled trials (studies 0004, 0006, 0008, and 0013). The sponsor's table from the integrated summary of safety displaying the data obtained in this manner is presented in the appendix as table 8.1.5.3. The minimum incidence for events shown was 1% in quetiapine treated patients, and events which were actually more common in placebo treated patients have been omitted.

Appendix table 8.1.5.4 displays other adverse events arising among quetiapine treated patients in the primary integrated database of 2162 subjects. Data from the 4 month safety update is not included. Note that this table was adapted from the sponsor's proposed labeling, and that adverse event terms displayed in the 1% table are omitted. In addition, the sponsor has chosen to omit certain other adverse event terms, i.e., "those events for which causality has not been established, and those event terms which were so general as to be uninformative." The sponsor has not provided a list of the adverse event terms deleted for these reasons.

8.1.5.4 Identifying Common and Drug-Related Adverse Events

A number of methods can assist in determining which adverse events are common in incidence and possibly causally related to the drug. One approach is statistical. As shown in the table above, statistical significance testing was performed on the incidences of adverse events occurring at a rate of 1% or more. (This should not be regarded as hypothesis testing in the usual sense, particularly since there was no accounting for multiple comparisons. Rather, the p-values can be regarded as reflecting the magnitude of difference in incidence between the quetiapine and placebo groups.) The following adverse events had incidences for which the p-value comparing quetiapine to placebo was less than or equal to 0.05:

Dizziness, Somnolence, SGPT increased, SGOT increased, Weight gain, Dry mouth, Abdominal pain.

A second method is to determine which adverse events are at least twice as frequent among drug treated patients as among placebo treated patients, and which are also observed at an incidence of at least 5 per cent with the drug. These are often referred to as the "common and drug related" adverse events. Applied to the table above, this method yields the following list of common, drug related adverse events:

Dizziness, SGPT increased, dry mouth, dyspepsia, postural hypotension.

Note that dizziness, SGPT increased, and dry mouth appear in both lists. Specific adverse events will be discussed under the review of systems.

8.1.5.5 Additional Analyses and Explorations

Dose Response

The short term placebo controlled fixed dose study, trial 0013, permitted analysis of dose

response. As previously described, this was a 6 week fixed dose study using doses of 75, 150, 300, 600, and 750 mg/d, with roughly 50 patients per group. Zeneca performed an analysis of dose response for adverse events occurring at an overall incidence of 3% among quetiapine treated patients, using logistic regression. Dyspepsia, weight gain, and abdominal pain showed p-values less than 0.05, and dry mouth, postural hypotension, and leukopenia showed marginal p-values (between 0.1 and 0.05). Extrapyramidal symptoms did not show a dose related pattern. In addition, the long term relapse prevention trial, study 0015, employed doses of 75, 300 and 600 mg/d with approximately 90 patients in each dose group. This data permits consideration of treatment emergent adverse experiences arising in long term therapy. Here, a logistic regression analysis of dose response produced statistically significant p-values for the adverse events of nervousness and weight gain. Additionally, marginal p-values were obtained for the adverse events of hypertension, cataract specified, and dry mouth. Note that weight gain and dry mouth showed some indication of dose relatedness in both long term and short term treatment data.

Demographic Analyses

The sponsor compared adverse event incidences from the pool of short term placebo controlled trials with respect to age, race and gender. For this analysis, the odds ratios (quetiapine versus placebo) by demographic subgroup were determined for every adverse event having an overall quetiapine incidence of 1%. Then, the Breslow-Day test for homogeneity of the odds ratio across the subgroups was applied.

For the sponsor's comparisons by demographic group, the following numbers of patients contributed data:

Gender

Women: n=124 quetiapine, n=47 placebo

Men: n=386 quetiapine, n=159 placebo

Age

Under 40: n=317 quetiapine, n=125 placebo

40 and over : n=193 quetiapine, n=81 placebo

Race

White: n=345 quetiapine, n=143 placebo

Black: n=121 quetiapine, n=47 placebo

Other: too few to analyze

By the Breslow-Day test, no adverse event showed a significant difference in odds ratio by gender at a probability level of 5%. There was a marginally significant difference for the event dyspepsia ($p=0.09$), with a higher odds ratio for men.

For age subgroups, somnolence showed a higher odds ratio in younger patients ($p=0.05$), as did headache ($p=0.07$) and rash ($p=0.08$).

For race, the Breslow Day test showed a significant difference for myalgia, which was associated with quetiapine treatment in whites, but was not reported in blacks receiving quetiapine. Additionally, dry mouth showed a higher odds ratio in whites than in blacks ($p=0.08$).

In my opinion, these differences are not likely to be clinically meaningful, and may even be due to

chance.

8.1.6 Laboratory Findings

8.1.6.1 Extent of Laboratory Testing in the Development Program

The primary source for the review of laboratory findings will be the integrated Phase II-III studies; I will not focus on laboratory findings from phase I studies, unless a significant adverse event was associated with a laboratory abnormality.

Appendix table 8.1.6.1 displays the specific laboratory measures obtained in each trial in the original NDA submission. This table displays only which clinical laboratories were obtained, not how frequently they were obtained. In the short term placebo controlled trials clinical laboratories were obtained at least weekly (more often for study 0004).

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

The review of clinical laboratory data to be presented here will focus on data pooled from the set of short term placebo controlled trials, consisting of studies 0004, 0006, 0008, and 0013. With the exception of study 0004, a 3 week study with relatively few patients, these studies were 6 weeks in duration. In my judgement, this pool of studies represents the best choice for review of clinical laboratory findings, since the placebo control group affords an opportunity for comparison. Additionally, the duration of exposure is not a confounding variable as it would be if long term quetiapine treatment data were to be compared to placebo data involving briefer treatment; in these studies, duration of treatment was more consistent between quetiapine and placebo.

8.1.6.3 Standard Analyses and Explorations of Laboratory Data

8.1.6.3.1 Analyses Focused on Measures of Central Tendency

Appendix tables 8.1.6.3.1(a, b and c) display the mean changes from baseline for quetiapine and placebo groups with respect to hematology, clinical chemistry, and urinalysis values. The sponsor did not perform hypothesis testing on these data. By inspection, notable findings associated with quetiapine treatment include a roughly 10% increase in cholesterol and triglycerides, and changes in some thyroid function tests. These findings will be discussed under the review of systems.

8.1.6.3.2 Analyses Focused on Outliers

Appendix table 8.1.6.3.2 presents the The sponsor's criteria for defining laboratory abnormalities as clinically significant. These criteria, although necessarily arbitrary, appear reasonable in my opinion. Appendix tables 8.1.6.3.2 a,b and c display the proportion of patients meeting these criteria for each treatment group in short term placebo controlled trials. For the following parameters, quetiapine treatment was associated with a statistically significantly greater proportion of patients meeting the criterion values compared to placebo: low total T4, high ALT, high triglycerides, high reverse T3. Statistical significance was marginal (i.e., p value between 5 and 10%) for these additional parameters: low free T4, low hematocrit. With respect to hematocrit, there did not appear to be a similar excess of quetiapine patients having low hemoglobin.

8.1.6.3.3 Dropouts for Laboratory Abnormalities

In the primary phase II-III integrated database of 2387 quetiapine treated patients, the following laboratory abnormalities accounted for premature discontinuation in 0.3% or more of patients:

Leukopenia	0.6%
ALT increased	0.4%
AST increased	0.3%

Zeneca provided narrative summaries and case report forms for all patients prematurely discontinued because of laboratory abnormalities. These cases will be discussed under the appropriate body system in review of systems.

8.1.6.4 Additional Analyses and Explorations

The sponsor submitted a supplemental analysis of thyroid function test data from controlled clinical trials. Zeneca also submitted a special analysis of white blood cell laboratory abnormalities associated with quetiapine treatment. These analyses will be discussed under the Review of Systems.

8.1.7 Vital Signs

8.1.7.1 Extent of vital sign testing in the development program

The discussion of vital sign data will draw primarily upon data presented in the original integrated summary of safety, as there was little additional data presented in the safety update.

Appendix Table 8.1.7.1 shows the type of vital sign assessments performed for each trial in the integrated database (not including the safety update).

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

As with the laboratory data, the most informative pool of vital sign clinical trial data for comparing quetiapine and placebo treated patients will be the short term placebo controlled trials. The approach will be similar to that outlined above for laboratory data.

8.1.7.3 Standard Analyses and Explorations of Vital Sign Data

8.1.7.3.1 Analyses Focused on Measures of Central Tendency

Appendix table 8.1.7.3.1 summarizes mean vital sign changes from baseline for the pool of short term placebo controlled trials. Both quetiapine and placebo data are shown. Zeneca performed no hypothesis testing on these data. Overall, there was a modest mean increase in pulse (both standing and supine) associated with quetiapine treatment, and a mean weight increase of over two kgs, relative to placebo patients. On average, vital signs did not show much in the way of orthostatic changes.

8.1.7.3.2 Analyses Focused on Outliers

Appendix table 8.1.7.3.2 displays the criteria that Zeneca chose for defining vital signs as potentially clinically significant. These appear reasonable to me, although they are necessarily arbitrary. As seen in appendix table 8.1.7.3.2b, the proportion of quetiapine patients with a high standing pulse was statistically significant compared to the placebo group, consistent with an

orthostatic drug effect. The proportion of quetiapine patients with increased weight was also statistically significant compared to placebo.

8.1.7.3.3 Dropouts for vital sign Abnormalities

The following table enumerates patients who dropped out for vital sign abnormalities in the original NDA submission database. The sponsor did not provide a similar table for the safety update data.

Table: Subject withdrawals for abnormal vital signs or weight measurements during Phase II-III controlled trials (does not include safety update data. Adapted from sponsor's electronic ISS submission)

COSTART term	Quetiapine (n = 1710)	Placebo (n = 206)	Haloperidol (n = 320)	Chlorpromazine (n = 100)
	Number of subjects (%)	Number of subjects(%)	Number of subjects (%)	Number of subjects (%)
Hypotension	5 (0.42)	0	0	0
Postural hypotension	7 (0.59)	0	0	0
Hypertension	0	0	0	1(1.0)
Weight gain	1 (0.08)	0	0	0
Syncope	2 (0.17)	0	0	0
Tachycardia	3 (0.25)	1 (0.4)	0	2 (2.0)
Sinus bradycardia	1 (0.08)	0	0	0

Uncontrolled Trials (n=1256)

	Number of subjects (%)
Cardiovascular	
Bradycardia	1 (0.1)
Heart arrest	1 (0.1)
Hypotension	1 (0.1)
Postural hypotension	4 (0.3)
Syncope	1 (0.1)
Tachycardia	2 (0.2)
Total subjects	10 (0.8)

The sponsor provided narrative summaries of these cases. Specific adverse events will be discussed under the review of systems.

8.1.7.4 Additional Analyses and Explorations

None to report.

8.1.8 ECGs

8.1.8.1 Extent of ECG testing in the development program

Twelve lead electrocardiogram monitoring was performed in 8 of the primary integrated database phase II-III clinical trials (see appendix table 8.1.8.1), and during open label treatment with quetiapine at U.S. sites. I found no reference to any Holter monitoring studies.

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

As with the clinical laboratory and vital sign analyses, the primary data set for consideration of ECG findings will be the pool of short term placebo controlled Phase II-III trials. This provided roughly 400 quetiapine patients with baseline and on treatment ECG tracings, and roughly 150 placebo patients for comparison.

8.1.8.3 Standard Analyses and Explorations of ECG Data

8.1.8.3.1 Analyses Focused on Measures of Central Tendency

Appendix table 8.1.8.3.1 presents a summary of mean changes from baseline for ECG parameters with quetiapine treatment in Phase II-III studies. Except for a slight mean increase in heart rate, there were no notable mean changes in ECG parameters associated with quetiapine. The sponsor performed no statistical hypothesis testing on these data.

8.1.8.3.2 Analyses Focused on Outliers

Appendix table 8.1.8.3.2a shows the sponsor's criteria for considering ECG abnormalities possibly clinically significant. Applying these criteria to the short term placebo controlled trial data, there were no statistically significant differences between the quetiapine and placebo patient groups for the numbers of patients meeting these criteria, as seen in appendix table 8.1.8.3.2b. Note that the sponsor chose a relatively conservative criterion value for QTc, i.e., 450 msec.

8.1.8.3.3 Dropouts for ECG Abnormalities

The following table enumerates the patients discontinued for ECG abnormalities. The sponsor did not provide a similar table for the safety update data.

TABLE ECG-Related Withdrawals (Adapted from sponsor's ISS; does not include safety update) Controlled trials

	Quetiapine n = 1710	Placebo n = 206	Haloperidol n = 320	Chlorpromazine n = 100
Tachycardia	3	1	0	2
Bradycardia	1	0	0	0

Uncontrolled trials	(n = 1256)
Tachycardia	2
Bradycardia	1
ECG abnormal (nonspecific ST-T changes)	1
Heart arrest (fatal)	1
Pericarditis (later deemed normal ECG variant)	1

The sponsor provided narrative summaries of these cases. The specific adverse events involved will be discussed under the review of systems.

8.1.8.4 Additional Analyses and Explorations

There were none to describe.

8.1.9 Special Studies

In pharmacodynamic interaction studies to explore the psychomotor effects of quetiapine combined with ethanol (study 0024) and lorazepam (study 0027), involving 10 subjects each, the combination exacerbated the psychometric deficits observed with either ethanol or lorazepam alone.

8.1.10 Withdrawal Phenomena/Abuse Potential

The sponsor did not perform any studies to determine the abuse potential of quetiapine, or the safety of sudden versus gradual discontinuation of treatment.

8.1.11 Human Reproduction Data

The following table summarizes pregnancy experience with quetiapine.

Table Summary of pregnancy exposures with quetiapine (from sponsor's 2/12/97 submission)

Trial;subject	age	quetiapine exposure	Outcome and comments
5077IL/0012:4515		1st trimester	Elective abortion at 5 weeks
5077IL/0061:113	18	500 mg/d for 3-4 weeks of 1st trimester	Healthy baby girl

No conclusions can be drawn from such a limited number of pregnancy exposures.

8.1.12 Overdose Experience

The sponsor defined an overdose as an ingestion of 900 mg or more of quetiapine. Zeneca performed a search of the integrated safety database including the safety update data and found a total of 7 quetiapine overdoses of 900 mg or more. Additionally, an elderly subject mistakenly received 600 mg and a 5 year old boy ingested 600 mg. These cases are described in the following table.

Table Summary of overdoses with quetiapine

Trial;subject	Age	Sex	over-dose mg	Concomitant drugs	Comments
0014OLE; UK-0067/6707	42	m	2800	diazepam 1000 mg	Emesis induced, recovered after 24 hours
5077IL/0048;US-0010/1011	73	f	600		accidental overdose in patient with dementia. Somnolence and hypotension; treated with sorbitol and charcoal, recovered within hours
5077IL/0012 OLE:0001/0108	23	f	1500		No information on treatment or signs and symptoms. Patient recovered and continued in trial.
5077IL/0012ole;0003/0301	36	m	1200		No symptoms reported and subject continued in trial
5077IL/0012 OLE:0035/3504	25	f	2000	temazepam 50 mg	Patient hospitalized and received IV fluids. Two to three days after overdose developed increased CPK, rash, back pain, fever, myalgia, and buccal dyskinesia; recovered.
5077IL/0012 OLE:0084/8414	36	f	6400	pimozide, chlorazepate, biperiden, asa, diclofenac, paracetamol, haloperidol, codeine, dexchlorpheniramine	Hospitalized in a coma and placed on mechanical ventilation. Developed elevated LFTs, aspiration pneumonia and ARDS. Recovered after 11 weeks in hospital.
5077IL/0013 OLE:0011/1104	25	m	9300		obtundation, sinus tachycardia to 140 bpm, hypokalemia, (2.8 mmol/l), 1st degree heart block. Treated with lavage and charcoal, cathartic, Kcl, diazepam for agitation, recovered
5077IL/0014 OLE:0026/2610	28	f	6500	tenox 600 mg	Patient became unconscious but recovered; no further details
not a subject	5	m	600		Developed sedation, hospitalized, recovered

This limited number of reported overdoses does not seem to indicate extraordinary toxicity from the compound. Several cases involved overdose on multiple medications.

8.2 Review of Systems

8.2.1 Cardiovascular

8.2.1.1 Adequacy of assessment of cardiovascular system effects

Orthostatic vital signs and electrocardiograms were obtained during the majority of clinical trials. Cardiovascular adverse events were recorded in the usual fashion. I am aware of only one patient who had a holter monitor recording, which was obtained as part of a syncope evaluation. On balance, the evaluation of the cardiovascular system appears to have been adequate.

8.2.1.2 Cardiovascular Adverse events Considered Possibly, probably, or Definitely Related to Quetiapine

Postural hypotension and syncope

Quetiapine's alpha adrenergic blocking properties suggest that it may have a capacity to induce orthostatic hypotension. In the pool of short term controlled trials, dizziness and postural hypotension were among the common and drug related adverse events. The statistical analyses of vital sign data did not show much evidence for orthostatic hypotension, except that the increase in the proportion of quetiapine patients meeting the criterion for high standing pulse was statistically significant versus placebo patients. In the pool of all controlled trials, postural hypotension was the second most common reason for quetiapine patients discontinuing prematurely; no patients from the control groups discontinued prematurely for postural hypotension.

Syncope is an event that is sometimes attributed to postural hypotension. The sponsor's analysis of adverse events judged to represent syncope (see table in section 8.1.4 above) showed the following:

TABLE Incidence of syncope (adapted from sponsor's electronic ISS)**

Quetiapine (n = 2162) SY = 585.1		Quetiapine with safety update (n = 2387) SY = 865.3		Haloperidol (n = 320) SY = 42.3		Chlorpromazine (n = 100) SY = 9.2		Placebo (n = 206) SY = 14.6	
k (%)*	ER	k (%)*	ER	k (%)*	ER	k (%)*	ER	k (%)*	ER
21 (1.0)	3.7	26 (1.1)	3.0	1 (0.3)	2.4	1 (1.0)	10.9	0	0

*Number of subjects with adverse events (%).

SY = Subject years of follow up ER = Event rate per 100 subject-years exposure

** syncope, for investigators terms that do not indicate seizure

In my own search of the adverse event data including the safety update data, (electronic search using data set 4msudbol/adversev), there were 1/320 haloperidol patients, 1/100 chlorpromazine patients, no placebo patients, and 27/2387 (1.1%) quetiapine treated patients having adverse events with the Costart term syncope. Among the patients so identified, the median time on quetiapine when syncope occurred was 14 days, while the mean was considerably greater (88 days). Thus syncope is frequently encountered early in treatment, but not always so. Review of the narrative summaries for cases of syncope revealed that in a number of cases the subject was noted to have postural hypotension, but in other cases no orthostatic vital signs were obtained, so that generalizations about the association of syncope with vital sign changes are difficult.

Increased heart rate

Although palpitation was not a common, drug related adverse events in the short term controlled studies, there was a 3-4 bpm mean increase in both supine and standing pulse in the short term controlled trials among quetiapine patients, at endpoint, compared to a 1-2 bpm increase with placebo, suggesting that the increase in heart rate is not necessarily limited to the standing position. In addition, ECG data from controlled trials showed a mean increase in heart rate of 7 bpm for quetiapine compared to 1 bpm for placebo, at endpoint. With respect to dose dependency, in study 0013, mean increase in supine pulse from baseline to endpoint for the various quetiapine dose groups ranged from 2-6 bpm, but without a clear dose relationship.

Similarly, in the same study the increase in heart rate on ECG ranged from 2-10 bpm among quetiapine dose groups, but without a clear dose related trend.

One subject, 0048/0008/0810, a 77 year old man with pre-existing cardiac disease, developed persistent tachycardia (roughly 150 bpm) for which a cardiologist was unable to find an etiology; the tachycardia resolved 3 days after discontinuing quetiapine. Patient 0013/0018/1808, a 28 year old male, discontinued quetiapine because of tachycardia; he complained of episodes of palpitation, dizziness, weakness and dyspnea; only mild sinus tachycardia was ever documented.

QT prolongation

Preclinical data does not provide evidence of a QT prolonging effect of quetiapine in the animals studied; please refer to the pharmacology review for details.

Two cases involving QT prolongation merit description. Patient 0048/0013/1301, a 73 year old female with dementia, suffered syncope after 5 days on quetiapine (dose 25 mg/d); concomitant medication was carbamazepine. The patient was hospitalized for evaluation; an ECG that same day showed a prolonged QT interval (QTc 0.612 sec). The QTc interval returned to 0.412 a few days later while the patient continued quetiapine. A cardiology consultation was obtained, and the patient underwent an echocardiogram (normal) and Holter monitoring (also normal). No etiology other than quetiapine treatment was specified for the syncope. An additional patient, 0048/0013/1305, a 69 year old female with vascular dementia, was hospitalized after 12 weeks on quetiapine (dose 275 mg/d) for a prolonged QTc interval of 606 msec (baseline QTc =409 msec). A repeat ECG showed a QTc interval of 476 msec; quetiapine was discontinued and the patient's QTc remained below 500 msec. An echocardiogram was normal. In my opinion, these cases in themselves are inconclusive regarding a causal relationship to quetiapine treatment.

In the pool of short term controlled trials, there was little mean change in QTc interval (for all quetiapine doses combined); nor was there a significant number of quetiapine patients with treatment emergent QTc prolongation beyond 500 msec in comparison to placebo (please see appendix tables 8.1.8.3.1 and 8.1.8.3.2). Thus from this analysis there was no signal of QT prolongation, and this is what Zeneca notes in their draft labeling.

With the electronic CANDADA database, it was possible to perform a broader search for clinically significant QT prolongation. I was able to search the entire controlled Phase II-III trial database for treatment emergent QTc prolongation, using the ISS database and ECG data set. This was the largest database for which electronically formatted ECG data was provided (i.e., no open label data was included). Patients with baseline QTc intervals greater than or equal to 500 msec, and those missing a baseline QTc interval, were excluded. The remainder constituted the number of patients at risk for documented treatment emergent QTc prolongation \geq 500 msec. Results are shown below.

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Treatment group	Patients at risk	Pts with at least one QTc \geq 0.5 sec N (%)	Mean no. of ECG tracings per pt in group
Quetiapine	698	10 (1.4)	3.1
Placebo	151	2 (1.3)	3.1
Chlorpromazine	88	2 (2.3)	3.5
Haloperidol 12 mg	37	0	3.0

Thus, as with the smaller pool of short term controlled studies, the data did not provide evidence for a QT-prolonging effect of quetiapine.

In the analyses described thus far, all quetiapine doses were combined. To examine the possibility that a QT prolonging effect might occur only at relatively high doses, data from the two fixed dose controlled studies was considered.

Study 0013: In this short term fixed dose trial with doses up to 750 mg, there was a mean increase from baseline to endpoint in QTc interval of 10 msec in the 600 mg group; this was statistically significant in comparison to placebo. However, there were negligible mean changes in the other quetiapine dose groups, including the 750 mg group; thus the data were not consistent with a dose response pattern. From the CANDA electronic dataset ISS/QTc Summary, searched with the JMP statistical application, no patients in the study had treatment emergent QTc above 0.500 sec.

Study 0015: In the long term fixed dose, the largest mean increase from baseline for QTc interval among any treatment groups at endpoint was 0.01 sec, in the high dose (600 mg) group; the corresponding values for the other treatment groups were 0.00 sec for quetiapine 300 mg, -0.01 sec for quetiapine 75 mg, and -0.01 sec for haloperidol 12 mg. No statistical comparison between groups was provided for this study. From the CANDA electronic dataset ISS/QTc summary, four patients in the 600 mg group had treatment emergent QTc greater than or equal to 500 msec, compared to one each in the 300 and 75 mg groups and none in the haloperidol group.

Thus, the data from study 0015 could be interpreted as representing a QT prolonging effect at the high dose; however, the sponsor did not provide a statistical comparison between dose groups, so inferences are limited. Also, the data from study 0013 was not consistent with a dose dependent effect.

On balance, the data do not consistently reflect a QT prolonging effect of quetiapine.

Deep vein thrombophlebitis and thrombosis

Three quetiapine treated patients developed deep vein thrombophlebitis (DVT), and one patient developed an intracardiac thrombus despite the lack of obvious cardiac disease. The cases are summarized below.

- 0048/US0013/1307 66 year old female with deep vein thrombosis of lower extremity after 5 mo. on quetiapine; patient was receiving conjugated estrogen
- 0015 OLE/0005/0502 63 year old woman developed deep vein thrombosis after 180 days on quetiapine (this patient had other serious adverse events also: intestinal obstruction, breast carcinoma, sepsis, described under the corresponding body system)
- 0008/0035/0808 42 year old male on quetiapine for 16 days (dose 250 mg) developed thrombophlebitis of left lower extremity and was treated with anticoagulation; discontinued quetiapine. Past history of thrombophlebitis.
- 0012 OLE/0091/9143 46 year old male on quetiapine 400 mg/d for 55 days developed right sided hemiplegia, diagnosed as having a completed stroke; echocardiogram showed a left ventricle thrombus; no significant past medical history

In addition, there was one death from cerebral vascular disease in which the patient was found to have a basilar artery thrombus at autopsy; this patient had no significant past medical history (patient 0012/0023/2303). Also, an IND safety report subsequent to the NDA submission (see appendix table 8.1.1.1) reported the death of a 69 year old man from pancreatic cancer; this patient had DVT, but of course DVT has been associated with pancreatic malignancy.

For comparison, there were no reports of DVT, or pulmonary embolism for that matter, in the risperidone or olanzapine premarketing NDA clinical trial databases. These cases raise the possibility of thrombophilic effects from quetiapine, although a few cases involving events that have a non-negligible expected rate are obviously not conclusive. It is perhaps relevant that a chemically similar compound, clozapine, may be associated with an increased risk of pulmonary embolism.

If these cases do, in fact, represent a true association of quetiapine treatment with thrombotic events, there may be a biologically plausible mechanism. Hughes' syndrome, also known as the antiphospholipid antibody syndrome, is a well described immune phenomenon involving circulating antiphospholipid antibodies. These antiphospholipid antibodies may include anticardiolipin antibodies or the lupus anticoagulant, the latter so called because it was first described in association with lupus erythematosus and because it results in a paradoxical elevation of the partial thromboplastin time. Presence of these factors has been linked to increased risk of venous or arterial thromboembolic events and to recurrent fetal loss. While often associated with autoimmune disease, presence of these antibodies has also been linked to treatment with neuroleptic drugs such as chlorpromazine, although the clinical significance is uncertain (Mueh et al., Ann Intern Med 1980; 92:156-159; Lillicrap et al, Am J Clin Pathol 1990;93:771-775). (As there are now routine serum assays for these antibodies, it should be feasible to test the possibility of an association of quetiapine treatment with antiphospholipid antibodies.)

8.2.1.3 Adverse cardiovascular events considered unlikely to be quetiapine related

As shown in appendix table 8.1.1.1, quetiapine patient 0012OLE/0045/4502 died from cardiovascular causes that did not appear related to quetiapine therapy (cardiopulmonary arrest following worsening angina). In addition, two subjects in study 0048 were reported to have died from cardiac disease after the NDA cutoff date, one from a myocardial infarction and one from possible cardiopulmonary arrest, but only incomplete information is available at this time.

The following were nonfatal but clinically significant adverse cardiovascular events, deemed

unlikely to be related to quetiapine.

0031/0009/0903

42 year old man with chest pain, tachycardia; MI was ruled out

0048/0002/0201

70 year old man with congestive heart failure; also chronic obstructive pulmonary disease anemia and acute renal failure

0048/0018/1811

70 year old man with new onset (presumably) of atrial fibrillation accompanied by chest pain

0012 OLE/0019/1904

52 year old male with ischemic heart disease was hospitalized for chest pain

0017 OLE/0001/0102

63 year old diabetic male suffered acute myocardial infarction

0061/0001/0107

45 year old man hospitalized for angina pectoris, underwent angioplasty

0035/0001/0132

Phase 1 study. 30 year old male with history of intravenous drug abuse. Subacute bacterial endocarditis with renal embolus.

0014/0016/1605

47 year old male hospitalized with diagnosis of poor cerebral perfusion secondary to mitral and aortic valve lesions

0017/0002/0202

66 year old male hospitalized with unstable angina

Trial H-15-33 Subject B

A 24 year old volunteer receiving quetiapine 10 mg/d in a phase I study had 18 beats of ventricular tachycardia, without symptoms, noted on holter monitoring

8.2.2 Gastrointestinal

8.2.2.1 Adequacy of assessment of gastrointestinal (GI) system effects

In the clinical development program, adverse GI events were collected by spontaneous report, and standard clinical laboratories were obtained. In my opinion, this was adequate assessment of the GI system. At the level of individual cases, however, the sponsor did not always obtain adequate followup information for patients discontinuing because of GI adverse events.

8.2.2.2 GI adverse events considered possibly, probably, or definitely related to quetiapine

Increased liver enzymes

In the pool of placebo controlled short term trials, 6% of quetiapine treated patients had ALT during treatment of greater than or equal to 165 U/l, compared to 1.5% of placebo patients ($p=0.0051$). Group mean changes from baseline at end of treatment did not show very great disparities between quetiapine and placebo for liver enzymes, however. Increased AST and ALT were among the more common reasons for premature discontinuations among quetiapine patients, although not occurring at a greater incidence than for control group patients (see tables in section 8.1.3.2 above). Increased ALT was a common and drug related adverse event, as

noted above in section 8.1.5.4.

I found no reference to specific criteria for withdrawal of patients having liver enzyme elevations, and it appears that this judgement was left to the investigators. Nonetheless, it may be useful to review the cases in which liver enzyme abnormalities resulted in dropout. The following table presents a summary of individual patients who discontinued quetiapine for liver enzyme elevation, based on the sponsor's case summaries.

Dropouts for liver enzyme elevations

Trial/subject	Age/ sex	Dose/duration	Maximum levels (IU/L)	Outcome/comments
5077IL/0005, Subject US-0001/0003	29 m	250 mg 22 d	ALT 267 AST 79	Returned to near normal roughly 2 weeks after d/c
H-15-22, Subject 27-2	22 m	300 mg 21 d	ALT 309; AST 104; Alk Ph 290; GGT 110	Returned to near normal roughly 2 weeks after d/c. Received unspecified agent for treatment of liver
H-15-22, Subject 45-1	43 f	450 mg 34 d	ALT 151; AST 116; Alk Ph 287; GGT 54	Returned to normal after d/c
H-15-22, Subject 62-2	33 f	300 mg 14 d	AST 103 ALT 206	Returned to normal 14 days after d/c
H-15-23, Subject 004/4-3	52 f	225 mg 101 d	AST 113 ALT 105	Concomitant carbamazepine. Liver treated with ursodesoxycholic acid, protoporphyrin disodium, liver hydrolysate, and glycyron. Continued slight elevation after d/c
H-15-22, Subject 18-2	45 m	225 mg 15 d	AST 397 ALT 529	subject was treated with GLUTATHION 150 mg/day and protoporphyrin disodium 60 mg/day, VITANEURIN 3 capsules/day, SAIREITO (chinese medicine) 7.5 mg. Normal levels 6 weeks after d/c
H-15-22, Subject 27-2	22 m	300 mg 21 d also chlorpromazine	ALT 309 AST 104 Alk Ph 290 GGT 110	Received unspecified compound to treat liver. Near normal values 15 days after d/c
H-15-22, Subject 45-1	43 f	450 mg 34 d	SGOT: 116 , SGPT: 151, Al-p: 287 , γ-GTP: 54	Returned to normal after d/c
H-15-22, Subject 62-2	33 f	300 mg 14 d	AST 103 ALT 206	Returned to normal 2 weeks after d/c
5077IL/0006, Subject US-0005/0502	29 m	400 mg 20 d	ALT 302 AST 123	Returned to normal 17 days after d/c

204636/0008, Subject UK-0001/0020	22 m	100 mg 20 d	ALT 252 AST 119 GGT 82	Returned to normal 8 days after d/c
204636/0007, UK-Subject 0026/0004	33 f	100 mg 34 d	Alk Ph 987; AST 158; ALT 403; GGT 332	No Follow Up Information
50771L/0012, Subject UK-0001/0118	38 m	400 mg 14 d	Alk Ph 285; ALT 448; AST 132	Normal liver ultrasound Day 7. Only ALT obtained in follow up (normal)
50771L/0012, Subject UK-0029/2909	62 f	450 mg 25 d	Alk Ph 759; ALT 134; AST 89	Non A Non B hepatitis positive; liver enzymes increased during treatment; no followup
50771L/0012, Subject UK-0086/8603	23 m	450 mg 36 d	ALT 395; AST 149	Normal 12 days after d/c
50771L/0005 OLE, Subject US 0022/0003	29 m	250 mg 22 d	ALT 267; AST 79	ALT normal 2 weeks after d/c
50771L/0012 OLE, Subject 0078/7807	40 f	150 mg 15 d	AST 123; ALT 258; Alk Ph 376	No follow up
50771L/0012 OLE, Subject 0084/8402	29 m	250 mg 7 d	ALT 244	ALT actually decreased on treatment but investigator withdrew patient; no follow up

Note that in 4 cases no followup information was provided. For the other 14 cases, followup information indicated improvement after discontinuation of quetiapine. No patients were symptomatic. I am not aware of any patient discontinued for liver enzyme elevation who was later rechallenged with quetiapine.

The sponsor notes that of 21 quetiapine patients in short term controlled trials with treatment emergent ALT levels 3 times the upper limit of normal, 17 recovered without discontinuation of quetiapine.

In sum, elevation of ALT was associated at a statistically significant level with quetiapine treatment, relative to placebo, in short term studies. No cases of hepatitis or other clinical manifestations of hepatic dysfunction, other than liver enzyme increases, have been observed with quetiapine treatment. Nonetheless, it cannot be known whether liver enzyme monitoring during the clinical trial program prevented some cases of more severe hepatic disorder, by prompting discontinuation of treatment when liver enzyme abnormalities occurred.

Dyspepsia and abdominal pain

In the pool of short term placebo controlled trials, treatment emergent abdominal pain was observed in more quetiapine than placebo patients by a statistically significant margin, and dyspepsia met the definition for common and drug related. These findings suggest some association of gastrointestinal distress with quetiapine therapy. Dyspepsia and abdominal pain were among the adverse events to have a statistically significant association with dose in the fixed dose controlled study 0013.

One adverse event involving GI distress met criteria for seriousness: A 23 year old male had to discontinue quetiapine for vomiting, anemia and weight loss of 9.5 kg, and required hospitalization (5077IL/0012 OLE, Subject 0002/0203). Also, subject 0014OLE/0026/2602, a 42 year old male, withdrew from quetiapine treatment after 183 days because of severe vomiting which had resulted in weight loss of 10 kg and malnutrition. This same patient had been hospitalized at week 6 for pancreatitis, but it appears from the sponsor's narrative summary that the later episode of vomiting was not due to a recurrence of pancreatitis.

Dry mouth

The adverse event dry mouth, in the short term placebo controlled trials, was statistically significantly more frequent among quetiapine patients than placebo patients. Dry mouth also met the criteria for common and drug related.

8.2.2.3 Adverse GI events considered unlikely to be quetiapine related

The following lists patients that developed surgical problems while receiving quetiapine.

Trial and subject	Event and comments
5077IL/0031, Subject US-0006/0609	49 year old man (blind not broken) underwent surgery for a sigmoid volvulus
5077IL/0015, Subject US-0034/3407	39 year old female; laparotomy for a ruptured appendix
5077IL/0015 Subject US-0034/3408	27 year old male, surgery for appendicitis
0012 OLE/0032/3201	23 year old male; surgery for appendicitis
0014 OLE subject 0014/1402	surgery for suspected appendicitis; no outcome reported
0015/US -0005/0502	63 year old female developed intestinal obstruction attributed to post-surgical adhesions
0048 Subject US-0005/0502	small bowel obstruction attributed to post surgical adhesions in a 66 year old man; this resolved without surgery or discontinuation of quetiapine
5077IL/0048, Subject US-0001/0101	Stomach carcinoma in an 87 year old male
5077IL/0012, Subject UK-0003/0306	62 year old female with metastatic adenocarcinoma of the bowel

The following patients had non-surgical serious events related to the GI system.

5077IL/0017 OLE, Subject US-0004/0401	85 year old male hospitalized for severe constipation with impaction
5077IL/0012 OLE, Subject 0034/3402	42 year old male hospitalized for diarrhea; resolved without discontinuation of quetiapine.
0014 OLE/0026/2602	42 year old male hospitalized for pancreatitis after 6 weeks of quetiapine treatment; recovered without discontinuation of quetiapine. (Patient later discontinued quetiapine for vomiting, at week 26 of treatment.)
5077IL/0012 OLE, Subject 0019/1903	35 year old male hospitalized for vomiting, but this resolved while quetiapine was continued
5077IL/0048 Subject US-0001/0104	91 year old female, hematemesis of unknown etiology

0048/US-0016/1612

75 year old man hospitalized for evaluation of abdominal pain. No etiology found, patient continued quetiapine therapy.

5077IL/0016, Subject 0001/0054
phase I

36 year old female diagnosed with hepatitis C

5077IL/0012 OLE, Subject 0086/8605

Elevated liver enzymes, ultimately deemed a lab error

8.2.3 Hemic and Lymphatic

8.2.3.1 Adequacy of assessment of Hemic and Lymphatic effects

Complete blood counts were monitored during every phase II-III quetiapine trial. In my opinion, this level of monitoring was adequate. In addition, Zeneca submitted a report from Dr. Stanton Gerson, of the Hematology/Oncology division at Case Western Reserve University, on the hematologic findings associated with quetiapine treatment. One weakness in the clinical development program was the lack of follow up for patients with documented neutropenia, to ensure that their WBCs returned to normal after discontinuation of quetiapine. In a number of cases, as will be seen, no follow up was obtained after the patient had discontinued quetiapine for leukopenia.

8.2.3.2 Hemic and Lymphatic Adverse events Considered Possibly, probably, or Definitely Related to Quetiapine

(In this section, units for blood counts are $10^9/l$.)

Leukopenia/neutropenia

In the pool of short term placebo controlled trials, examination of mean changes from baseline for white blood cell (WBC) and absolute neutrophil count (ANC) reveals only modest changes associated with quetiapine (see appendix tables). Likewise, the number of patients having clinically significant changes in these counts was not significantly different compared to placebo. From the long term study 0015, the sponsor reports 7 out of 235 quetiapine treated patients, and 2 out of 40 haloperidol patients had ANCs below 1.5; however, one of these haloperidol patients had a baseline ANC below 1.5. Excluding that patient, the incidence of treatment emergent ANC below 1.5 was 3.0% for quetiapine patients and 2.6% for haloperidol patients.

Dr. Gerson provided an analysis of ANC and WBC values across the complete primary integrated database. The table below is adapted from his report submitted by Zeneca.

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Numbers of patients with specific hematologic findings at any time during treatment [n (%)]

Finding (units =10 ⁹ /l)	Quetiapine (n=2387)	Placebo (n=206)	Active control (n=420)
Agranulocytosis (ANC < 0.5 and infection)	0	0	0
Severe neutropenia (ANC <0.5, no infection)	4 (0.2)	0	0
Moderate neutropenia (ANC ≥0.5 and <1.0)	19 (0.8)	1 (0.5)	1 (0.2)
Mild neutropenia (ANC ≥1.0 and <1.5)	65 (2.8)	3 (1.5)	6 (1.4)
Any Neutropenia (ANC <1.5)	88 (3.7)	4 (1.9)	7 (1.7)
Severe Leukopenia (<3.0 WBC))	42 (1.8)	0	2 (0.5)

There were proportionately more quetiapine patients in each of these categories, except agranulocytosis for which there were none; however, absolute incidence analysis is biased towards the quetiapine patient group which had a disproportionately longer exposure (due to open label extension treatments) and thus more time under observation to develop one of these findings. To examine this further, it is possible to calculate the incidence of neutropenia in terms of person time of exposure. For this, I have counted all patients who had an on-treatment ANC below 1.0 (10⁹/l). The results are shown in the following table.

TABLE Neutropenia in the integrated Phase II-III clinical program

Treatment group	Number of subjects	Subject-years exposure*	Cases of neutropenia**	Crude incidence rate (%)	Incidence per 100 subject-years
Quetiapine	2387	865.3	23	0.96	2.7
Haloperidol and Chlorpromazine	420	51.7	1	0.24	1.9
Placebo	206	14.6	1	0.49	6.8

*Subject-years is defined as the sum of all subjects' days on treatment (duration) divided by 365 days.

** Combining agranulocytosis (no cases), severe neutropenia and moderate neutropenia

Of most concern clinically are patients who developed ANCs below 0.5x10⁹/l. These patients are summarized below. Units are 10⁹/l. No patients had symptoms related to their neutropenia reported.

Trial/subject	Comments
0006/0008/0814	33 y.o. male; ANC=0.28 and WBC 2.8 at week 2; repeat CBC the following day at another lab showed ANC=3.3 and WBC=7.4. Continued quetiapine and ANC returned to 1.96 at week 4.
0005/0017/0002	29 y.o. male; ANC=0.51 and 0.48, weeks 3 and 4 respectively; discontinued as lost to follow up after week 4 but later seen alive and well. [At week 2, patient's ANC was higher than total WBC, which is inconsistent. Also, the neutropenia was documented only at Zeneca's central laboratory; WBC and ANC from the investigator's local laboratory were normal.]

0012/0045/4508

36 y.o. male; ANC=0.43 at week 6, returned to 2.0 one week later without discontinuation of quetiapine

0012/0011/1106

34 y. o. male; ANC=0.27 at week 3, returned to 2.5 the following week with continuing quetiapine treatment

In three of the above cases, the neutropenia resolved while quetiapine was continued, and in one case the fact that the ANC was normal the next day by a different clinical laboratory casts doubt on the validity of the laboratory result. Resolution of neutropenia while the potentially offending drug is continued argues against a causal relationship, but does not rule it out completely (CIOMS report on Drug-induced cytopenia, Int J Clin Pharmacol Ther Toxicol 29:75-81,1991). The fourth patient's findings may have been a laboratory error and would be explained if someone mistook percent neutrophils for absolute neutrophils; i.e., if 0.51 was the proportion of neutrophils and not the absolute neutrophil count.

The sponsor provided case summaries, prepared by their consultant, Dr. Gerson, of all individual cases of neutropenia with quetiapine treatment. This summary is reproduced in appendix 8.2.3.2. Note that Dr. Gerson considered 6 cases of neutropenia (0007/0017/0002, 0007/0017/0003, 0015/0018/1815, 0005/0018/0001, 0013/0007/0711, and 0014/0001/0103) as likely to be causally related to quetiapine treatment, based on clinical factors such as persistence and positive dechallenge. I find no reason to dispute his assessment.

A total of 14 quetiapine patients were withdrawn for the adverse event of leukopenia. However, there was no specific criterion for discontinuing patients based upon WBC, and in fact 3 patients with ANC below 0.5 were continued on quetiapine (and the fourth was lost to follow-up). In my opinion, because of these inconsistencies in withdrawing patients due to leukopenia, further analysis of dropouts for this adverse event is not likely to be informative.

Three patients were hospitalized for neutropenia during quetiapine treatment; however, no symptoms were reported. Patient 0012OLE/0064/6406, a 33 year old man, was hospitalized when his ANC fell to 1.3. Two days after quetiapine was discontinued his ANC returned to 3.5. Patient 0014OLE/0045/4506, a 24 year old female, was hospitalized when her WBC dropped to 2.5 with an ANC of 1.1; her counts improved after quetiapine discontinuation. Patient 0012OLE/0005/0506 was hospitalized for an ANC of 1.1; the count returned to normal after quetiapine was discontinued. As with dropouts for decreased WBC, there were no specific clinical criteria that lead to these particular patients being hospitalized, other than clinical judgement; and other patients with more severe decreases in WBC were not hospitalized.

The Division sought consultation on the question of quetiapine associated leukopenia from the Division of Gastrointestinal and Coagulation Drug Products. Please refer to the consultation by Dr. Lilia Talarico. She concluded that certain instances of quetiapine associated neutropenia were causally related to administration of the drug, but that these were apparently benign. She based this judgement on the pattern of decline in WBC following quetiapine treatment in certain cases and the fact that recovery often occurred after the drug was discontinued. Additionally, she observed that for the total primary integrated safety database, the incidence of neutropenia was slightly increased in the quetiapine patient group compared to the control groups.

In sum, quetiapine treatment was not prominently associated with neutropenia relative to the active control or placebo treatments. However, both the sponsor's consultant, Dr. Gershon, and Dr. Talarico from the FDA Division of Gastrointestinal and Coagulant Drug Products felt that quetiapine treatment induced leukopenia and neutropenia in certain individual patients. No

cases are known to have progressed to agranulocytosis. What cannot be known, of course, is to what extent the WBC monitoring which resulted in discontinuation of a number of patients from quetiapine treatment prevented more serious cases of neutropenia.

Thrombocytopenia

In her consultation report, Dr. Talarico commented upon the fact that a number of quetiapine treated patients had thrombocytopenia of a significant degree (less than 75K/uL). She notes that one of these patients had simultaneous leukopenia (patient 0048/0010/1014). Review of this patient's laboratory data revealed that on the day following the result showing thrombocytopenia and leukopenia, the CBC had returned to normal, casting doubt on the clinical significance. (Dr. Talarico also noted in her consult that patient 0015/0005/0502 had not only thrombocytopenia but pancytopenia; however, the most persistent abnormality for this patient was anemia, and so the patient is listed below in the section on anemia.)

With the CANDA data review function, patients with thrombocytopenia were identified and their platelet count data were examined individually. A total of 11 patients had platelet counts below 75K while receiving quetiapine; however, in all but two cases these were isolated low values which resolved with continued quetiapine exposure. In the remaining two cases which involved more persistent low platelet counts (patients 0014/0033/3307 and 0048/0002/0208) the baseline platelet counts were also low (57K and 78K, respectively). Thus there does not seem to be a strong signal for drug induced thrombocytopenia from these data.

Anemia

Aggregate data from the short term controlled trials, as shown in the appendices, suggested mean decreases in hematocrit with quetiapine, but no corresponding decrease in hemoglobin. However, in her hematology consultation report, Dr. Talarico noted that a number of quetiapine treated patients had a significant degree of anemia (Hgb less than 10 g/dl). To investigate this further, an electronic search of the CANDA primary integrated database (data set 4msudbol) was conducted, using the JMP statistical application, for patients whose minimum Hgb on treatment was less than 10 g/dl. This yielded 19 such patients; however, 4 had baseline Hgb below 10 g/dl as well. Excluding these patients, there were 14 quetiapine and 1 chlorpromazine patients with treatment emergent Hgb less than 10 g/dl. The individual patient data for the quetiapine patients was reviewed. In the majority of these cases the anemia resolved while quetiapine was continued, although one patient (0012/0092/9207) was noted to have received unspecified treatment for the anemia. A few of these cases, however, involved anemia that was not transient and are described in the table below:

Selected cases of treatment emergent anemia (Hgb < 10 g/dl) with quetiapine

Trial/patient number	Comments
0013/0016/1605	43 y.o. female with anemia and deep vein thrombophlebitis (DVT), discontinued for lack of efficacy
0015/0005/0502	63 year old female with multiple serious adverse events described elsewhere (sepsis, bowel obstruction, DVT); also had anemia (Hgb nadir =6.4 g/dl) without an etiology reported. Thrombocytopenia, neutropenia, and eosinophilia were also documented but did not persist as long as the anemia. The final on-treatment CBC was normal.
0048/0004/0405	81 year old male patient had Hgb less than 10 g/dl on several occasions while receiving quetiapine; anemia not recorded as adverse event

0014ole/0046/4609

51 year old male, mild anemia pretreatment (Hgb 13.7 g/dl), hospitalized for severe anemia after 135 days of quetiapine treatment. The lowest hgb recorded was 8.6; hgb improved after quetiapine was discontinued.

0048/0002/0201

70 year old man with congestive heart failure, hospitalized with acute renal failure attributed to concomitant trimethoprim-sulfa by sponsor. (This event will also be noted under the Genitourinary system.); simultaneously had profound anemia (hct 20), with total bilirubin of 8.6 umol/l. Little additional information was available

One other patient had anemia that became a serious adverse event: Patient 0012OLE/0002/0203 was hospitalized with weight loss, vomiting and anemia (Hgb 10.2); according to the case report form the anemia was attributed to vomiting and the patient also had an esophageal ulceration. The vomiting, however, was not described as hematemesis (which could have accounted for a drop in hemoglobin).

Little additional information relating to anemia was available for these cases. At the time of writing this review, the sponsor had been asked to provide additional clinical information regarding some of the above patients. With the limited information available at present, it is not possible to rule out a drug related cause (e.g., hemolysis).

Eosinophilia

In study 5077IL/0014 OLE, Subject 0026/2608, a 38 year old female, was withdrawn for eosinophilia after 3 weeks of quetiapine treatment, with eosinophil count increased from a baseline of 0.2 to 2.0 (with WBC 11.4); no follow up counts were obtained. The patient also had an episode of bronchitis. Eosinophilia is often an adverse drug reaction.

8.2.3.3 Adverse Hemic and Lymphatic events considered unlikely to be related to quetiapine

There were none.

8.2.4 Metabolic and Endocrine

8.2.4.1 Adequacy of assessment of metabolic and endocrine effects

Body weight was assessed regularly during the quetiapine clinical trials. With respect to clinical laboratories, cholesterol and triglyceride levels were obtained in certain of the domestic studies, although these were not required to be fasting samples. Some type of thyroid hormone monitoring was performed in 11 phase II-III trials, although the specific tests obtained varied from study to study. Prolactin was measured in the majority of phase II-III clinical trials. Of particular interest with respect to hormonal measurements is the data from the one year dose comparison long term treatment trial, study 0015, which provides some data on long term effects. On balance, this body system received an adequate evaluation during the quetiapine clinical trials, in my opinion.

8.2.4.2 Metabolic and Endocrine System Adverse events Considered Possibly, probably, or Definitely Related to Quetiapine

Hypothyroidism

In animals, the sponsor reports that quetiapine enhances hepatic clearance of thyroxine, resulting in elevated TSH, which in turn leads to thyroid follicular cell hypertrophy and benign thyroid tumors. Additionally, thyroid glands in rats exposed to quetiapine chronically contained pigment granules of drug derived substance.

Analyses of central tendency for thyroid function

In the pool of short term, placebo controlled trials, quetiapine treatment was associated with mean decreases in total T4 and free T4 of around 20%, but was not associated with an increase mean TSH levels. Complete data is shown in appendix table 8.1.6.3.1b.

It may be instructive to consider the thyroid function test data from the one year relapse prevention study, trial 0015. The following is an adaptation of a table from the sponsor's study report.

TABLE Mean change from baseline to final evaluation for thyroid function tests, study 0015 (adapted from sponsor's study report)

Parameter	Treatment Group					
	Quetiapine			Haloperidol		
	75 mg mean Δ (SD)	300 mg mean Δ (SD)	600 mg mean Δ (SD)	mean Δ (SD)		
n	n	n	n	n	n	n
Total T ₄ (nmol/L) (57.9 to 160.9 nmol/L)	69 0.52 (18.6)	73 -12.16 (22.0)	69 -24.02 (24.5)	36 0.86 (24.2)		
Free T ₄ (pmol/L) (15.4 to 29.6 pmol/L)	69 -0.88 (3.8)	73 -1.50 (4.2)	69 -3.25 (3.0)	38 0.68 (4.5)		
Total T ₃ (nmol/L) (1.3 to 2.8 nmol/L)	68 -0.05 (0.4)	72 -0.08 (0.4)	69 -0.19 (0.4)	36 -0.04 (0.4)		
Reverse T ₃ (nmol/L) (0.04 to 0.29 nmol/L)	50 -0.01 (0.1)	62 -0.01 (0.1)	56 -0.03 (0.1)	32 0.01 (0.1)		
TSH (μ U/L) (0.4 to 5.5 μ U/L)	69 -0.16 (0.9)	73 0.03 (1.1)	69 -0.13 (1.3)	38 -0.14 (0.8)		
TBG (nmol/L) (20592 to 43758 nmol/L)	52 -1114 (5490)	63 -1471 (5132)	59 -1112 (6397)	32 1086 (4905)		

SD Standard deviation

It can be seen that the pattern of reduction in thyroxine, both free and total, is dose related. Examination of the mean changes for thyroxine levels in this study by week showed that after an initial decrease at the four week visit, mean values remained fairly constant in each group, suggesting that the decreases were not progressive over time.

Note that in both the short term and the long term trials, only minor variations in mean TSH levels are seen.

In the fixed dose study 0013, mean decreases in total thyroxine were statistically significant compared to placebo, and also followed a dose related pattern.

Analysis of outliers for thyroid function tests

A statistically significant number of quetiapine patients in short term placebo controlled trials had

treatment emergent decreased total T4, defined as a level more than 20% below the lower normal limit, compared to placebo (see appendix table 8.1.6.3.2b).

In the report to the U.K., the sponsor noted the results of a search of the Phase II-III trials (including safety update) for patients who had clinically significant TSH elevation, defined as a persistent treatment emergent TSH elevation or one that resulted in prescription of thyroid replacement therapy. There were 11 such quetiapine patients, although one had a recent history of lithium induced hypothyroidism and was excluded from the total. This left a total of 10 such patients (incidence of 0.4%, or 1.2 per 100 patient years), compared to 0/420 active control patients (with 51.7 patient years) and 0/206 placebo patients (with 14.6 patient years). Of the ten patients, 6 were prescribed thyroid hormone replacement.

Other data

A total of 13 quetiapine patients in the primary integrated database had hypothyroidism reported as an adverse event; no patients from the control groups had this event. In all cases the diagnosis was based on laboratory rather than clinical findings. It should be remembered, however, that the clinical diagnosis of incipient hypothyroidism can be subtle, relying as it does on symptoms such as lethargy and weight gain which might be particularly difficult to detect in a chronically mentally ill population. In one case (50771L/0031 OLE, Subject US-0008/0801), hypothyroidism was a serious event. This patient, a 33 year old man, had a progressive increase in his TSH level, beginning during double blind treatment (blind not yet broken) and continuing during open label quetiapine treatment. He was hospitalized for evaluation after his TSH and T₄ levels reached 66.5 mIU/L and 0.8 ng/dl, respectively. He responded to treatment with levothyroxine and continued quetiapine therapy.

The sponsor's report to the U.K. CSM indicates that treatment emergent reduction in free T4 has been observed in quetiapine treated patients with pre-existing hypothyroidism receiving concomitant L-thyroxine, but without an accompanying increase in TSH. No specific data were provided to support this observation.

Because of the histopathology findings in rats exposed to quetiapine chronically, the available autopsy reports for patients who expired during clinical trials were reviewed for evidence of histologic changes in the thyroid. Patient 0048/0007/0703, a 92 year old male who died of respiratory related causes after receiving quetiapine for 191 days, at autopsy had a thyroid gland with a nodular goiter and a microscopic papillary carcinoma. Patient 0014/0043/4304, who died suddenly while receiving haloperidol in a clinical trial, at autopsy had a small papillary carcinoma of the thyroid. Patient 0031/0021/2104, who drowned while receiving treatment that is still blinded, at autopsy had an enlarged thyroid with a cystic mass in the left lobe. No other autopsy reports mentioning the thyroid were available (only a summary report was available for patient 0012/0091/9103). With so few cases, inferences are not possible regarding histologic findings in the thyroid gland.

Zeneca has proposed that the pattern of thyroid function test findings for quetiapine is similar to those found with phenytoin and carbamazepine, and thus of no great clinical consequence. Recently it has been proposed that the observed decrease in free T4 and T3 in patients receiving these anticonvulsant drugs is actually a laboratory artifact. The usual assay for these hormones involves dilution of the serum prior to measurement of the free hormone levels. Surks and DeFesi (JAMA 1996;275:1495-1498) determined that free hormone levels in patients receiving these drugs were normal when measured without dilution of the serum, but were low when the serum was diluted for the standard assay technique. Their conclusion was that in undiluted

serum the drugs competitively displace thyroid hormones from binding proteins; when the samples are diluted in vitro the equilibrium is altered, displacement is reduced and the result is underestimated free hormone levels. In fact, one of Zeneca's consultants (Dr. Toft, 4/14/97 submission) suggested assaying free T4 with a different technique (i.e., the Amerlite-MAB technique); I am not aware that Zeneca has done so.

Consultation was requested from the Division of Metabolism and Endocrine Drug Products regarding the thyroid hormone abnormalities observed with quetiapine. Dr. Jean Temeck responded to the consult; please refer to her review dated 5/29/97. For her review, the sponsor made a special submission of individual patient data (3/27/97). Additionally, the sponsor provided a review of thyroid data including reports from two consultants, prepared for the U.K. Committee on Safety of Medicines (4/14/97). Dr. Temeck concluded that quetiapine was associated with decreased total T4 (TT4) and free T4 (FT4), not accounted for by concomitant drugs that might have affected thyroid function (e.g., lithium). These changes were dose related. She indicates that the observation that the majority of changes in TT4 and FT4 were not accompanied by increased TSH is consistent with a peripheral mechanism. Dr. Temeck noted that it might be reasonable to monitor thyroid function in patients receiving quetiapine who are at risk for hypothyroidism (either by virtue of past history of hypothyroidism, or a family history).

In summary, quetiapine treatment is associated with decreased thyroxine (both free and total) in a dose dependent manner. The decreases are rarely associated with an increase in TSH and infrequently associated with frank clinical hypothyroidism. The clinical significance of these abnormalities is therefore uncertain. The mechanism is unknown but it is possible that it is related to the assay method employed.

Weight Gain

In short term placebo controlled trials, roughly 23% of quetiapine patients experienced clinically significant weight gain (increase of 7% or more), compared to approximately 6% of placebo patients, a statistically significant difference. In these trials, quetiapine patients had a mean weight gain of 2.3 kg at the end of treatment compared to 0.1 kg for placebo. Complete data is displayed in appendix tables 8.1.7.3.1 and 8.1.7.3.2. In the short term fixed dose study 0013, and the long term fixed dose study 0015, weight gain reported as an adverse event showed a statistically significant relationship to dose. There was only one patient receiving quetiapine who discontinued with weight gain (as a contributing factor to withdrawal, along with somnolence and abdominal distension): in trial 5077IL/0012, Subject UK-0007/0708, a 37 year old female.

Cholesterol and triglycerides

Plasma triglyceride and cholesterol levels were obtained in certain of the placebo controlled trials, but these were not necessarily fasting levels. Expressed as percent change from baseline, the results show a mean increase from baseline of 11% for cholesterol and 17% for triglycerides with quetiapine treatment, without similar increases in the placebo group. These data are displayed in appendix table 8.1.6.3.1b.

In dogs and monkeys, quetiapine was associated with a decrease in cholesterol levels, attributed to inhibition of cholesterol biosynthesis. In humans, the data are more consistent with an increase in cholesterol, although fasting blood concentration data would be more reliable. It should be recalled that increased cholesterol concentrations are associated with clinical hypothyroidism. Cardiovascular risk is believed to be related to cholesterol levels in a continuous manner; i.e., there is no threshold for the increase in risk associated with an increase in serum

cholesterol.

Prolactin

Hyperprolactinemia is commonly associated with neuroleptic treatment and is attributed to dopamine blockade in the hypothalamus. In the quetiapine animal chronic toxicity studies, prolactin concentrations were elevated in rats and in male monkeys, but not in female monkeys or dogs. The only patient in the primary integrated database to have prolactin increase reported as an adverse event was receiving chlorpromazine. No patients withdrew because of hyperprolactinemia. In the quetiapine short term placebo controlled trials, mean prolactin concentrations for quetiapine subjects actually decreased, as they did with placebo. No quetiapine patients in this pool of placebo controlled clinical trials had a prolactin concentration above the criterion value of 100 ug/l., although 3.1% of quetiapine patients had a shift in prolactin concentration from normal to high with treatment compared to 1.6% of placebo patients. Study 0013 affords an opportunity to assess the change in prolactin concentrations by quetiapine dose, with placebo and haloperidol as comparison treatments. The table below displays prolactin data from study 0013.

TABLE Analysis of covariance of change from baseline in prolactin concentrations (mg/L) at final evaluation, Study 0013 (adapted from sponsor's study report)

	Treatment group						
	Quetiapine					Haloperidol	Placebo
	75 mg (n = 19)	150 mg (n = 25)	300 mg (n = 31)	600 mg (n = 28)	750 mg (n = 28)	12 mg (n = 24)	(n = 19)
Baseline mean	10.00	17.12	12.03	9.93	17.25	9.50	11.84
LS mean change (SE)	-0.51 (2.85)	-2.10 (2.50)	-0.21 (2.23)	-0.76 (2.35)	-1.93 (2.36)	18.30* (2.54)	1.99 (2.84)

*Significantly different from placebo group
LS = least squares SE = standard error

In the data shown above from study 0013 there was an increase in prolactin concentrations for the haloperidol group but not for any quetiapine group. It may be that the decreases from baseline that were observed reflected prolactin elevation at baseline arising from the patient's previous neuroleptic therapy. With the aid of the Seroquel CANADA data review function (trial 0013 data set n_prolac, imported to JMP statistical application), I was able to subset the prolactin data from this study by sex, and there did not appear to be significant sex differences in the mean changes from baseline to endpoint. This is in contrast to the animal data noted above.

In the active controlled study 0007, mean prolactin concentrations did not increase for the chlorpromazine group or the quetiapine group, although this would have been expected for the chlorpromazine group at least.

On balance, quetiapine treatment does not appear to have a very robust effect on plasma prolactin concentrations, from these clinical data. Conceivably, however, a modest effect on prolactin could be obscured because many of the patients in the clinical trials were previously receiving dopamine blocking drugs.

Neuroleptic Malignant Syndrome

Two patient receiving quetiapine had episodes consistent with neuroleptic malignant syndrome (NMS), a hypermetabolic drug induced state associated with neuroleptic use. These two cases are summarized below.

Table Summary of possible NMS cases with quetiapine

Trial;subject	age	sex	quetiapine dose (mg) and duration	concomitant drugs	comments
5077IL/0012, UK-0049/4903	33	f	50 mg/d X 4 d	levothyroxine	Ridigidy, unresponsiveness, drooling, tachypnea, tachycardia, creatine kinase (ck) peaked at 1131 iu/l. Recovered after intensive care admission with dantrolene, bromocriptine and phenytoin therapy. Dx was NMS versus catatonia.
5077IL/0015, US-0009/0901	36	m	300 mg/d maximum x 13 d	benztropine	Altered mental status, rigidity, catatonia, tachycardia to 131 bpm, leukocytosis, fever, CK=2050. Recovered after hospitalization; treated with haloperidol afterwards.

There were no similar cases among patients receiving control group therapies. In my judgement, it is reasonable to label these cases as possible NMS. These two cases represent an incidence of 8.4 per 10,000 patients exposed to quetiapine, or 2.3 per 1000 patient years of exposure.

8.2.4.3 Adverse metabolic and endocrine system events considered unlikely to be related to quetiapine

Three patients had serious adverse events involving glucose dysregulation:

Trial and Subject	Event and Comments
5077IL/0048, Subject US-0007/0706	hypoglycemia (Suspected inadvertent administration of hypoglycemic agent by staff at the subject's nursing home)
5077IL/0012 OLE, Subject 0093/9304	Hyperglycemia in a diabetic female
5077IL/0013 OLE, Subject 0001/0109	Hyperglycemia in a 44 y.o. male with past history of hyperglycemia

Three patients had serious adverse events involving electrolyte abnormalities:

5077IL/0048, Subject US-0007/0714	Dehydration in an elderly female with dementia
5077IL/0013 OLE, Subject US-0006/0613)	Hyponatremia and convulsion
5077IL/0013 OLE, Subject 0023/2312	Water intoxication

Polydipsia is a common problem among chronic schizophrenic patients.

8.2.5 Musculoskeletal

8.2.5.1 Adequacy of assessment of musculoskeletal system

No formal evaluations of the musculoskeletal system were incorporated in the clinical trials, to my knowledge, other than general physical examinations. However, I believe this was reasonable.

8.2.5.3 Adverse events considered related to quetiapine

Falls and Fractures

Three patients had fractures associated with postural hypotension or syncope (events discussed under Cardiovascular system). A 58 year old female fainted while on quetiapine and fractured an ankle (5077IL/0012, Subject UK- 0005/0501); similarly, a 46 year old female fractured a bone in her foot with a syncopal episode (5077IL/0015 OLE, Subject 0019/1903). A 58 year old female with treatment emergent postural hypotension fell and fractured her ankle (5077IL/0012, Subject UK-0005/0501). syncope is discussed under cardiovascular events.

Other such events, however, were not so clearly linked to orthostasis. An 89 year old woman fell and sustained an intertrochanteric hip fracture; the cause was uncertain (5077IL/0048, Subject 0006/0601) but could have been drug related. Likewise, in study 5077IL/0048, Subject US-0007/0714, a 74 year old woman with dementia, fell and lacerated her scalp with no clear precipitant. In study 5077IL/0015, Subject US-0030/3002, a 65 year old man receiving quetiapine 75 mg/d, fell and hit his head on a sink sustaining head trauma and facial injuries requiring hospitalization. In study 5077IL/0012 OLE, Subject 0059/5907, a 45 year old man, fell without an obvious cause and sustained oral and dental injuries and was discontinued from quetiapine.

Altogether, there were a total of 20 adverse events coded as pathological fracture in the primary integrated database; all occurred in quetiapine treated patients. Since hip fracture in the elderly can be a particularly significant injury, the electronic database was searched (data set adverse from trial category 4msudbol) to identify patients 65 years old and older who sustained hip fractures. There were a total of 4 such patients (5077IL/0048, Subject 0006/0601, 5077IL/0048, Subject US-0013/1303, 5077IL/0048, Subject US-0002/0208, 5077IL/0048, Subject US-0013/1307). Ignoring for the moment the fact that some cases may not have been related to the drug (see below), and combining males and females, with 190 patients over 64 years old contributing 84.5 patient years in the quetiapine primary integrated database (calculated with CANADA electronic data set 4msudbol/ddemog), these cases represent an incidence of 2.1%, or 4.7 per 100 patient years, for hip fracture associated with quetiapine treatment. For reference, Weintraub and Handy (Clin Pharmacol Ther 1993; 54(3):252-6) reported data from New York State showing a rate of hip fracture in the general population aged 75 years and older of approximately 1.4 per 100 person years for women and 0.7 per 100 person years for men. While hip fracture is not rare in this age group, it is plausible that quetiapine's sedative and/or orthostatic effects may have contributed to falls among the elderly.

8.2.5.4 Adverse musculoskeletal events considered unlikely to be related to quetiapine

Trial/subject	Event and comments
5077IL/0048, Subject US-0013/1307	66 year old female; hip fracture after falling out of bed while hospitalized for evaluation after a seizure
5077IL/0048, Subject US-0013/1303	71 year old male with dementia; fell over his dog and fractured hip
5077IL/0048, Subject US-0002/0208	75 year old female with dementia fractured her femur; fall attributed to parkinson's disease

5077IL/0048, Subject US-0007/0713 80 year old male attempted to climb out of hospital bed and fractured fibula

5077IL/0013, Subject US-0026/2614 30 year old male fractured malleolus during a fight

5077IL/0015 OLE, Subject US-0026/2614 65 year old male tripped and fractured his arm while boarding a bus

In addition, one placebo patient in a Japanese trial sustained a femur fracture with a syncopal episode (H-15-21, Subject 9-1).

8.2.6 Nervous

8.2.6.1 Adequacy of assessment of nervous system events

Adverse nervous system events were reported spontaneously in the usual manner. In addition, the sponsor employed the Simpson-Angus scale for measuring extrapyramidal symptoms (EPS), and the Abnormal Involuntary Movement Scale (AIMS) for assessment of dyskinesia. Zeneca also analyzed the use of anti-EPS medication during clinical trials. In my view, this was an adequate assessment of the nervous system.

8.2.6.2 Nervous System Adverse events Considered Possibly, probably, or Definitely Related to Quetiapine

Extrapyramidal symptoms (EPS)

The 6 week fixed dose placebo controlled trial 0013 affords an opportunity to examine dose response with respect to EPS. The table below presents the results from the Simpson EPS rating scale by dose group.

TABLE: Simpson scale: Mean change from baseline to final evaluation in total score, Trial 0013 (adapted from sponsor's ISS)

	Treatment group						
	Quetiapine					Haloperidol	Placebo
	75 n = 50	150 mg n = 46	300 mg n = 49	600 mg n = 49	750 mg n = 49	12 mg n = 49	n = 50
Baseline mean (SD)	12.8 (4.2)	12.8 (3.6)	13.0 (4.1)	13.4 (4.6)	13.4 (4.0)	12.6 (3.2)	12.9 (3.7)
Change from baseline mean (SD)	-1.0 (3.2)	-1.2 (2.7)	-1.6 (2.6)	-1.8 (3.6)	-1.8 (3.9)	1.1 (5.6)	-0.6 (3.3)

Note the absence of a dose effect. There was a slight mean worsening of scores for the haloperidol group. The sponsor also analyzed the use of anti-EPS medication (benztropine) during the study by dose group, as shown below.

TABLE Number of subjects receiving benztropine mesylate for EPS concurrently with quetiapine, haloperidol, or placebo in Trial 0013 (adapted from sponsor's ISS)

	Quetiapine				Haloperidol	Placebo	
	75 mg (n = 53)	150 mg (n = 48)	300 mg (n = 52)	600 mg (n = 51)	750 mg (n = 54)	12 mg (n = 52)	(n = 51)
Number of subjects (%)	6 (11)	5 (10)	4 (8)	6 (12)	6 (11)	25 (48)	7 (14)

The most use of benztropine was among the haloperidol group. The number of quetiapine treated patients who used benztropine was similar across dose groups and was comparable to the placebo group.

EPS was not a common drug related adverse event in the short term placebo controlled trials, nor was it among the adverse events most often accounting for withdrawals.

The adverse event dystonia showed a trend for a dose response ($p < 0.10$) in the long term relapse prevention trial (0015).

Examination of the sponsor's compilation table of dropouts from quetiapine treatment reveals that for the primary integrated database ($n = 2387$), the following numbers of patients discontinued for EPS adverse events: akathisia, 2; dystonia, 1; EPS unspecified, 1; hypokinesia, 1; movement disorder, 1. These numbers are taken from controlled and uncontrolled studies; Although precise comparisons to control groups are not possible due to the difference in exposure duration, these cases represent relatively few of the adverse events leading to withdrawal in the primary integrated database.

One patient in a Japanese trial developed akathisia that was deemed a serious adverse event, while receiving quetiapine 75 mg/d (H-15-22, Subject 6-1). Another Japanese patient developed choreoathetoid movements which resolved after discontinuation of quetiapine (H-15-22, Subject 47-1).

In sum, quetiapine's propensity to induce EPS appears modest.

Tardive Dyskinesia

Tardive dyskinesia (TD) is a movement disorder that develops with chronic neuroleptic therapy; consequently, evaluation of the hazard associated with a new antipsychotic drug is difficult from a premarketing database that comprises a substantial proportion of short term exposure. Another complication results from the fact that many patients have a previous history of exposure to neuroleptics, making attribution to a particular drug difficult if TD is observed.

To evaluate tardive dyskinesia manifestations associated with quetiapine treatment the sponsor conducted AIMS assessments, as noted above. For tardive dyskinesia, it is most appropriate to consider long term treatment data; accordingly, the findings from the one year relapse prevention study are shown below.

TABLE Frequency distribution for change from baseline in AIMS total score at the final evaluation, Study 0015 (adapted from sponsor's study report)

	Treatment group			
	75 mg n(%)	Quetiapine 300 mg n(%)	600 mg n(%)	Haloperidol 12 mg n(%)
Change from baseline				
-3 or less	12 (17)	12 (17)	13 (18)	5 (14)
-2 to -1	15 (22)	10 (14)	16 (23)	5 (14)
0	28 (38)	27 (38)	27 (38)	17 (46)
+1 to +2	4 (6)	6 (8)	10 (14)	1 (3)
+3 or greater	12 (17)	17 (24)	5 (7)	9 (24)
Total	69 (100)	72 (100)	71 (100)	37 (100)

Here, the pattern of changes in AIMS scores was fairly similar for all 3 doses and for haloperidol. However, haloperidol is a drug that is accepted to cause TD, so negative findings with quetiapine in this trial are not completely reassuring given the absence of a positive finding with haloperidol.

One patient (0015/0034/3404, a 47 year old man) discontinued quetiapine 600 mg daily because of treatment emergent TD which developed over several months. The patient had a history of TD with haloperidol, but had no manifestations of TD at the beginning of quetiapine treatment. In a similar case, patient 0027OLE/0001/0103 had worsening of buccolingual movements during quetiapine treatment. Also, a Japanese patient (H-15-23/010/11-6, a 61 year old woman) developed TD after 75 days on quetiapine (maximum dose 750 mg). This patient, although not naive to neuroleptics, did not have TD at baseline.

In sum, quetiapine treatment has been associated with TD in some patients. There is inadequate data from which to estimate a cumulative incidence at present. Assessment of this adverse drug reaction is further complicated by the fact that many patients had previous exposure to other neuroleptics.

Somnolence

In the pool of short term controlled studies, somnolence was a common and drug related adverse event, with an incidence of 17.5% for quetiapine compared to 10.7% for placebo ($p=0.0005$). Somnolence did not show a statistically significant dose response relationship in either the long term fixed dose study (0015) or the short term fixed dose study (0013). Somnolence was the most frequently reported adverse event leading to premature discontinuation ($n=27$ for the primary integrated database of 2387 quetiapine treated patients.) One patient, a 36 year old woman (0014/0053/5307), had to be hospitalized because of sedation but apparently recovered after a dosage reduction. Another patient (0012/UK0070/7006), a 21 year old man, had somnolence so severe on his first day of quetiapine treatment that he awoke only to painful stimuli; an EEG showed rapid activity consistent with a drug reaction, and he recovered within a few hours.

Convulsions

The table below summarizes patients who had one or more seizures while receiving quetiapine. The primary source for this list was the sponsor's patient narratives for serious adverse events; all convulsions were considered serious adverse experiences by the sponsor.

Table Summary of seizure (sz) cases with quetiapine treatment

Trial;subject	a g e	s e x	quetiapine dose (mg) and duration	concomitant drugs	comments
0048/0013/1306*	64	f	≥50 d ≥200 mg	Carbamazepine Tenormin, iron	3 seizure episodes during trial
0048/0013/1307*	66	f	5 mo 150 mg	numerous	Tonic clonic sz; recent DVT
H-15-22, 58-4	40	m	8 d/75 mg		"severe seizure"
0033OLE-0002/0001*	34	m	5 d	clonazepam (dose recently reduced)	Sz attributed to clonazepam withdrawal
0048/ 0001/0109*	65	m	500 mg 29 wk		Patient with alzheimer's dementia
0048/0001/0115*	70	m	6 days after d/c quetiapine	chloral hydrate, lorazepam, haloperidol	Sz while hospitalized for CVA
0048/0006/0601*	89	f	75 mg 12 wk	numerous	Patient with dementia; treated with DPH and remained in study
0012/0005/0543*	23	f	800 mg 3 mo		Newly diagnosed with temporal lobe epilepsy
0012 OLE/0036/3604*	55	f	700 mg 19 mo		Diagnostic evaluation unrevealing
0031 OLE/0023/2302	39	m	600 mg d/c 2 days prior to sz	Lorazepam, thiothixene, clonazepam	3 tonic-clonic sz over 2 days
0007/0013-0007	24	m	500 mg 9 d		One sz. quetiapine continued. EEG normal.
0012/0029/2902*	55	f	4 d	flunitrazepam, diazepam, lormetazepam	
0012/0042/4203*	34	f	2 d	temazepam	Past history of seizure; completed 6 weeks without any more seizures
0015/0024/2408	38	f	75 mg 2 d	phenylpropanola mine	Syncope, hit head, later had seizure
0014/0059/5903*	50	m	500 mg 8 d		Grand mal convulsion; history of previous sz attributed to hypoglycemia, but serum glucose normal at time of this sz
0033OLE/0002/0001*	34	m	800 mg 5 mo		Past history of seizure; two seizures while on quetiapine (one following clonazepam withdrawal)
0007/0025/0009	27	f	550 mg 7 d		Past history of sz with chlorpromazine

0035/0001/0106	29	m	400 mg IR formulation 7 d	recent clozapine	Phase i study
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* In primary integrated database

Patient 0013OLE/0006/0613, who had a seizure while hyponatremic, is described under metabolic adverse events. In addition, patient 0048/0007/0702, a 76 year old female, had unexplained syncope which was felt to have possibly been a seizure based on an EEG finding of sharp waves after the event and a Holter monitor evaluation negative for arrhythmia.

From the above table, it will be seen that 12/2387 (0.5%) of quetiapine exposed patients in the phase II-III primary integrated database experienced at least one seizure. This incidence is comparable to the incidence in the control groups (see table in section 8.1.4).

Hostility

A search of the phase II-III primary integrated database (electronic data set 4msudbol/adversev) for the Costart term hostility as an adverse event deemed serious revealed only five such cases among quetiapine treated patients. (0014/0014/1444; 0014/0064/6410; 0048/0004/0405; 0048/0007/0709; 0048/0011/1102). No such events were reported among the control group patients. These data do not suggest that quetiapine treatment has a significant propensity to induce hostile behavior.

Suicidality and Depression

Please refer to the sponsor's data presented in section 8.1.4 above. Based on the sponsor's search of the ISS database (prior to the safety update), the rate of suicidality was actually lower with quetiapine than with the active control treatments or placebo. Of course, there is a potential source of bias if patients receiving open label quetiapine tended to be more stable than the acutely ill patients in the controlled trials. Similarly, the event rate for non-suicidal depression, listed in the sponsor's table as depression, was lower for the quetiapine treated patients, although the same bias is possible here as well.

Quetiapine treated patients 0012/0023/2303 and 0012 OLE/0067/6702 committed suicide, as well as one patient whose treatment remains blinded (please refer to appendix table 8.1.1.1).

8.2.6.3 Adverse nervous system events considered unlikely to be related to quetiapine

The following lists such events. I have excluded serious adverse events that appeared to me to represent manifestations of a patient's underlying psychotic illness, such as agitation and the like. Not listed here, but shown in appendix table 8.1.1.1, are the quetiapine patients who died from cerebrovascular disease: 0012/0091/9103, and 0012OLE/0080/8013. Of course, if quetiapine is thrombophilic, as discussed previously under Cardiovascular System, deaths from stroke could be drug related.

Trial/subject	Event and comments
0048, Subject US-0013/1302	66 year old male collapsed due to weakness but did not have syncope; continued quetiapine
0012 OLE, Subject UK-0005/0502	38 year old female with schizophrenia hospitalized for manic reaction; was receiving paroxetine
0014 OLE Subject 0014/1402	32 year old male suffered concussion in an assault. Later hospitalized for anxiety
0012 OLE Subject UK-0005/0506	41 year old female diagnosed as paranoid schizophrenic was hospitalized for mania, but resumed quetiapine without further manic symptoms
/0048, Subject US-0007/0713	80 year old man with Alzheimer's dementia hospitalized for aggression and agitation.
0048, Subject US-0007/0714	74 year old female with Alzheimer's dementia, while hospitalized for dehydration had a staring spell; neurological evaluation was negative but the patient was treated empirically with carbamazepine.
0012 OLE, Subject UK-0032/3203	31 year old male with paranoid schizophrenia hospitalized for mania
0013, Subject 0022/2204	65 year old male developed aphasia and dysarthria which resolved and were attributed to vertebrobasilar insufficiency. Blind not broken.
0012, Subject UK-0052/5204	28 year old female with schizophrenia hospitalized for insomnia
0014, Subject UK-0053/5312	46 year old female with chronic schizophrenia hospitalized for anxiety
0012 OLE, Subject 0087/8703	43 year old female with sciatica
0048, Subject US-0010/1015	66 year old female with bipolar disorder and multiinfarct dementia developed confusion, sedation, tachycardia, hypertension; also receiving lithium and clonazepam
0014 OLE/0064/6401	30 year old male with schizophrenia hospitalized after exposing himself in public
0012, Subject UK-0001/0104	44 year old male with malignant brain tumor (ependymoma) which became symptomatic on day 4 of quetiapine
0014 OLE, Subject 0069/6903	40 year old male diagnosed with brain tumor (probable ependymoma of 3rd ventricle) after 11 days of quetiapine
0015, Subject US-0003/0311	34 year old male hospitalized for alcohol and cocaine abuse
0048/0003/0307	75 year old man suffered a transient ischemic attack and was hospitalized for evaluation
0012/0029/2901	50 year old male with subdural hematoma

8.2.7 Respiratory

8.2.7.1 Adequacy of assessment of respiratory system events

To my knowledge, there were no chest X-rays or other special assessments of the respiratory system performed. Respiratory system adverse events were reported in the usual manner during clinical trials. In my opinion, this was adequate.

8.2.7.2 Respiratory System Adverse events Considered Possibly, probably, or Definitely Related to Quetiapine

There were no respiratory adverse events among the common and drug related events in the short term controlled trials.

Pneumonia

There were 3 deaths from pneumonia associated with quetiapine treatment: patients 0048/0007/0703 and 0048/0007/0708, as shown in appendix table, and an additional patient who died with pneumonia more than 30 days after quetiapine treatment had ended, patient 0048/0017/1703; in the last case the pneumonia began while the patient was receiving quetiapine.

The following table describes nonfatal cases of pneumonia during quetiapine clinical trials.

Table Summary of nonfatal pneumonias deemed serious adverse events associated with quetiapine (one patient not un-blinded)

Trial;subject	age	sex	quetiapine dose (mg) and duration	concomitant drugs	comments
50771L/0031, US-0022/2204	52	m	BLINDED	glipizide,metformin, chloral hydrate, lorazepam	Left Lower Lobe Pneumonia
50771L/0015OLE, US-0026/2614	65	m	600 mg 4 mo	lorazepam docusate, theophylline	Left lower lobe pneumonia, sepsis, pneumoperitoneum of unknwn etiology
50771L/0048, US-0001/0114	87	m	600 mg 9 wk	betaxolol, carbidopa,ldopa,bromocriptine , chloral hydrate, lorazepam	Right lower lobe pneumonia Pt with dementia
50771L/0048, US-0003/0308	80	f	450 mg 6 mo	ranitidine, Kcl, nifedipine, furosemide, ntg	pnuemonia
50771L/0012OLE, UK-0042/4201	41	m	450 mg 8 mo		Bronchopulmonary infection required hospitalization
50771L/0061 US-0001/0103	33	m			viral pneumonia, and pyelonephritis; discontinued
50771L/0013OLE, CN-0022/2214	50	m	700 mg 79 d	Lovastatin, glyburide, lorazepam, sulindac, insulin	pnuemonia
204636/0008, UK-0019/0001	60	m	250 mg 7 d		bronchopneumonia

In addition, a submission to the Seroquel IND 7/11/96 noted 3 additional cases of pneumonia in quetiapine treated patients from after the NDA cutoff date (patient 0302 in study 0031, and patients 0308 and 0817 in study 0048).

Because pneumonia in the elderly is of particular concern, and because it has been proposed that neuroleptic treatment can be associated with aspiration pneumonia, the rate of pneumonia in quetiapine treated patients aged 65 years and older was calculated for the primary integrated

database. A total of 7 cases with the costart term pneumonia among patients of this age were identified in the primary integrated database(electronic search using CANADA data set 4msudbol:adversev). In addition, patient 0048/0007/0703 was found at autopsy to have had pneumonia even though pneumonia was not noted as an adverse event by the investigator. With a total of 190 quetiapine patients in this age range contributing 84.5 patient years of exposure, these 8 cases yield an incidence for pneumonia of 4.2 per 100 patients or 9.5 per 100 patient years for patients 65 years and older.

It has been suggested that neuroleptic use can increase the risk of pneumonia, perhaps through impairing swallowing with a consequently greater risk of aspiration (Bazemore PH, Tonkonogy J, Ananth R, *Dysphagia* 6:2-5, 1991). This may be the case for quetiapine.

8.2.7.3 Adverse respiratory events considered unlikely to be related to quetiapiene

Patient	Comments
0048 /0007/0712	64 year old man died with respiratory failure, aspiration in setting of progressive supranuclear palsy (after NDA cutoff date)
0048/0002/0201	70 year old male suffered exacerbation of chronic obstructive pulmonary disease.

8.2.8 Dermatological

8.2.8.1 Adequacy of assessment of dermatologic events

There were no particular diagnostic tests employed other than general physical examination to address dermatologic events. However, in my opinion this was adequate.

8.2.8.2 Adverse dermatologic events considered related to quetiapine

Rash was not a common, drug related adverse event in the quetiapine placebo controlled trials. Neither was the incidence of rash and allergic events increased over the control groups when expressed in terms of patient years, according to the sponsor's analysis (see table under section 8.1.4 above). Nonetheless, certain individual cases of rash that led to discontinuation of treatment were consistent with a drug etiology, as shown below.

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ON ORIGINAL**

Table Summary of rashes leading to discontinuation of quetiapine

Trial;subject	age	s e x	quetiapine dose (mg) and duration	concomitant drugs	comments
0006, Subject US-0007/0703	32	f	75 mg x 2 d	lorazepam, oral contraceptive, chloral hydrate	Papular rash all extremities, resolved after 4 days off quetiapine with antihistamine tx.
204636/0008, Subject US-0014/1406	59	m	13 d	chloral hydrate, lorazepam, acetaminophen	Nonpruritic, maculopapular rash on trunk and all extremities; concomitant lower extremity edema. Skin biopsy: perivascular lymphocytic infiltrate, possible leukoclastic vasculitis. Resolved after drug stopped.
5077IL/0015, Subject US-0024/2407	31	m	150 mg x 40 days	Albuterol, acetaminophen	Pruritic blotchy rash on trunk and extremities with leukocytosis and eosinophilia; rash deemed an allergic response by dermatologist. Treated with antihistamine and topical steroid.
5077IL/0013 OLE, Subject 0013/1304	21	m	500 mg x 7 days	vitamins, acetaminophen	Non pruritic, erythematous macular rash on trunk and extremities, resolved several days after drug stopped.
5077IL/0014 OLE, Subject 0003/0341	31	m	300 mg x 43 days	trifluoperazine	facial rash, no further details

Thus, while there was not a statistically apparent association of rash with quetiapine treatment in short term placebo controlled trials, certain of the clinical characteristics of the individual cases noted above suggest a relationship to drug.

8.2.8.3 Adverse dermatologic events considered not likely to be related to quetiapine

Trial and subject	Event
5077IL/0012 OLE, Subject 0001/0119	Withdrawn for rash that proved to be scabies (Sarcoptes scabiei)
5077IL/0015, Subject US-0034/3411	hospitalized for treatment of cellulitis
5077IL/0048, Subject US-0008/0807	hospitalized for treatment of cellulitis

8.2.9 Special Senses

8.2.9.1 Adequacy of assessment of special senses

Mindful of the finding of cataracts associated with quetiapine treatment in dogs, the sponsor incorporated ophthalmologic assessments in the quetiapine clinical development program. This Division made recommendations about these assessments in a letter to the sponsor dated 1/5/90, and ophthalmologic surveillance was also discussed at the End of Phase II meeting with Zeneca. Slit lamp examinations were performed by ophthalmologists or optometrists during the course of many of the trials, with results categorized simply as normal or abnormal. At Canadian sites, a more elaborate rating system was employed, the Lens Opacities Classification Scale

(LOCS III). This requires rating on four scales: cortical cataract, posterior subcapsular cataract, nuclear opalescence, and nuclear color. A normal exam is rated as 0.1, and top (i.e., worst) scores for each scale are up to 6.9. A grand total of 391 quetiapine subjects in controlled clinical studies had at least a baseline and followup slit lamp exam. For haloperidol and placebo treated patients, the numbers were 33 and 122, respectively. Certain open label trials also included slit lamp exams. During the one year controlled study 0015, examinations were obtained roughly every 3 months; given the gradual nature of the development of cataract, the long term study under protocol 0015 was considered the most relevant for evaluation of lens opacities.

The Division obtained consultation on this issue from Dr. Wiley Chambers of the Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550). In his opinion, the sponsor's monitoring for cataracts was inadequate. Please refer to his consult report for details.

8.2.9.2 Adverse special senses events Considered Possibly, probably, or Definitely Related to Quetiapine

Cataracts

Cataracts were associated with quetiapine exposure of 3 months or longer in dogs. The findings included lens opacity after 3 months and development of posterior subcapsular cataracts at 6 months. Zeneca believes this to be the result of inhibition of cholesterol biosynthesis by quetiapine, leading to reduced cholesterol and increased cholesterol precursor sterols in the lens (and the blood). Monkeys did not show this toxicity.

In the pool of all controlled trials, the following numbers of patients had normal pretreatment slit lamp exams and abnormal on-treatment exams:

Quetiapine	11/391 (2.8%)
Haloperidol	1/33 (3.0%)
Placebo	3/122 (2.5%)

Ten of the eleven quetiapine patients with changes were enrolled in study 0015, the one year relapse prevention study.

For the LOCS III score results from placebo controlled trials, there was no clear cut pattern of lens abnormality associated with quetiapine treatment. One limitation of these data is that the majority of scores were obtained in the short term studies, so that late appearing effects would not necessarily be apparent.

With the CANADA data review function, all patients in the Phase II-III primary integrated database with a Costart term of "cataract specified" were identified (from data set 4msudbol: adversev). There were a total of 14/2387 (0.6%) quetiapine treated patients with this adverse event, none out of 206 placebo patients and 1/320 (0.3%) haloperidol treated patients. Expressed in terms of incidence per patient year of exposure, the incidence for quetiapine was 1.6 per 100 patient years, while the incidence for haloperidol was 2.4 per 100 patient years. The mean duration of treatment with quetiapine for these 14 patients was 276 days, and the mean age was 35 years, relatively young for age-related cataracts. For comparison, the overall mean duration of treatment with quetiapine in the phase II-III integrated primary database was 136 days (calculated from dataset 4msudbol:ddemog), and the mean age in the primary integrated database was 40 years. Thus patients with longer exposures were relatively overrepresented

among the patients identified as having cataracts; this could be consistent with a delayed drug effect or it could simply reflect a greater number of eye examinations performed during long term treatment.

Zeneca performed a somewhat broader search of the database for adverse events involving cataract, as shown in the following table.

TABLE Incidence of adverse events of cataract (adapted from sponsor's electronic ISS)**

Quetiapine (n = 2162) SY = 585.1		Quetiapine with safety update (n = 2387) SY = 865.3		Haloperidol (n = 320) SY = 42.3		Chlorpromazine (n = 100) SY = 9.2		Placebo (n = 206) SY = 14.6	
k (%)*	ER	k (%)*	ER	k (%)*	ER	k (%)*	ER	k (%)*	ER
15 (0.7)	2.6	16 (0.7)	1.8	1 (0.3)	2.4	0	0	0	0

*Number of subjects with adverse event (%).

SY = Subject years of follow up

ER = Event rate per 100 subject-years exposure

**cataract= cataract , cataract specified, eye disorder for investigators' terms that indicate cataract

The sponsor's search included more events than just those categorized under "cataract specified." The results were not markedly different from the results of the search I performed with the CANDAs, however. Note that although the event rate for haloperidol exceeds that for quetiapine, this is because a single haloperidol patient developed cataract (patient 0015/035/03502, who had diabetes, underwent cataract surgery.) Diabetes is, of course, a risk factor for cataract.

With the help of Dr. Greg Burkhart, the relative risk and confidence limits were calculated for the adverse event of cataracts in study 0015, the one year controlled trial. The relative risk for the adverse event of cataract with quetiapine 600 mg/d compared to haloperidol was 1.4 (95% confidence limits 0.12-74 by Fisher exact), and for quetiapine 600 mg compared to the quetiapine 75 mg and 300 mg groups combined was 4.4 (95% confidence limit 0.35-228). Thus, the point estimate is consistent with an increased risk of cataracts, but the confidence limits are large and include the possibility of a reduced risk.

Dr. Chambers, in his consult report, notes that the small number of patients in the control groups makes comparisons of little value. Instead, he considered the proportion of patients receiving quetiapine who exhibited worsening on the LOCS III scale compared to patients whose scores improved; for both controlled trials and uncontrolled trials more patients worsened than improved. Reasoning that equal numbers would have worsened and improved by chance alone, Dr. Chambers concluded that these data are consistent with a drug effect.

Dr. Chambers has recommended that labeling for quetiapine carry a statement under Warnings regarding cataract development, and requiring periodic slit lamp exams for patients treated with quetiapine. Please refer to his consultation report for details.

8.2.9.3 Adverse special senses events considered unlikely to be related to quetiapine

There were no serious adverse events among quetiapine treated patients involving the special senses.

8.2.10 Genitourinary

8.2.10.1 Adequacy of assessment of genitourinary events

Clinical laboratories obtained during the quetiapine development program included urinalyses and assessment of BUN, creatinine and electrolytes. Spontaneously reported adverse events involving the genitourinary (GU) system were recorded as such. I am not aware of any special studies performed regarding the effects of quetiapine on renal function. In my opinion, the assessment of the GU system was less than adequate in one respect: for the two quetiapine treated patients who developed acute renal failure, the clinical information provided was very limited.

8.2.10.2 Adverse genitourinary events considered Possibly, probably, or Definitely related to quetiapine

There were no common and drug related adverse GU events in the short term placebo controlled trials; neither was any GU adverse event among the more common reasons for premature discontinuation. Findings from the pool of short term placebo controlled trials did not suggest any changes in serum BUN or creatinine, or urinalysis parameters associated with quetiapine treatment.

Nonetheless, two cases of acute renal failure were reported with quetiapine, in one case accompanied by profound anemia raising the possibility of renal failure secondary to hemolysis. While there is no specific evidence causally linking these cases to quetiapine, the meager clinical data provided do not establish a non-drug related cause for the renal failure, and so I have included them here.

Renal Failure

0048/0002/0201

70 year old man with congestive heart failure, hospitalized with acute renal failure attributed to concomitant trimethoprim-sulfa by sponsor. Patient simultaneously had profound anemia (hct 20), with total bilirubin of 8.6 umol/l at the time.

0012/0019/1903

33 year old white male, acute renal failure with hyponatremia and increased serum creatinine; renal function improved several days after d/c of quetiapine with after oral rehydration. Renal ultrasound was normal.

8.2.10.3 Adverse genitourinary events considered not likely to be related to quetiapine

Urinary retention

0012 OLE 0093/9308

20 year old female hospitalized for urinary retention; resolved 12 days after the d/c

0017 OLE US-0004/0401

85 year old male required foley catheter for urinary retention; resolved after drug d/c

0007, UK 0031/0003

42 year old female withdrawn for urinary retention

Other

0048 US-0008/0804

Elderly female developed urosepsis

0061 US-0001/0103

33 year old male developed viral pneumonia and pyelonephritis

8.2.11 Miscellaneous

8.2.11.1 Adequacy of assessment of miscellaneous adverse events

Not applicable.

8.2.11.2 Miscellaneous adverse events Considered Possibly, probably, or Definitely Related to Quetiapine

There were none.

8.2.11.3 Miscellaneous adverse events considered unlikely to be related to quetiapine

Deaths

Please refer to Appendix tables 8.1.1.1 and 8.1.1.1a.

A 40 year old male patient in a Japanese study was found dead; the investigator suspected water intoxication as a cause of death. The patient was receiving haloperidol.

The following deaths involved malignancy:

Patient 0015OLE/0005/0514 died from metastatic carcinoma with an unknown primary.

A 65 year old female in study 0048 who died from esophageal cancer and sepsis (after the NDA cutoff date).

A 69 year old male died from pancreatic carcinoma in study 0015 (after the NDA cutoff date).

Other:

Patient 0021/2104 in study 0031, whose treatment remains blinded, died from accidental drowning.

Patient 0012/0062/6203 escaped from the hospital and died in a car accident.

Nonfatal events:

Infections

50771L/0012, Subject UK-0034/3404	34 year old female hospitalized for otitis
50771L/0015 OLE, Subject 0005/0509	40 year old female with sepsis secondary to periodontal abscess (not neutropenic)
50771L/0012 OLE, Subject 0034/3404	34-year-old woman hospitalized due to a flare up of chronic otitis
50771L/0014, Subject UK-0044/4402	25-year-old man with hospitalization due to severe ethmoidal sinusitis

Other

50771L/0048, Subject US-0004/0404	75 year old man with syncope; negative work up; possible hypoglycemia (patient was on insulin)
50771L/0048, Subject US-0016/1606	85 year old male underwent hernia repair
50771L/0048, Subject US-0018/1813	78 year old female hospitalized for dehydration
50771L/0015, Subject US-0005/0502	63 year old female with breast cancer

50771L/0012 OLE, Subject 0080/8001	24 year old female had surgery for benign cervical tumor
50771L/0015, Subject US-0027/2706	30 year old male inhaled bleach fumes accidentally
50771L/0014 OLE, Subject 0014/1402	32-year-old man with concussion and fractured nasal bone following assault
50771L/0014 OLE, Subject 0046/4601	25 year old male hospitalized for EtOH intolerance and aggression
50771L/0013 OLE, Subject 0005/0508	40 year old male ingested cleaning fluid (to "get younger")
50771L/0031, US-0009/0903-(blinded)	42 year old male hospitalized with chest pain; MI was ruled out; possible GI etiology

8.3 Summary of Key Adverse Findings

The following is a summary of important adverse events that are considered drug related. Please see the Review of Systems for more detailed data on each of the following adverse drug reactions.

Cardiovascular Adverse events

Postural hypotension and syncope: Postural hypotension was a common and drug related adverse event. Syncope, which is often a related phenomenon, occurred in roughly 1% of quetiapine treated patients.

Tachycardia: There were statistical increases in mean heart rate observed with quetiapine treatment in comparison to placebo, not limited to orthostatic-type changes in pulse.

QT interval prolongation: This was not consistently associated with quetiapine across clinical trials.

Thromboembolic events: There were a number of individual cases of deep vein thrombosis and stroke, raising the possibility that quetiapine treatment may be thrombophilic in certain patients.

Gastrointestinal

Increased liver enzymes: Asymptomatic increased liver enzymes were a common and drug related adverse event. No cases were documented to be symptomatic, although a number of patients were discontinued from quetiapine treatment for elevations in liver enzymes. What is not known, of course, is whether such discontinuations prevented more clinically significant cases of hepatic injury.

Dyspepsia and abdominal pain: These events were found to have a dose dependency in study 0013, and dyspepsia met the definition for common and drug related.

Hemic and lymphatic

Leukopenia/neutropenia: In a few patients, the clinical profile suggested a relationship between quetiapine treatment and decreased neutrophils or leukocytes. Four patients had ANC's less than 500; three recovered while on quetiapine and one was lost to followup but was later seen to be alive and well.

Anemia: Two patients had serious adverse events involving anemia, one with concurrent renal failure raising the possibility of hemolysis. Additional patients had severe anemia that was not considered a serious event. The clinical data provided regarding these cases are insufficient to draw inferences about the causal role of quetiapine treatment (additional information has been requested from Zeneca).

Metabolic and Endocrine

Hypothyroidism: Quetiapine treatment is associated with a decrease in thyroxine, but the clinical significance of this is not clear.

Weight gain: In short term placebo controlled trials, 23% of quetiapine treated patients had a weight increase of 7% or more.

Cholesterol and triglyceride elevation: Expressed as percent change from baseline, placebo controlled short term trial data show a mean increase of 11% for cholesterol and 17% for triglycerides with quetiapine treatment, without similar increases in the placebo group.

Hyperprolactinemia: There was little evidence for an association of quetiapine treatment with prolactin increase.

Neuroleptic malignant syndrome: There were 2 cases of possible NMS with quetiapine treatment.

Musculoskeletal system

Falls and fractures: These events may be tied to postural hypotension. Among patients over age 64, there was an incidence of 2.1%, or 4.7 per 100 patient years, for hip fracture associated with quetiapine treatment.

Nervous

EPS: quetiapine appears to induce generally modest EPS.

TD: quetiapine treatment has been associated with TD in some patients.

Somnolence: Somnolence was a common and drug related adverse event, with an incidence of 17.5% for quetiapine compared to 10.7% for placebo ($p=0.0005$). Somnolence did not show a statistically significant dose response relationship in either the long term fixed dose study (0015) or the short term fixed dose study (0013). Somnolence was the most frequently reported adverse event leading to premature discontinuation.

Convulsion: My review showed that 12/2387 (0.5%) of quetiapine exposed patients in the phase II-III primary integrated database experienced at least one seizure. The sponsor's incidence was somewhat higher (see table in section 8.1.4).

Respiratory

Pneumonia: There were 3 deaths from pneumonia among quetiapine treated patients. Among elderly patients receiving quetiapine, there was an incidence for pneumonia of 4.2 per 100 patients or 9.5 per 100 patient years for patients 65 years and older. Impairment of the gag reflex is a possible mechanism.

Rash: A number of individual cases of rash associated with quetiapine treatment had clinical or histological features suggesting a drug etiology.

Special senses

Cataracts: In preclinical studies there was a clear association between cataracts and quetiapine exposure. In clinical studies, 14 quetiapine patients had "cataract specified" recorded as an adverse event, with a mean age of 35 years among these 14 patients. The relative infrequency of lens abnormalities makes comparisons between treatment groups of limited inferential value. Dr. Chambers from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products has recommended that patients on quetiapine therapy have periodic slit lamp examinations.

Genitourinary

Acute renal failure: This was reported in 2 quetiapine treated patients; available clinical information is insufficient to draw inferences about the role of quetiapine treatment in these cases.

9.0 Labeling Review

I will comment briefly on a few labeling issues.

Clinical Pharmacology: The inclusion of a lengthy discussion of PET study results is questionable, in my view. I am inclined to agree with the statement about lack of prolactin elevation, however.

Clinical Trials: The sponsor has overstated the results at a few points with respect to comparisons that did not achieve statistical significance, but this is generally a balanced presentation.

Warnings: I do not believe that the labeling should suggest a reduced potential for tardive dyskinesia.

Regarding NMS, using the adjective "rare" may be too reassuring and it might be better to state the actual number of possible NMS cases (n=2).

Labeling regarding cataracts and thyroid abnormalities is needed. With respect to cataracts, I believe the labeling should recommend slit lamp examinations as indicated by Dr. Chamber's consult review, unless the sponsor can make a more persuasive case to forgo such monitoring.

The overdose section of labeling requires revision. There have now been 7 reports of quetiapine overdose. The precautions about QT prolongation described in the labeling, which appear to have been adapted from the Risperdal labeling, may be unnecessary for this compound.

11.0 Conclusions

The sponsor has provided evidence from adequate and well controlled studies establishing the efficacy of quetiapine in the treatment of acutely ill schizophrenic patients. There are no safety issues that cannot be addressed with appropriate labeling or that would adversely affect the risk-benefit assessment for quetiapine.

12. Recommendations

This NDA is approvable, in my opinion.

At this time, a request for additional clinical information about patients with certain adverse events is pending. If the sponsor has not responded by the time of the approvable letter, a request should be made in the letter.

The sponsor should be asked to perform an adequate relapse prevention study.

 6/13/97

Andrew Mosholder, M.D.
Medical Officer, Division of Neuropharmacologic Drug Products

NDA 20-639
Div File
HFD-120:Laugren/Hardeman/Glass/Mosholder/Burkhart

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PHARMACOKINETIC STUDIES IN HEALTHY SUBJECTS	
204636/0001-UK*	DB, randomized, three-arm incomplete crossover comparison of three single doses, placebo controlled trial; normal males (n=9 quetiapine, n=3 placebo), quetiapine doses (25, 50 and 100 mg).
204636/0002-UK*	DB, randomized, placebo controlled, three-arm incomplete crossover comparison of three increasing single doses of quetiapine; normal males (n=5 for 2 mg; n=6 for 5 mg; n=6 for 10 mg).
204636/0003-UK*	DB, randomized, parallel, placebo controlled trial; normal males (n=5 quetiapine, n=2 placebo); quetiapine dose (25 mg), 9 days.
H-15-11 & H-11-12-Japan*	Single-blind, randomized, placebo-controlled, comparison of single dose of quetiapine; normal males (n=6 for 1 mg and 10 mg quetiapine; n=6 for 5 mg and 20 mg quetiapine, n=4 placebo).
H-15-13-Japan*	Single-blind, randomized, multiple dose, placebo-controlled trial; normal males (n=6 quetiapine, n=2 placebo); quetiapine dose (10 mg), 4 days.
PHARMACOKINETIC STUDIES IN SCHIZOPHRENIC SUBJECTS	
5077IL/0016-US	Open-label, multiple dose trial; schizophrenic subjects (n=41); quetiapine doses (25-375 mg bid), 16 days.
5077IL/0008-US	Open-label, multiple dose trial; schizophrenic men (n=13); quetiapine doses (25-150 mg tid), 12 days.
5077IL/0004-US	DB, parallel, placebo-controlled, multiple dose; inpatient schizophrenic males (n=8 quetiapine; n=4 placebo); quetiapine doses (25-250 mg tid), 21 days.
SPECIAL STUDIES	
5077IL/0064-US	Open label, single site, randomized, 2 period, multidose safety and pharmacokinetic study of quetiapine coadministered with thioridazine, haloperidol or risperidone; psychotic disorders (n=36); quetiapine (25-300 mg BID).

5077IL/0035-US	Open-label, comparison of immediate-release (IR) to two sustained-release (SR) formulations; schizophrenic males; quetiapine IR (25-250 mg bid for 9 days; n=16), quetiapine SR (Two preparations both were 400 mg n=16 combined); open-label extension.
5077IL/0044-US	Open-label, 3 center, randomized, crossover, multiple dose, relative bioavailability trial; psychotic disorder; quetiapine doses (25-200 mg bid), six days, n=33.
5077IL/0026-UK	DB, randomized, single dose, comparative crossover, bioavailability trial for two tablet formulations; normal males (n=35); quetiapine dose (25 mg).
5077IL/0025-UK	Open-label, randomized, single dose three-way crossover, bioequivalence trial for 2 tablet formulations; normal males (n=24); quetiapine dose (25 mg).
5077IL/0007-US	Open-label, randomized crossover, single dose, relative bioavailability trial; normal males (n=24); quetiapine dose (25 mg).
5077IL/0018-US	Open-label, single dose, comparative PK trial; hepatically impaired (n=8), normal subjects (n=8); quetiapine dose (25 mg).
5077IL/0019-US	Open-label, single dose, comparative PK trial; renally impaired subjects (n=8), normal subjects (n=8); quetiapine dose (25 mg).
5077IL/0017-US	Open-label, multi center, multiple dose, PK trial; elderly subjects with psychotic disorders (n=12); quetiapine dose (25-250 tid), 27 days with open-label extension.
5077US/0002-US	Open-label, PK trial; schizophrenic subjects (n=8); quetiapine dose (25-150 mg tid for 10 days), C-Quetiapine dose (150 mg, single radioactive dose after 10 day dosing of quetiapine).
5077IL/0044 US	Open label, multicenter, crossover bioavailability study; men with psychotic disorders (n=33); quetiapine single dose (200 mg as to be marketed and investigational formulation).
5077IL/0020-US	Open-label, PK interaction study of antipyrine and quetiapine; male subjects with psychotic disorder (n=13); quetiapine doses (25-250 tid) antipyrine (1000 mg single dose before and after administration of quetiapine), 9 days.
5077IL/0047-US	Open-label, PK interaction study with quetiapine & cimetidine; male subjects with psychotic disorder (n=13); quetiapine doses (25-150 tid, 17 days), cimetidine (400 mg tid for 4 days); with open-label extension.

5077IL/0045-US	Open-label, multiple dose, PK interaction with quetiapine and phenytoin; male subjects with psychotic disorder (n=17); quetiapine doses (25-250 mg tid x 10 days), phenytoin doses (100 mg days 13-22); open-label extension.
5077IL/0027-US	Single-blind quetiapine and open-label lorazepam, PK interaction study; male subjects with psychotic disorder (n=10); quetiapine doses (25-250 tid x 13 days), lorazepam dose (2 mg before and after administration of quetiapine).
5077IL/0046-US	Open-label, multiple dose, PK interaction study of lithium and quetiapine; male subjects with psychotic disorder (n=10); quetiapine doses (25 mg-250 mg), lithium doses (300-1200 mg tid), eleven days with open-label extension.
5077IL/0061 US	Multicenter 3 period safety trial to evaluate withdrawal and switching from other antipsychotic drugs to quetiapine; psychotic disorders (n=33); haloperidol 5-30 mg/d, risperidone 4-10 mg/d, or thioridazine 200-600 mg/d X 3 d followed by quetiapine titrated to 600 mg/d followed by randomization to continued quetiapine or placebo.
5077IL/0029-EUR	Open-label, nonrandomized multiple dose, PET Scan, PK trial; schizophrenic males (n=11); quetiapine doses (25-150 tid x 7 days, 150 tid x 21 days), C-racloprides (4 doses), C-N-methyl spiperone (4 doses); open-label extension.
5077IL/0033-EUR	Open-label, 2 center, multiple dose, randomized, PET Scan, PK trial; schizophrenic male subjects (n=4); quetiapine doses (50-250 mg tid for 4 weeks, then decreased weekly by 100 mg x 1 week, 50 mg tid x 2 weeks).
5077IL/0024-US (Part A)	Single-blind, placebo-controlled, PK interaction trial of multiple doses quetiapine and single dose alcohol; male subjects with psychotic disorder (n=10); quetiapine doses (25-250 mg tid x 18 days), alcohol dose (0.8 g/kg), eighteen days.
5077IL/0024-US (Part B)	Single-blind, placebo-controlled, PK interaction trial of multiple doses quetiapine and single dose alcohol; male subjects with psychotic disorder (n=1), quetiapine(25-250 mg x 18 days), alcohol (0.8 g/kg); eighteen days with open-label extension.
PHASE 2-3 STUDIES	
PLACEBO CONTROLLED STUDIES	
5077IL/0006-US	DB, parallel group, placebo-controlled, double-blind, 13-center; inpatient schizophrenic subjects (n=109); quetiapine doses (75-750 mg/day), six weeks.

204636/0008-US/ EUR	DB, parallel group, placebo-controlled, randomized, 46-center, comparison of low and high doses of quetiapine; inpatient schizophrenic subjects (n=286); quetiapine doses (low: up to 250 mg/day; high: up to 750 mg/day), six weeks.
5077IL/0013-US/ CAN	DB, parallel group, placebo-controlled, randomized, 26-center, fixed dose comparison trial to haloperidol; inpatient schizophrenic subjects (n=361); quetiapine dose (75/150/300/600/750 mg/day), haloperidol dose (12 mg/day), six weeks with open label extension.
ACTIVE CONTROLLED STUDIES	
5055IL/0015-US/ CAN	DB, 37-center, randomized, fixed-dose, relapse prevention trial of quetiapine and haloperidol; schizophrenic outpatients; quetiapine doses (75/300/600 mg/day; n=85/group), haloperidol (12 mg/day; n=41); one year with open label extension.
204636/007-EUR/ SOUTH AFRICA	DB, multi center comparison trial of quetiapine and chlorpromazine; schizophrenic inpatients; quetiapine doses (75-750 mg/day; n=101), chlorpromazine (75-750 mg; n=100); six weeks.
5077IL/0012-EUR/ ISRAEL/ CANADA	DB, multi center, randomized, comparison of dose regimen, control was subtherapeutic dose (50 mg quetiapine); schizophrenic subjects (n=618); quetiapine doses (225 mg bid 150 mg tid, and 25 mg bid), six weeks with open label extension.
5077IL/0014-EUR/ SOUTH AFRICA/ AUSTRALIA	DB, multi center, randomized comparison trial of quetiapine and haloperidol; schizophrenic subjects; quetiapine doses (50-800 mg/day; n=221), haloperidol doses (0.5-16 mg/day; n=221), 6 weeks with open label extension.
UNCONTROLLED STUDY	
5077IL/0005-US/ EUROPE/ SOUTH AFRICA	Open-label, multi center, multiple oral dose; inpatient subjects with psychotic disorder (n=35); quetiapine doses (25-750 mg/day); UK: six weeks, US: four weeks.
OTHER TRIALS	
5077IL/0056 US	Open label, multicenter, comparison of quetiapine versus usual care with respect to health outcomes; schizophrenia and schizoaffective disorder (n= 540 planned); ONGOING.
5077IL/0048-US	Open-label, 12 center, safety trial; elderly patients with psychotic disorder, including Parkinson's disease (n=78); quetiapine doses (25-800 mg/day), 52 weeks.

5077IL/0031-US/ CAN	DB, randomized, 23 site, comparison trial of quetiapine, chlorpromazine, and haloperidol; treatment-resistant schizophrenic subjects (n=122; 264 planned, ongoing); quetiapine doses (600 mg: 4-6 weeks), haloperidol dose (40 mg qd: 4 weeks), chlorpromazine dose (1200 mg 4-6 weeks). Open label extension.
H-15-21-Japan*	Open-label, nonrandomized, early Phase II trial; schizophrenic subjects (n=54); quetiapine doses (60-750 mg/day), 8 weeks.
H-15-22-Japan*	Open-label, nonrandomized, late Phase II trial; schizophrenic subjects (n=165); quetiapine doses (75-750 mg/day), 8 weeks with open label extension.
H-15-23 Japan*	Open label extension of H-15-22-Japan (see above).

* Data is not included in primary integrated data base.

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TABLE 5.1.1.1 Summary of all trials (adapted from sponsor's safety update submission)				
Pools by trial design	Emuneration by treatment group			
	Quetiapine	Active control		Placebo
		Haloperidol	Chlorpromaznie	
PHASE I (CLINICAL PHARMACOLOGY)				
Single dose	111			
Multiple dose	232			
SUBTOTAL	343			
PHASES II - III (ANTIPSYCHOTIC STUDIES)				
Placebo controlled				
Inpt/fixed dose	258	52		51
Inpt/dose titration	252			155
Active controlled				
Outpt/fixed dose	260			
Outpt/flexible dose	1			
Inpt/fixed dose	618			
Inpt/flexible dose	322	227	100	
Uncontrolled*				
Outpt/flexible dose	1378 (915)*			
Inpatient/flexible dose	118			
SUBTOTAL	3207 (915)*	320	100	206
SINGLE DOSE TOTAL	111			
MULTIPLE DOSE TOTAL	2524	320	100	206
GRAND TOTAL**	2635	320	100	206

*Number represents all quetiapine treated subjects for the cell; number in parentheses represents subjects also counted under previous headings (95 of whom were previous Phase I exposures). Subtracting the number in parentheses from the first number provides the number of unique exposures for the cell.

*Of the 409 new exposures to quetiapine in uncontrolled trials, 173 had received placebo or active comparator in controlled trials.

**All subjects who received drug had follow-up safety measurements.

Inpt = Inpatient; Outpt = Outpatient

Appendix Table 5.1.2.1 Demography for subjects exposed to quetiapine in Phase I clinical trials (adapted from the sponsor's electronic safety update submission)

Number of subjects exposed	343
Age, y	
n	343
Mean (SD)	38 (12)
Range	
Age distribution, n (%)	
< 40 years	214 (62)
40 - 64 years	119 (35)
65 years	10 (3)
Sex, n (%)	
Men	318 (93)
Women	25 (7)
Weight, kg	
n	343
Mean (SD)	79 (13)
Range	
Race, n (%)	
White	218 (64)
Black	84 (25)
Hispanic	25 (7)
Asian/Oriental	9 (3)
Other ^a	7 (2)

^aIncludes East Indian.

^aOther includes special subgroups and mixed or undefined races.

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APPENDIX TABLE 5.1.2.2 Demographic profile for Phase II and III trials (adapted from sponsor's electronic submission)

Parameter	Quetiapine (n = 2387)	Placebo (n = 206)	Active Control (n = 420)
Age (years)			
n	2386	206	420
Mean	40 (15)	37 (9)	36 (11)
Range			
Age distribution (%)			
< 40 years	1407 (59)	125 (61)	271 (65)
40 - 64 years	789 (33)	81 (39)	144 (34)
≥ 65 years	190 (8)	0 (0)	5 (1)
Sex			
Male	1666 (70)	159 (77)	290 (69)
Female	721 (30)	47 (23)	130 (31)
Race			
White	1875 (79)	143 (69)	355 (85)
Black	266 (11)	47 (23)	34 (8)
Hispanic	74 (3)	5 (2)	6 (1)
Asian/Oriental*	35 (2)	4 (2)	4 (1)
Other	53 (2)	7 (3)	21 (5)
Weight (kg)			
n	2285	197	412
Mean	76 (17)	78 (16)	72 (17)
Range			

*Includes 1710 subjects exposed to quetiapine in controlled trials and 452 new exposures to quetiapine in uncontrolled trials (804 subjects were exposed in controlled trials and entered uncontrolled trials).

*Includes East Indian.

*Other includes special subgroups and race undefined, not specified or not collected.

APPENDIX TABLE 5.1.3.1 Number and percent of all subjects receiving quetiapine according to mean daily dose and duration in Phase I trials (n = 343) (adapted from sponsor's electronic safety update submission)

Duration (days)	≤75 mg	>75 mg ≤150 mg	>150 mg ≤300 mg	>300 mg ≤450 mg	>450 mg ≤600 mg	>600 mg ≤800 mg	Total (%)
1	34	0	0	0	0	0	34 (10)
2-7	84	7	11	2	0	0	104 (30)
8-14	1	3	49	18	29	0	100 (29)
15-21	0	0	21	46	9	7	83 (24)
22-28	0	0	1	5	1	1	8 (2)
29-35	0	8	0	0	0	1	9 (3)
36-42	1	0	0	0	4	0	5 (2)
Total	120	18	82	71	43	9	343 (100)
%	35	5	24	21	13	3	100

APPENDIX TABLE 5.1.3.2 Number (%) of all subjects receiving quetiapine according to mean daily dose and duration in Phase II and III trials (n = 2317*) (adapted from sponsor's electronic safety update submission)

Duration (days)	≤75 mg	>75 mg ≤150 mg	>150 mg ≤300 mg	>300 mg ≤450 mg	>450 mg ≤600 mg	>600 mg ≤800 mg	> 800 mg	Total (%)
1	18	0	0	1	1	0	0	20 (1)
2-7	76	37	69	7	2	0	0	191 (8)
8-14	34	16	67	50	18	2	0	187 (8)
15-21	24	24	44	40	23	5	0	160 (7)
22-28	13	12	49	58	26	4	0	162 (7)
29-35	10	5	18	29	12	8	0	82 (4)
36-42	11	9	82	114	101	25	0	342 (15)
43-112	36	46	103	131	82	20	0	418 (18)
113-183	25	31	50	37	36	14	0	193 (8)
184-365	28	47	63	57	59	27	0	281 (12)
366-548	3	11	64	26	26	16	1	147 (6)
549-730	2	5	35	26	14	7	0	89 (4)
> 730	1	1	8	17	11	6	1	45 (2)
Total	281	244	652	593	411	134	2	2317 (100)
%	12	11	28	26	18	6	0.09	100

*Does not include 70 subjects who did not have first dose dates for open label therapy

Appendix table 5.1.3.3 Patient years of exposure in the primary integrated database (adapted from sponsor's table 4.7 of safety update)

	Number of patients	Patient-years exposure*
Quetiapine	2387	865.3
Haloperidol	320	42.5
Chlorpromazine	100	9.2
Placebo	206	14.6

*Patient-years is defined as the sum of every subject's days on treatment (duration) divided by 365 days.

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Appendix table 7.2.1.1 INVESTIGATOR AND CENTER LIST, Study 0006 (adapted from sponsor's electronic submission)

Center number	Investigator	Address
008	RL Borison MD PhD Principal Investigator B Diamond PhD	Psychiatry Service, 116A-U Augusta VA Medical Center One Freedom Way Augusta, GA 30910
001	JP McEvoy MD	John Umstead Hospital 12th Street Butner, NC 27509
002	JS Carman MD	Brawner Psychiatric Institute 3180 Atlanta Street SE Smyrna, GA 30080
003	W Ryan MD N Smith MD	University Hospital Jefferson Towers, North Wing University of Alabama at Birmingham School of Medicine 619 S. 19th Street Birmingham, AL 35233
004	LD Alphas MD	Lafayette Clinic 951 East Lafayette Avenue Detroit, MI 48207 and Detroit VA Medical Center Southfield and Outer Drive Allen Park, MI 48101
005	R Hirshfeld MD	Department of Psychiatry and Behavioral Sciences University of Texas Medical Branch 1014 Texas Avenue Galveston, TX 77550
006	S Mukherjee MD	Creedmoor Psychiatric Center Research Division, Building 74 80-45 Winchester Boulevard Queens Village, NY 11427
007	C Tamminga MD	Maryland Psychiatric Research Center Inpatient Unit, PO Box 21247 Spring Grove Hospital Grounds Baltimore, MD 21228
009	G Gewirtz MD (deceased)	New York State Psychiatric Institute 722 West 168th Street New York, NY 10032
010	M Hamner MD	VA Medical Center Inpatient Psychiatry: 5BN 109 Bee Street, Charleston SC 29045

011	G Oxenkrug MD PhD	Psychiatric Services, 116A VA Medical Center 830 Chalkstone Avenue Providence, RI 02908
012	H Nasrallah MD	Department of Psychiatry The Ohio State University College of Medicine 473 W. 12th Avenue Columbus, OH 43210

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Appendix table 7.2.1.2 Trial 0006 - Demographic characteristics (adapted from sponsor's electronic submission)									
Treatment groups	n	Age (years)		Sex (n [%])		Race (n [%])			
		Mean	Range	Male	Female	Caucasian	Black	Hispanic	Other
Quetiapine	54	36		48 (89)	6 (11)	32 (59)	21 (39)	1 (2)	0
Placebo	55	37		50 (91)	5 (9)	34 (62)	18 (33)	1 (2)	2 (4)

Appendix table 7.2.1.3 Study 0006 - Patient completion rates (adapted from sponsor's electronic submission)								
Treatment groups	Number randomized	Intent-to-treat sample*	Number (%) of patients completing					
			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6 ^a
Quetiapine	54	53	53 (100)	46 (87)	41 (77)	35 (66)	32 (60)	28 (53)
Placebo	55	53	53 (100)	47 (89)	39 (74)	30 (57)	27 (51)	23 (43)

*Patients who received assigned medication and had one or more efficacy assessments.

^aPatient 004/00406 withdrew from the trial at Day 40. Efficacy data obtained at this time were included with Day 42 data for the placebo group (n = 23 at Day 42). However, this patient was not considered to have completed the trial.

Appendix table 7.2.1.4 Trial 0006 - Mean quetiapine dose by trial week for all patients (adapted from sponsor's electronic submission)			
	Quetiapine dose (mg)		
	n	Mean	SD
Week 1	53	151	95
Week 2	46	334	153
Week 3	41	402	173
Week 4	35	418	160
Week 5	32	431	160
Week 6	28	420	180

SD = Standard deviation.

TABLE Trial 5077IL/0006 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Treatment groups	Treatment Week													
	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
Quetiapine	53	55.79	53	-3.18	53	-5.55	53	-7.00	53	-8.44	53	-8.66	53	-8.08
Placebo	53	54.09	53	-0.73	53	-0.47	53	-2.03	53	-1.78	53	-1.25	53	-2.13
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo*			0.2023		0.0508		0.0888		0.0224		0.0186		0.0694	

TABLE Trial 5077IL/0006 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	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
Quetiapine	53	55.79	53	-3.51	46	-7.35	41	-11.80	35	-13.11	32	-14.64	28	-13.64
Placebo	53	54.09	53	-0.83	47	-2.61	39	-9.43	30	-11.91	27	-13.17	23	-13.85
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo*			0.1648		0.0656		0.3572		0.6045		0.6296		0.9510	

*Baseline comparison p value =0.019 (ANOVA)

TABLE Trial 5077IL/0006 - Mean change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Treatment groups	Treatment week													
	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
Quetiapine	53	4.96	53	0.03	53	-0.07	53	-0.30	53	-0.28	53	-0.30	53	-0.22
Placebo	53	4.64	53	0.15	53	0.29	53	0.24	53	0.28	53	0.28	53	0.23
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo*			0.4776		0.0770		0.0192		0.0122		0.0191		0.0693	

TABLE Trial 5077IL/0006 - Mean change from baseline in CGI - Severity of Illness score(adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	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
Quetiapine	53	4.96	53	-0.01	46	-0.32	41	-0.72	35	-0.74	32	-0.86	28	-0.65
Placebo	53	4.64	53	0.13	47	0.04	39	-0.24	30	-0.58	27	-0.67	23	-0.72
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo*			0.4003		0.0592		0.0269		0.4367		0.4981		0.8410	

*Baseline comparison p value = 0.03 (ANOVA)

TABLE Trial 5077IL/0006 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Treatment groups	Treatment week													
	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
Quetiapine	53	4.32	53	-0.34	53	-0.65	53	-0.73	53	-0.96	53	-0.99	53	-0.89
Placebo	53	4.03	53	-0.13	53	-0.21	53	-0.30	53	-0.22	53	-0.19	53	-0.33
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo			0.2236		0.0470		0.0704		0.0038		0.0030		0.0557	

TABLE Trial 5077IL/0006 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	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
Quetiapine	53	4.32	53	-0.37	46	-0.76	41	-1.12	35	-1.33	32	-1.34	28	-1.10
Placebo	53	4.03	53	-0.15	47	-0.33	39	-0.88	30	-0.90	27	-0.98	23	-1.15
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo			0.2115		0.0547		0.2968		0.1183		0.2328		0.8892	

*Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

TABLE Trial 5077IL/0006 - Mean change from baseline in SANS summary score (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Treatment groups	Treatment week													
	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
Quetiapine	51	14.06	49	-0.05	51	-0.13	51	-0.57	51	-0.87	51	-1.05	51	-1.04
Placebo	51	13.96	50	0.57	51	0.92	51	0.85	51	0.70	51	0.62	51	0.56
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo			0.2449		0.1153		0.0437		0.0240		0.0299		0.0519	

TABLE Trial 5077IL/0006 - Mean change from baseline in SANS summary score (adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	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
Quetiapine	51	14.06	49	-0.04	45	-0.15	38	-0.85	27	-0.75	31	-1.11	28	-0.88
Placebo	51	13.96	50	0.62	44	0.49	34	-0.65	24	-1.40	26	-1.35	23	-1.40
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo			0.2084		0.3766		0.8116		0.5172		0.8189		0.6783	

Appendix 7.2.2.1

INVESTIGATOR AND CENTER LIST: Study 0008 (adapted from sponsor's electronic submission) N.B. U.S. and foreign sites had different protocols and study nos.

Center number	Investigator	Address
STUDY 5077US/0001		
0001	Joyce G Small MD	Department of Psychiatry
	Principal Investigator	Larue D Carter Memorial Hospital
		1315 W 10th Street
		Indianapolis, IN 46202
		USA
STUDY 204,636/0008		
0001	Prof S R Hirsch	Department of Psychiatry
	Principal Investigator	Charing Cross Hospital
		Fulham Palace Road
		London W6 8RF
		UK
STUDY 5077US/0001		
0002	Charles L Bowden MD	Audie L Murphy Veterans Memorial Hospital
		7400 Merton Minter Blvd
		San Antonio, TX 78284
		USA
0003	Charles P O'Brien MD PhD	VA Medical Center (116)
		University and Woodland Avenue
		Philadelphia, PA 19104
		USA
0004	Richard M Steinbook MD	Department of Psychiatry
		Mental Health Institute
		Jackson Memorial Medical Centre
		1611 NW 12th Avenue
		Miami, FL 33136
		USA
0005	Richard L Wagner MD	Institute of Mental Health
		Louis Pasteur Building
		Howard Avenue
		Cranston, RI 02920
		USA
0006	Wesley M Pitts MD	University of Mississippi Medical Center
	Brian Crabtree PharmD	2500 N State Street
		Jackson, MS 39216
		USA
		and
		VA Medical Center
		1500 E Woodrow Wilson Avenue
		Jackson, MS 39216
		USA
0007	Mark H N Corrigan MD	Clinical Research Unit
		Edgerton Building
		Dorothea Dix Hospital
		809 Ruggles Drive
		Raleigh, NC 27603
		USA

0008	James B Lohr MD	Department of Psychiatry, 116A VA Medical Center 3350 LaJolla Village Drive San Diego, CA 92161 USA
0009	Alexander Miller MD	University of Texas Health Science Center at San Antonio
	Larry Ereshefsky PharmD	San Antonio State Hospital
	Cheryl Anderson PharmD	Clinical Pharmacy Programs 7703 Floyd Curl Drive San Antonio, TX 78284 USA
0010	Mary Ann Knesevich MD	Terrell State Hospital 1200 East Brin Terrell, TX 75160 USA
0011	John Rotrosen MD	Department of Veterans Affairs New York VA Medical Center 423 East 23rd Street New York, NY 10010 USA
0012	Richard R Owen MD	VA Medical Center
	Craig Karson MD	North Little Rock Division 116A/NLR 2200 Fort Roots Drive North Little Rock, AR 72114-1706 USA and Arkansas State Hospital 4313 N. Markham Street Little Rock, AR 72205 USA
0013	J P Lindenmayer MD	Schizophrenic Research Unit Bronx Psychiatric Center 1500 Waters Place Bronx, NY 10461 USA

0014	Adolph Pfefferbaum MD	Stanford/VA Mental Health Clinical Research Center
	William O Faustman PhD	Unit 4C2 and 4B2
		DVA Medical Center
		3801 Miranda Avenue
		Palo Alto, CA 94304
		USA
0015	Paul E Keck Jr MD	University of Cincinnati College of Medicine
		Biological Psychiatry Program
		231 Bethesda Avenue ML 559
		Cincinnati, OH 45267
0016	William M Patterson MD	Birmingham Research Group/
		Hillcrest Hospital
		6869 Fifth Avenue South
		Birmingham, AL 35212
		USA
0017	Robert Riesenber MD	DeKalb Medical Center
	Michael Gladson MD	2701 North Decatur Road
		Decatur, GA 30033
		USA
0018	Irving S Kolin MD	Psychiatric Unit
		Sand Lake Hospital
		9400 Turkey Lake Road
		Orlando, FL 32819
		USA
STUDY 204,636/0008		
0001	Dr T R E Barnes	Horton Hospital
		Long Grove Road
		Epsom
		Surrey KT19 8PZ
		UK
	Dr T Sensky	Department of Psychiatry
		West Middlesex Hospital
		Isleworth
		Middlesex TW7 6AF
		UK
	Dr M Riccio	Consultant Psychiatrist
		St Mary Abbots Hospital
		Marloes Road
		Kensington
		London W8 5LQ
		UK
	Dr S Franks	Department of Psychiatry
		Gordon Hospital
		126 Vauxhall Road
		London SW1
		UK

	Dr A Jolley	Department of Psychiatry St Bernards Wing Ealing Hospital Uxbridge Road Southall Middlesex UB1 3EU UK
	Dr C Hallstrom	Department of Psychiatry Charing Cross Hospital London UK
0002	Dr E Bennie	Department of Psychology Leverdale Hospital 510 Crookson Road Glasgow G53 7TU UK
0005	Professor G Darcourt	Clinique de Psychiatrie et de Psychologie Hopital Pasteur Avenue de la Voie Romaine 06000 NICE France
0008	Professor Patris	CHU - Clinique Psychiatre 1 Place de l'Hopital BP No 426 57091 Strasburg Cedex France
0009	Dr M DeSilva	Department of Mental Health Heatherwood Hospital London Road Ascot Berkshire SI5 8AA UK
0010	Dr Patel	Department of Mental Services Fairfield Hospital Stotfold Near Hitchin Hertfordshire SG5 4AA UK
0011	Professor W W Fleischhacker	Biological Psychiatry Research Unit Department of Psychiatry Innsbruck University Clinic Anichstrasse 35 A-6020 INNSBRUCK Austria
0012	Dr M Dietzel	Psychiatric University Clinic Wahringergurtel 18 - 20 A-1090 Wien Austria

0013	Dr Seifertova	Psychiatric Research Institute Ustavni 91 PRAGUE 8 Czech
0014	Dr O Vinar	Psychiatric Hospital Ustavni 91 CS 18103 Prague 8-Bohnice Czech
0015	Dr F Faltus	Department of Psychiatry Charles University Ke Karlovu 11 Prague 2 Czech
0017	Dr I Bitter	Semmelweis Orvostudományi Egyetem Balassa utca 6 H-1083 Budapest Hungary
0018	Professor K Ozsvath	University Medical School of Pecs Department of Psychiatry Ret u 2 H-7623 Pecs Hungary
0019	Dr S Shaw	Department of Psychiatry Stanley Road Hospital Aberford Hospital Wakefield West Yorkshire UK
0020	Dr S Mahapatra	Department of Psychiatry The General Hospital Hartlepool UK
0021	Dr T Szulecka	Department of Psychiatry Bassetlaw District General Hospital Worksop Nottingham UK
0022	Dr K Sundararajan	Department of Psychiatry Halifax General Hospital Halifax West Yorkshire UK

0023	Dr F Creaven	St Mary's Psychiatric Hospital Castlebar County Mayo Ireland
0024	Dr J Lynch	St Luke's Hospital Clonmel County Tipperary Ireland
0025	Dr E Klieser	Psychiatrische Klinik Universität Dusseldorf Bergische Landstr 2 4000 Dusseldorf 12 Germany
0026	Dr S J Cooper	Department of Therapeutics and Pharmacology Queens University of Belfast Whitla Medical Building 97 Lisburn Road Belfast Northern Ireland
0027	Dr H Aschauer	University Clinic of Vienna Department of Psychiatry Wahringer Gurtel 18 - 20 A-1090 Wien Austria

APPENDIX TABLE 7.2.2.2 Trial 0008 - Demographic characteristics (adapted from sponsor's electronic submission)

Treatment groups	n	Age (years)		Sex (n [%])		Race (n [%])				
		Mean	Range	Male	Female	Caucasian	Black	Hispanic	Asian	Other
Quetiapine High dose	96	36		66 (69)	30 (31)	66 (69)	19 (20)	7 (7)	1 (1)	3 (3)
Quetiapine Low dose	94	37		73 (78)	21 (22)	63 (67)	20 (21)	6 (6)	3 (3)	2 (2)
Placebo	96	38		64 (67)	32 (33)	73 (76)	16 (17)	2 (2)	2 (2)	3 (3)

APPENDIX TABLE 7.2.2.2 Study 0008 - Patient completion rates (adapted from sponsor's electronic submission)

Treatment groups	Number randomized	Intent-to-treat sample*	Number (%) of patients completing					
			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Quetiapine High dose	96	95	95 (100)	80 (84)	70 (74)	61 (64)	52 (55)	49 (51)
Quetiapine Low dose	94	93	93 (100)	85 (91)	69 (74)	56 (60)	46 (49)	39 (41)
Placebo	96	94	94 (100)	81 (86)	60 (64)	50 (53)	45 (48)	41 (43)

* Patients who received assigned medication and had one or more efficacy assessments.

APPENDIX TABLE 7.2.2.3 Trial 0008 - Mean quetiapine dose daily dose (mg) by trial week for all patients (adapted from sponsor's electronic submission)

	Quetiapine Low dose			Quetiapine High dose		
	n	Mean	SD	n	Mean	SD
Week 1	93	154	71	95	184	136
Week 2	85	242	38	80	410	191
Week 3	69	245	24	70	502	166
Week 4	56	246	27	61	538	149
Week 5	46	246	23	52	534	134
Week 6	40	248	19	49	489	126

TABLE Trial 0008 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Treatment groups	Treatment week													
	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
Quetiapine														
High dose	94	41.04	94	-2.41	94	-4.55	94	-6.32	94	-7.58	94	-7.84	94	-8.74
Low dose	92	38.89	92	-1.00	92	-2.00	92	-3.27	92	-4.28	92	-4.00	92	-4.16
Placebo	94	38.35	93	-0.46	94	0.11	94	-0.68	94	-0.45	94	-0.21	94	-0.96
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.1675		0.0108		0.0059		0.0007		0.0003		0.0006	
Low dose vs placebo			0.7019		0.2450		0.2030		0.0658		0.0718		0.1515	
High dose vs low dose			0.3175		0.1628		0.1357		0.1139		0.0699		0.0413	

TABLE Trial 0008 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	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
Quetiapine														
High dose	94	41.04	94	-2.23	80	-6.97	70	-12.90	61	-12.10	52	-13.56	49	-15.12
Low dose	92	38.89	92	-0.22	85	-3.13	69	-9.00	55	-9.50	46	-10.15	39	-11.39
Placebo	94	38.35	93	-0.02	81	-2.14	60	-9.58	50	-7.93	44	-7.60	41	-9.65
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.1243		0.0136		0.0807		0.0450		0.0102		0.0297	
Low dose vs placebo			0.8889		0.5965		0.7510		0.4472		0.2659		0.5001	
High dose vs low dose			0.1598		0.0429		0.0301		0.1899		0.1361		0.1454	

TABLE Trial 0008 - Mean change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Treatment groups	Treatment week													
	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
Quetiapine														
High dose	95	5.07	95	-0.08	95	-0.26	95	-0.40	95	-0.47	95	-0.55	95	-0.61
Low dose	92	5.05	92	-0.05	92	-0.16	92	-0.19	92	-0.23	92	-0.32	92	-0.30
Placebo	94	4.94	94	0.01	94	0.00	94	-0.04	94	-0.03	94	-0.01	94	-0.08
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.4074		0.0766		0.0184		0.0071		0.0012		0.0030	
Low dose vs placebo			0.5791		0.2630		0.3445		0.2230		0.0625		0.2282	
High dose vs low dose			0.7880		0.5194		0.1584		0.1403		0.1690		0.0768	

TABLE Trial 0008 - Mean change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	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
Quetiapine														
High dose	95	5.07	95	-0.05	80	-0.54	70	-0.97	61	-0.87	52	-0.93	49	-1.05
Low dose	92	5.05	92	0.00	84	-0.39	69	-0.62	56	-0.51	46	-0.66	39	-0.65
Placebo	94	4.94	94	0.04	81	-0.29	60	-0.73	50	-0.63	45	-0.49	41	-0.60
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.3989		0.1007		0.1315		0.2071		0.0290		0.0408	
Low dose vs placebo			0.6927		0.5212		0.4925		0.5252		0.3934		0.8518	
High dose vs low dose			0.6552		0.2976		0.0234		0.0525		0.2027		0.0786	

TABLE Trial 0008 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Treatment groups	Treatment week													
	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
Quetiapine High dose	94	3.61	94	-0.35	94	-0.52	94	-0.72	94	-0.81	94	-0.86	94	-0.90
Quetiapine Low dose	92	3.63	92	-0.32	92	-0.48	92	-0.58	92	-0.65	92	-0.60	92	-0.61
Placebo	94	3.52	94	-0.29	94	-0.36	94	-0.39	94	-0.37	94	-0.35	94	-0.37
2-sided p-values for pairwise comparisons														
Quetiapine High dose vs placebo			0.6205		0.2582		0.0486		0.0103		0.0035		0.0030	
Quetiapine Low dose vs placebo			0.7614		0.3912		0.2539		0.0996		0.1549		0.1728	
High dose vs low dose			0.8502		0.7891		0.4090		0.3611		0.1335		0.1080	

TABLE Trial 0008 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	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
Quetiapine														
Quetiapine High dose	94	3.61	94	-0.29	80	-0.62	70	-1.02	61	-1.06	52	-1.13	49	-1.22
Quetiapine Low dose	92	3.63	92	-0.24	85	-0.48	69	-0.80	55	-0.87	46	-0.84	39	-0.96
Placebo	94	3.52	94	-0.23	81	-0.41	60	-0.87	50	-0.78	44	-0.66	41	-0.70
2-sided p-values for pairwise comparisons														
Quetiapine														
Quetiapine High dose vs placebo			0.5904		0.2036		0.4073		0.1603		0.0384		0.0302	
Quetiapine Low dose vs placebo			0.9118		0.6656		0.7211		0.6277		0.4335		0.3067	
High dose vs low dose			0.6694		0.3831		0.2170		0.3459		0.2027		0.2847	

*Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

TABLE Trial 0008 - Mean change from baseline in SANS summary score* (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Treatment groups	Treatment week													
	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
Quetiapine High dose	55	15.76	54	-0.23	55	-0.67	55	-1.00	55	-1.41	55	-1.53	55	-1.65
Quetiapine Low dose	51	15.82	50	0.07	51	0.20	51	0.14	51	-0.11	51	0.27	51	0.27
Placebo	56	14.50	55	-0.17	56	-0.31	56	0.03	56	0.05	56	-0.09	56	-0.14
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.8957		0.5210		0.0737		0.0198		0.0220		0.0210	
Low dose vs placebo			0.6543		0.3750		0.8605		0.7982		0.5766		0.5381	
High dose vs low dose			0.5618		0.1283		0.0528		0.0407		0.0051		0.0041	

TABLE: Trial 0008 - Mean change from baseline in SANS summary score* (adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	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
Quetiapine High dose	55	15.76	54	-0.20	47	-1.01	44	-1.62	39	-2.37	35	-2.77	33	-3.52
Quetiapine Low dose	51	15.82	50	0.20	46	-0.09	36	-0.82	27	-1.42	30	-0.62	18	-0.94
Placebo	56	14.50	55	-0.18	47	-0.42	35	-0.52	31	-0.36	37	-0.50	26	-0.93
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.9741		0.3383		0.1011		0.0114		0.0079		0.0082	
Low dose vs placebo			0.4926		0.5934		0.6723		0.2100		0.8981		0.9981	
High dose vs low dose			0.4679		0.1309		0.2192		0.2390		0.0220		0.0180	

*SANS completed at US centers only.

TABLE Trial 0008 - Mean change from baseline in PANSS negative scale score* (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Treatment groups	Treatment week													
	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
Quetiapine High dose	38	27.47	38	-1.21	38	-2.25	38	-2.97	38	-3.68	38	-3.93	38	-4.39
Quetiapine Low dose	38	25.50	38	-0.01	38	-0.91	38	-1.53	38	-2.32	38	-2.39	38	-2.86
Placebo	37	24.43	37	0.02	37	0.36	37	-0.96	37	-1.33	37	-1.54	37	-1.88
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.2313		0.0369		0.1322		0.0966		0.1013		0.1047	
Low dose vs placebo			0.9797		0.2998		0.6632		0.4736		0.5538		0.5186	
High dose vs low dose			0.2358		0.2738		0.2742		0.3299		0.2826		0.3149	

TABLE Trial 0008 - Mean change from baseline in PANSS negative scale score* (adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	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
Quetiapine High dose	38	27.47	38	-4.02	29	-4.88	26	-5.63	22	-5.49	17	-4.06	16	-4.38
Quetiapine Low dose	38	25.50	38	-2.77	38	-2.89	31	-5.02	28	-5.20	25	-2.12	22	-2.57
Placebo	37	24.43	37	-2.15	32	-1.72	22	-5.13	19	-4.78	17	-1.94	15	-2.48
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.0641		0.0272		0.6484		0.6300		0.1550		0.2671	
Low dose vs placebo			0.5350		0.3648		0.9153		0.7575		0.8930		0.9561	
High dose vs low dose			0.2035		0.1343		0.5354		0.8256		0.1556		0.2478	

*PANSS(N) completed at European centers only.

Appendix 7.2.2.1 INVESTIGATOR AND CENTER LIST (adapted from sponsor's electronic study report)

Trial number: 5077IL/0013

The following investigators participated in this study:

Center number	Investigator	Address
001	Richard L. Borison, MD, PhD	Medical College of Georgia Dept of Psychiatry & Health Behavior 1515 Pope Avenue Augusta, GA 30912-3800 Psychiatry Service 116A Augusta VA Medical Center One Freedom Way Augusta, GA 30910
002	Wesley M. Pitts, MD	VA Medical Center 1500 E Woodrow Wilson Avenue Jackson, MS 39216-5199
003	George Gewirtz, MD (deceased) Zafar A. Sharif, MD	Creedmoor Psychiatric Center 80-45 Winchester Blvd Bldg 40, 11th Floor, SRU Queens Village, NY 11427
004	Mark B. Hamner, MD	VA Medical Center, 116A 109 Bee Street Charleston, SC 29401-5799
005	Marvin I. Herz, MD	University of Rochester Strong Ties Annex Department of Psychiatry 1650 Elmwood Ave Rochester, NY 14620
006	Janet E. True, MD Dawn Velligan, PhD	San Antonio State Hospital Clinical Research Unit-MC-4 6711 S New Braunfels San Antonio, TX 78223

007	Mary Ann Knesevich, MD	Terrell State Hospital 1200 East Brin Terrell, TX 75160
<hr/>		
008	Gregory Oxenkrug, MD, PhD	Psychiatry Services, 116A VA Medical Center 830 Chalkstone Avenue Providence, RI 02908
009	Joyce Small, MD	Department of Psychiatry Larue D. Carter Memorial Hospital 1315 W 10th Street Indianapolis, IN 46202
010	Richard Steinbook, MD	Jackson Memorial Medical Center Mental Health Institute, Rm 112B 1611 NW 12th Avenue Miami, FL 33136
011	Marc Hertzman, MD	North Arundel Hospital 301 Hospital Drive Glen Burnie, MD 21061-5803
012	Paul E. Keck, MD	University of Cincinnati College of Medicine Biological Psychiatry Center 231 Bethesda Avenue (ML 559) Cincinnati, OH 45267-0559
013	John W. Newcomer, MD	Washington University School of Medi- cine Department of Psychiatry 4940 Children's Place, Box 8134 St Louis, MO 63110
014	Jeffrey Grace, MD	Buffalo Psychiatric Center 400 Forest Avenue Buffalo, NY 14213

015	John Rotrosen, MD	Department of Psychiatry New York VA Medical Center 423 East 23rd Street New York, NY 10010
<hr/>		
016	Rajiv Tandon, MD	University of Michigan Medical Center Dept of Psychiatry, Unit 8D 1500 East Medical Center Drive Ann Arbor, MI 48109-0116
017	Sharon G. Dott, MD	University of Texas Medical Branch Dept Of Psychiatry and Behavioral Sciences 301 University Blvd, Graves Bldg D-28 Galveston, TX 77555-0428
018	James M. Ferguson, MD	Pharmacology Research Corporation Suite 350 448 East 6400 South, Suite 350 Salt Lake City, UT 84107
019	Donald E. N. Addington, MBBS	Foothills Hospital 1403 29th Street NW Calgary, Alberta T2N 2T9
020	Gordon W. MacEwan, MD	St. Vincent's Hospital 749 West 33rd Avenue Vancouver, BC V5Z 2K4
021	Vasavan N. P. Nair, MBBS, DPM	Douglas Hospital Research Centre 6875 La Salle Blvd Verdun, Quebec H4H 1R3
022	Christian L. Shriqui, MD, MSc	Hospital Robert-Giffard 2601 Rue de la Canardiere Beauport, Quebec G1J 2G3
023	Richard Williams, MBBS	Calgary General Hospital Department of Psychiatry 841 Centre Avenue East Calgary, Alberta T2E 0A1
024	David G. Daniel, MD	Neuropsychiatric Services of Greater Wash- ington, Inc 6404-P Seven Corners Place Falls Church, VA 22044

INVESTIGATOR AND CENTER LIST (continued)

025	G. Michael Shehi, MD William M. Patterson, MD	Birmingham Research Group 2120 Lynngate Drive Birmingham, AL 35216
026	Charles H. Merideth, MD	Affiliated Research Institute 7676 Hazard Center Drive, #1320 San Diego, CA 92108

APPENDIX TABLE 7.2.3.1 Trial 0013 - Demographic characteristics (adapted from sponsor's electronic submission)

Treatment Groups	n	Age (years)		Sex (n [%])		Race (n [%])				
		Mean	Range	Male	Female	White	Black	Hispanic	Asian	Other
Quetiapine 75 mg	53	37		39 (74)	14 (26)	36 (68)	14 (26)	2 (4)	1 (2)	0
150 mg	48	38		39 (81)	9 (19)	36 (75)	9 (19)	1 (2)	1 (2)	1 (2)
300 mg	52	38		37 (71)	15 (29)	36 (69)	13 (25)	3 (6)	0	0
600 mg	51	39		38 (75)	13 (25)	36 (71)	9 (18)	4 (8)	1 (2)	1 (2)
750 mg	54	35		38 (70)	16 (30)	38 (70)	11 (20)	3 (6)	1 (2)	1 (2)
Placebo	51	36		41 (80)	10 (20)	35 (69)	10 (20)	2 (4)	2 (4)	2 (4)
Haloperidol 12 mg	52	37		42 (81)	10 (19)	37 (71)	14 (27)	1 (2)	0	0

APPENDIX TABLE 7.2.3.2 Trial 0013 - Patients completion rates (adapted from sponsor's electronic submission)

Treatment groups	Number randomized	Intent-to-treat sample*	Number (%) of patients completing					
			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Quetiapine 75 mg	53	52	52 (100)	47 (90)	25 (48)	22 (42)	17 (33)	16 (31)
150 mg	48	48	48 (100)	46 (96)	37 (77)	25 (52)	23 (48)	21 (44)
300 mg	52	51	51 (100)	49 (96)	41 (80)	32 (63)	29 (57)	24 (47)
600 mg	51	51	51 (100)	42 (82)	35 (69)	30 (59)	29 (57)	27 (53)
750 mg	54	54	54 (100)	48 (89)	36 (67)	31 (57)	30 (56)	29 (54)
Placebo	51	51	51 (100)	46 (90)	30 (59)	26 (51)	22 (43)	17 (33)
Haloperidol 12 mg	52	50	50 (100)	45 (90)	36 (72)	24 (48)	20 (40)	18 (36)

*Patients who had at least one efficacy assessment on trial medication.

TABLE Trial 0013 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Treatment groups	Treatment week													
	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
Quetiapine 75 mg	52	45.71	52	-3.62	52	-3.56	52	-2.13	52	-1.91	52	-2.38	52	-2.24
150 mg	48	47.15	48	-3.83	48	-6.58	48	-6.77	48	-7.99	48	-8.66	48	-8.67
300 mg	51	45.29	51	-4.11	51	-7.07	51	-8.67	51	-9.64	51	-9.04	51	-8.59
600 mg	51	43.45	51	-3.94	51	-5.79	51	-6.72	51	-7.31	51	-6.92	51	-7.68
750 mg	53	45.72	53	-3.27	53	-4.65	53	-7.22	53	-7.55	53	-6.08	53	-6.33
Haloperidol 12 mg	50	44.00	50	-4.60	50	-8.60	50	-8.52	50	-7.53	50	-8.32	50	-7.58
Placebo	51	45.31	51	-2.23	51	0.02	51	1.05	51	1.17	51	1.76	51	1.71
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.9301		0.4162		0.6119		0.6620		0.4103		0.5041	
150 mg vs placebo			0.8909		0.0294		0.0143		0.0038		0.0010		0.0021	
300 mg vs placebo			0.8039		0.0143		0.0010		0.0003		0.0005		0.0019	
600 mg vs placebo			0.8562		0.0632		0.0132		0.0074		0.0076		0.0057	
750 mg vs placebo			0.9783		0.1800		0.0065		0.0050		0.0180		0.0224	
Haloperidol 12 mg vs placebo			0.2360		0.0004		0.0003		0.0014		0.0003		0.0016	
Quetiapine 300 mg* vs haloperidol 12 mg			0.9994		0.9534		1.0000		0.8952		0.9991		0.9967	

*Best quetiapine dose overall.

TABLE Trial 0013 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n		n	mean	n	mean
Quetiapine 75 mg	52	45.71	52	-3.62	46	-5.01	25	-10.16	22	-10.58	17	-14.87	16	-14.24
150 mg	48	47.15	48	-3.83	46	-7.09	37	-9.22	25	-14.79	23	-16.46	21	-16.75
300 mg	51	45.29	51	-4.11	49	-7.37	40	-11.26	32	-16.90	29	-16.01	24	-17.64
600 mg	51	43.45	51	-3.94	42	-7.32	35	-9.92	30	-14.94	29	-13.84	27	-16.53
750 mg	53	45.72	53	-3.27	48	-4.63	36	-11.15	31	-13.72	30	-11.14	29	-12.72
Haloperidol 12 mg	50	44.00	50	-4.60	45	-9.43	35	-11.75	24	-15.56	19	-17.74	18	-17.11
Placebo	51	45.31	51	-2.23	46	-0.91	30	-2.03	26	-3.86	21	-3.75	17	-7.06
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.9301		0.3441		0.0448		0.1765		0.0250		0.3804	
150 mg vs placebo			0.8909		0.0608		0.0531		0.0048		0.0034		0.1056	
300 mg vs placebo			0.8039		0.0412		0.0058		0.0002		0.0028		0.0556	
600 mg vs placebo			0.8562		0.0558		0.0306		0.0025		0.0194		0.0913	
750 mg vs placebo			0.9783		0.4270		0.0083		0.0081		0.1284		0.4788	
Haloperidol 12 mg vs placebo			0.2360		0.0010		0.0014		0.0009		0.0007		0.0364	
Quetiapine 300 mg* vs haloperidol 12 mg			0.9994		0.8752		0.9999		0.9907		0.9827		1.0000	

*Best quetiapine dose overall.

TABLE Trial 0013 - Mean change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Treatment groups	Treatment week													
	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
Quetiapine 75 mg	52	4.90	52	-0.20	52	-0.28	52	-0.18	52	-0.05	52	-0.13	52	-0.15
150 mg	48	5.00	48	-0.11	48	-0.18	48	-0.31	48	-0.32	48	-0.45	48	-0.49
300 mg	51	5.08	51	-0.28	51	-0.48	51	-0.64	51	-0.69	51	-0.73	51	-0.69
600 mg	51	4.88	51	-0.03	51	-0.33	51	-0.45	51	-0.52	51	-0.46	51	-0.46
750 mg	54	5.00	54	-0.17	54	-0.29	54	-0.49	54	-0.60	54	-0.54	54	-0.46
Haloperidol 12 mg	50	5.02	50	-0.36	50	-0.62	50	-0.64	50	-0.62	50	-0.71	50	-0.69
Placebo	51	4.92	51	-0.07	51	0.10	51	0.23	51	0.22	51	0.25	51	0.25
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.8494		0.1271		0.1348		0.5034		0.2321		0.2215	
150 mg vs placebo			0.9991		0.3803		0.0304		0.0331		0.0045		0.0039	
300 mg vs placebo			0.4219		0.0056		0.0001		<0.0001		<0.0001		0.0001	
600 mg vs placebo			0.9987		0.0625		0.0030		0.0013		0.0030		0.0049	
750 mg vs placebo			0.9205		0.1039		0.0011		0.0002		0.0007		0.0042	
Haloperidol 12 mg vs placebo			0.0468		0.0001		0.0001		0.0001		0.0001		0.0001	
Quetiapine 300 mg* vs haloperidol 12 mg			0.9805		0.8894		1.0000		0.9957		1.0000		1.0000	

*Best quetiapine dosage overall.

TABLE Trial 0013 - Mean change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	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
Quetiapine 75 mg	52	4.90	52	-0.20	47	-0.37	25	-0.79	22	-0.62	17	-1.03	16	-1.03
150 mg	48	5.00	48	-0.11	46	-0.23	37	-0.51	25	-0.74	23	-0.95	21	-1.10
300 mg	51	5.08	51	-0.28	48	-0.49	41	-0.70	32	-1.02	29	-1.06	24	-1.21
600 mg	51	4.88	51	-0.03	42	-0.49	35	-0.79	30	-1.16	29	-1.14	27	-1.19
750 mg	54	5.00	54	-0.17	48	-0.35	36	-0.67	31	-0.93	30	-0.78	29	-0.75
Haloperidol 12 mg	50	5.02	50	-0.36	45	-0.67	36	-0.82	24	-1.07	20	-1.35	18	-1.35
Placebo	51	4.92	51	-0.07	46	0.04	30	-0.04	26	-0.21	22	-0.13	17	-0.34
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.8494		0.1052		0.0173		0.4179		0.0143		0.1957	
150 mg vs placebo			0.9991		0.4403		0.1642		0.1705		0.0159		0.0990	
300 mg vs placebo			0.4219		0.0173		0.0166		0.0060		0.0024		0.0357	
600 mg vs placebo			0.9987		0.0219		0.0075		0.0011		0.0009		0.0381	
750 mg vs placebo			0.9205		0.1341		0.0332		0.0203		0.0559		0.5341	
Haloperidol 12 mg vs placebo			0.0468		0.0002		0.0015		0.0026		0.0001		0.0066	
Quetiapine 300 mg* vs haloperidol 12 mg			0.9805		0.7658		0.9808		0.9998		0.7048		0.9896	

*Best quetiapine dosage overall.

TABLE Trial 0013 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Treatment groups	Treatment week													
	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
Quetiapine 75 mg	52	3.84	52	-0.35	52	-0.46	52	-0.29	52	-0.29	52	-0.34	52	-0.38
150 mg	48	3.95	48	-0.27	48	-0.52	48	-0.57	48	-0.68	48	-0.70	48	-0.74
300 mg	51	3.77	51	-0.31	51	-0.71	51	-0.84	51	-0.93	51	-0.81	51	-0.87
600 mg	51	3.54	51	-0.38	51	-0.54	51	-0.77	51	-0.76	51	-0.70	51	-0.73
750 mg	53	3.63	53	-0.32	53	-0.47	53	-0.72	53	-0.68	53	-0.60	53	-0.58
Haloperidol 12 mg	50	3.63	50	-0.39	50	-0.74	50	-0.81	50	-0.72	50	-0.80	50	-0.74
Placebo	51	3.74	51	-0.24	51	-0.20	51	-0.07	51	-0.05	51	-0.02	51	0.05
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.9521	0.5886	0.8062	0.7417	0.5157	0.2446						
150 mg vs placebo			0.9998	0.4064	0.1164	0.0318	0.0216	0.0061						
300 mg vs placebo			0.9913	0.0553	0.0035	0.0007	0.0040	0.0007						
600 mg vs placebo			0.8678	0.3353	0.0095	0.0100	0.0177	0.0064						
750 mg vs placebo			0.9896	0.5170	0.0178	0.0264	0.0564	0.0379						
Haloperidol 12 mg vs placebo			0.3875	0.0091	0.0013	0.0045	0.0011	0.0013						
Quetiapine 300 mg [#] vs haloperidol 12 mg			0.9901	0.9999	1.0000	0.8072	1.0000	0.9741						

*Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

[#]Best quetiapine dosage overall.

TABLE Trial 0013 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	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
Quetiapine 75 mg	52	3.84	52	-0.35	46	-0.55	25	-0.95	22	-1.02	17	-1.48	16	-1.52
150 mg	48	3.95	48	-0.27	46	-0.55	37	-0.75	25	-1.03	23	-1.06	21	-1.08
300 mg	51	3.77	51	-0.31	49	-0.71	40	-1.00	32	-1.45	29	-1.22	24	-1.61
600 mg	51	3.54	51	-0.38	42	-0.62	35	-1.11	30	-1.43	29	-1.30	27	-1.39
750 mg	53	3.63	53	-0.32	48	-0.46	36	-1.01	31	-1.07	30	-0.96	29	-0.99
Haloperidol 12 mg	50	3.63	50	-0.39	45	-0.76	35	-1.03	24	-1.12	19	-1.43	18	-1.42
Placebo	51	3.74	51	-0.24	46	-0.27	30	-0.37	26	-0.52	21	-0.60	17	-0.68
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.9521		0.5933		0.2114		0.4232		0.0994		0.1651	
150 mg vs placebo			0.9998		0.5995		0.5016		0.3772		0.5758		0.7331	
300 mg vs placebo			0.9913		0.1626		0.0850		0.0121		0.2416		0.0647	
600 mg vs placebo			0.8678		0.3986		0.0393		0.0160		0.1560		0.2012	
750 mg vs placebo			0.9896		0.8587		0.0885		0.2584		0.7296		0.8452	
Haloperidol 12 mg vs placebo			0.3875		0.0292		0.0237		0.0809		0.0385		0.0859	
Quetiapine 300 mg [#] vs haloperidol 12 mg			0.9901		0.9994		1.0000		0.7303		0.9605		0.9791	

*Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

[#]Best quetiapine dose overall.

TABLE Trial 0013 - Mean change from baseline in SANS summary score (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Treatment groups	Treatment week													
	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
Quetiapine 75 mg	46	14.59	45	-0.10	46	-0.45	46	-0.17	46	-0.32	46	-0.40	46	-0.62
150 mg	45	14.73	44	-0.27	45	-0.50	45	-0.72	45	-0.42	45	-0.85	45	-0.78
300 mg	49	14.24	49	-0.46	49	-1.53	49	-1.92	49	-1.67	49	-1.47	49	-1.56
600 mg	49	14.35	48	-0.11	48	-0.46	49	-1.06	49	-1.23	49	-0.88	49	-0.98
750 mg	48	15.46	47	-0.18	47	-0.41	47	-0.82	47	-0.84	48	-0.57	48	-0.50
Haloperidol 12 mg	50	14.72	47	-0.84	50	-1.77	50	-1.79	50	-1.60	50	-1.75	50	-1.83
Placebo	50	13.88	50	0.82	50	0.68	50	0.88	50	0.80	50	1.12	50	0.76
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.3107		0.2707		0.3627		0.3604		0.1155		0.2068	
150 mg vs placebo			0.1702		0.2405		0.0667		0.2855		0.0230		0.1371	
300 mg vs placebo			0.0667		0.0024		0.0001		0.0018		0.0009		0.0059	
600 mg vs placebo			0.2798		0.2589		0.0131		0.0147		0.0168		0.0618	
750 mg vs placebo			0.2253		0.3054		0.0407		0.0754		0.0599		0.2771	
Haloperidol 12 mg vs placebo			0.0020		0.0001		0.0001		0.0006		0.0001		0.0003	
Quetiapine 300 mg* vs haloperidol 12 mg			0.9301		0.9952		0.9998		1.0000		0.9932		0.9950	

*Best quetiapine dosage overall.

TABLE Trial 0013 - Mean change from baseline in SANS summary score (adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	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
Quetiapine 75 mg	46	14.6	45	-0.10	41	-0.77	21	-1.52	16	-2.08	14	-2.10	13	-3.22
150 mg	45	14.7	44	-0.27	41	-0.74	35	-1.28	25	-1.01	23	-2.15	21	-2.02
300 mg	49	14.2	49	-0.46	47	-1.53	38	-2.39	32	-2.38	29	-2.30	24	-3.14
600 mg	49	14.2	48	-0.11	40	-0.89	34	-1.64	29	-2.80	28	-2.05	27	-2.67
750 mg	48	15.5	47	-0.18	46	-0.45	34	-1.47	28	-1.09	29	-0.82	27	-0.85
Haloperidol 12 mg	50	14.7	50	-0.84	45	-1.98	34	-2.55	23	-2.37	19	-3.27	16	-3.46
Placebo	50	13.9	50	0.82	42	0.38	27	0.68	23	0.54	19	1.29	16	-0.61
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.3107		0.3162		0.0445		0.0518		0.0058		0.0672	
150 mg vs placebo			0.1702		0.3345		0.0414		0.3081		0.0011		0.4248	
300 mg vs placebo			0.0667		0.0186		0.0003		0.0047		0.0003		0.0317	
600 mg vs placebo			0.2798		0.2323		0.0114		0.0012		0.0009		0.0956	
750 mg vs placebo			0.2253		0.5970		0.0217		0.2407		0.0630		0.9989	
Haloperidol 12 mg vs placebo			0.0020		0.0007		0.0001		0.0047		0.0001		0.0100	
Quetiapine 300 mg* vs haloperidol 12 mg			0.9301		0.9422		0.9995		1.0000		0.6690		0.9964	

*Best quetiapine dosage overall.

Appendix 7.2.4

STUDY 0012 INVESTIGATORS (ADAPTED FROM SPONSOR'S ELECTRONIC STUDY REPORT)

INVESTIGATOR AND CENTER LIST			
(Centers that recruited patients)			
Center number	Investigator	Address	Number of patients entered
002	Dr D J King (Principal investigator)	Queen's University of Belfast United Kingdom	9
001	Prof S R Hirsch	Department of Psychiatry Charing Cross Hospital United Kingdom	31
003	Dr B G Ferguson	Department of Psychiatry, Mapperley Hospital Nottingham United Kingdom	10
004	Dr R Didi	C.H.S. La Chartreuse France	4
005	Dr T K Szulecka	Department of Psychiatry Doncaster Royal Infirmary, U.K.	17
006	Dr J Lynch	Department of Psychiatry St Michael's Hospital Clonmel Ireland	15
007	Dr S B Mahapatra	Department of Psychiatry The General Hospital Hartlepool U.K.	9
008	Dr D J MacFarlane	Department of Psychiatry Ards Hospital Northern Ireland	3
011	Dr W Kissling	Psychiatrische Klinik der Tu Muenchen Munich	7
012	Dr S Shaw	Stanley Royd Hospital West Yorkshire U.K.	2
013	Dr P S Meats	Department of Psychiatry King's Mill Hospital Sutton-in-Ashfield U.K.	1
014	Prof G W Fenton	Department of Psychiatry University of Dundee U.K.	4
015	Prof T Burns	Department of Mental Health Sciences Cranmer Terrace London U.K.	5
016	Dr R Erkwow	Psychiatrische Klinik der RWTH Aachen Germany	4
017	Dr F M Corrigan	Department of Psychiatry Argyll and Bute Hospital Argyll U.K.	3
019	Dr C S Thomas	Department of Psychiatry University Hospital of South Manchester Manchester U.K.	5
020	Prof R Priest	Department of Psychiatry St Mary's Hospital Medical School London U.K.	2
021	Dr F Mesotten	Medisch Centrum St Jozef Belgium	3
022	Dr J M Martens	Sint Lucaskliniek Belgium	2

023	Dr G Beckers	Medister Jagersdreef 100 Belgium	5
024	Dr G Dierick	Ziekenhuis Reigerlo Belgium	3
025	Dr Y Schroeder	Psychiatrische Universitaetsklinik Heidelberg Germany	5
027	Prof W W Fleischhacker	Department of Psychiatry Innsbruck University Clinics Austria	4
028	Dr C Geretsegger	Landes-Nervenklinik Salzburg Austria	3
029	Dr J Stoessl	Psychiatrisches Krankenhaus der Stadt Wien Vienna Austria	12
030	Prof G Darcourt	C.H.R. Hopital Pasteur Nice Cedex France	7
031	Prof M Patris	C.H.U. Clinique Psychiatrique Strasbourg France	7
032	Dr P H Bern	Hotel Dieu France	3
033	Prof J M Azorin	C.H.U. La Timone Clinique de Psychiatrie 13385 Marseille Cedex 4 France	3
034	Dr F Ruyer	C.H.S. d'Evreux 27022 Evreux Cedex France	5
035	Prof J Tignol	C.H.S. Charles Perrens 33076 Bordeaux Cedex France	7
036	Dr M Marie-Cardine	C.H.S. Le Vinatier 59677 Bron Cedex France	11
037	Dr A Braconnier	Centre de l'Eau Vive 91450 Soisy-sur-Seine France	3
038	Dr C Gaussares	C.H.S. Charles Perrens 33076 Bordeaux Cedex France	4
039	Dr J Daumer	C.H.S. Charcot 56854 Caudan France	1
040	Dr G Clerc	C.H.S. de Pontorson 50170 Pontorson France	12
041	Dr J P Chabannes	C.H.S. de Bassens B P 1126 73011 Chambéry Cedex France	5
042	Dr G E Duboc	C.H.S. de Navarre	3

		27022 Evreux Cedex France	
043	Dr F Caroli	Hopital Sainte Anne 75674 Paris Cedex 14 France	7
044	Dr R de Beaurepaire	C.H.S. Le Bon Sauveur 14012 Caen France	5
045	Prof R H Belmaker	Psychiatric Center Beer Sheva Israel	19
046	Dr M Avnon	Psychiatric Center Shaar Menashe Israel	14
047	Prof A Weizman	Psychiatric Department Geha Psychiatric Hospital Israel	12
048	Dr J P Malanowski	Psychiatric Clinic Beverin Cazis Switzerland	1
049	Dr S P Kutcher	Department of Psychiatry Sunnybrook Health Sciences Center Toronto Ontario M4N 3M5 Canada	4
050	Prof G Buchkremer	Psychiatrische Universitätsklinik Tübingen 72076 Tübingen Germany	5
051	Prof R Michaelis	Krankenhaus Itzehoe Abt Psychiatrie 25524 Itzehoe Germany	6
052	Dr M Krausz	Psychiatrische und Nervenlinik Poliklinik der Universität Hamburg Germany	6
053	Prof E Ruther	Psychiatrische Klinik der Göttingen Universität Germany	6
054	Prof R Uebelhack	Humboldt-Universität Berlin Abteilung Psychiatrie Germany	3
055	Prof U H Peters	Med Einrichtung der Universität Köln Fachabteilung Psychiatrie Germany	2
056	Dr D Ebert	Psychiatrische Klinik und Poliklinik 91054 Erlangen Germany	6
057	Prof G A Rudolf	Klinik und Poliklinik für Psychiatrie der Wilhelms Universität Muenster Germany	7
059	Dr E Stip	Centre de Recherche Fernand - Seguin Quebec H1N 3V2 Canada	12
060	Dr R Manchanda	Department of Psychiatry University Hospital London Ontario N6A 5A5	8

		Canada	
061	Dr A Malla	Department of Psychiatry Victoria Hospital Corporation London Ontario N6G 4G5	7
		Canada	
062	Dr J Beau	Centre Hospitalier Malartic Malartic Quebec J0Y 1Z0	8
		Canada	
063	Dr P Silverstone	Department of Psychiatry University of Alberta Hospital Edmonton Alberta T6G 2B7	20
		Canada	
064	Dr A Parashos	Aristotelian University of Thessaloniki Thessaloniki Greece	10
065	Prof E Smeraldi	DSNP Ospedale S Raffaele 29-20127 Milan Italy	10
066	Prof L Ravizza	Universita di Torino 15-10126 Turin Italy	6
067	Dr G Covelli	Ospedale Bolognini 1-24068 Seriate Italy	9
068	Prof A Ermentini	Universita di Brescia Ospedale Civile Italy	9
069	Prof L Pavan	Universita di Padova Italy	4
070	Dr C A Robotti	Servizio di Psichiatria Ospedale Maggoire di Borgotrento 1-37126 Verona Italy	7
072	Prof P Pancheri	Universita di Roma Italy	3
073	Dr P Laddomada	Primario Servizio Psichiatrico Ospedale Sirai Italy	6
074	Dr M Bassi	Servizio di Salute Mentale 153-43036 Fidenza Italy	4
075	Prof G Invernizzi	Universita Degla Studi di Milano Ospedale Maggiore Policlinico Italy	8
076	Dr R Longoni	Unita Operativa di Psichiatria Ospedale Civile Milan Italy	3
077	Prof M Casacchia	Universita dell'Aquila Ospedale Santa Maria D Collemaggio Italy	8
078	Prof V Rapisarda	Universita di Catania Ospedale Policlin Italy	11
079	Prof F Rinaldi	Universita di Napoli	14

		Italy	
080	Prof A P Palha	Casa de Saude de Bom Jesus	13
		Nogueiro	
		4719 Braga	
		Portugal	
081	Dr M J Paes de Sousa	Hospital de Santa Maria	6
		Servicio de Psiquiatria	
		1600 Lisboa	
		Portugal	
082	Dr L M Ferreira	Hospital Magalhaes Lemos	8
		Servico Povia Vila do Conde	
		4100 Porta	
		Portugal	
083	Dr P Sirota	Department 6A	12
		Abarbanel Mental Health Center	
		Bat-Yam	
		Israel	
084	Dr A Chinchilla	Servicio De Psiquiatria	23
		Hospital Ramon y Cajal	
		Madrid	
		Spain	
085	Dr T Palomo	Servicio de Psiquiatria	8
		Hospital 12 de Octubre	
		Madrid	
		Spain	
086	Dr S Cervera	Servicio de Psiquiatria	7
		Clinica Universitaria de Navarra	
		31080 Pamplona	
		Spain	
087	Dr M Gutierrez	Servicio de Psiquiatria	9
		Hospital Santiago	
		Vitoria	
		Spain	
088	Dr J Izquierdo de la Torre	Servicio de Psiquiatria	7
		Hospital Clinico de Salamanca	
		Spain	
089	Prof A Vaz Serra	Hospitais da Universidade de Coimbra	12
		Servico de Psiquiatria	
		Portugal	
091	Dr G Bartko	Department of Psychiatry	11
		South-Pest Hospital	
		Budapest	
		Hungary	
092	Dr C Banki	Department of Psychiatry	13
		Regional Neuropsychiatric Institute	
		Nagykallo	
		Hungary	
093	Dr G Ostorharics	Department of Psychiatry	13
		Petz A Hospital	
		Gyor, Vasvari P U 2	
		Hungary	
097	Dr L Mauas	Department A	7
		Shalvata Mental Health Center	
		Hod-Hasharon	
		Israel	
098	Dr H Silver	Mazra Psychiatric Hospital	7
		Akko, Israel	

Appendix Table 7.2.4.1 Trial 0012 - Demographic characteristics (adapted from sponsor's electronic submission)

Treatment groups	n	Age (years)		Sex (n [%])		Race (n [%])				
		Mean	Range	Male	Female	Caucasian	Black	Hispanic	Asian/ Oriental	Other
Quetiapine										
150 mg TID	209	34		128 (61)	81 (39)	195 (93)	6 (3)	2 (1)	5 (2)	1 (1)
225 mg BID	200	37		135 (68)	65 (33)	191 (96)	3 (2)	1 (1)	2 (1)	3 (2)
25 mg TID	209	36		146 (70)	63 (30)	201 (96)	3 (1)	0 (0)	2 (1)	3 (1)

Appendix TABLE 7.2.4.2 Trial 0012 - Patient completion rates (adapted from sponsor's electronic submission)

Treatment groups	Number randomized	Intent-to-treat sample*	Number (%) of patients completing					
			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Quetiapine								
225 mg BID	200	195	195 (100)	180 (92.3)	142 (72.8)	121 (62.1)	108 (55.4)	103 (52.8)
150 mg TID	209	204	204 (100)	177 (86.8)	145 (71.1)	133 (65.2)	122 (59.8)	114 (55.9)
25 mg BID	209	198	198 (100)	175 (88.4)	134 (67.7)	117 (59.1)	100 (50.5)	94 (47.5)

*Patients who had at least one efficacy assessment on medication, omitting patients from excluded sites.

TABLE Trial 0012 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Quetiapine Treatment groups	Treatment week													
	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
225 mg BID	195	42.14	195	-3.74	195	-6.08	195	-7.79	195	-8.66	195	-9.49	195	-9.98
150 mg TID	204	42.74	203	-2.00	204	-4.36	204	-6.43	204	-7.09	204	-8.49	204	-8.59
25 mg BID	197	41.68	197	-1.99	197	-3.18	197	-4.68	197	-4.75	197	-5.54	197	-5.41
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.0811		0.0239		0.0307		0.0100		0.0140		0.0055	
150 mg TID vs 25 mg BID			0.9926		0.3545		0.2184		0.1199		0.0636		0.0503	
225 mg BID vs 150 mg TID			0.0804		0.1745		0.3395		0.2938		0.5274		0.3943	

TABLE Trial 0012 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Observed case analysis														
Quetiapine Treatment groups	Treatment week													
	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
225 mg BID	195	42.14	195	-4.10	180	-8.12	141	-13.15	121	-16.66	108	-19.33	103	-21.15
150 mg TID	204	42.74	203	-2.38	177	-6.57	145	-12.24	133	-14.67	122	-18.36	114	-19.62
25 mg BID	197	41.68	197	-2.33	174	-5.63	134	-10.51	117	-13.29	100	-16.52	94	-17.21
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.0776		0.0487		0.0766		0.0323		0.0977		0.0273	
150 mg TID vs 25 mg BID			0.9612		0.4561		0.2433		0.3672		0.2650		0.1682	
225 mg BID vs 150 mg TID			0.0836		0.2181		0.5302		0.1908		0.5507		0.3667	

TABLE Trial 0012 - Grouped change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission) Last observation carried forward analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Quetiapine 225 mg BID														
Baseline severity scores														
moderate (4)	51	26												
marked (5)	92	47												
severe (6)	44	23												
most severe (7)	8	4												
Change from baseline														
-3 or less			1	1	4	2	8	4	17	9	22	11	22	11
-2			8	4	16	8	23	12	18	9	21	11	23	12
-1			31	16	54	28	57	29	64	33	59	30	59	30
0			139	71	101	52	86	44	73	37	68	35	66	34
+1 or greater			16	8	20	10	21	11	23	12	25	13	25	13
Quetiapine 150 mg TID														
Baseline severity scores														
moderate (4)	54	26												
marked (5)	87	42												
severe (6)	58	28												
most severe (7)	6	3												
Change from baseline														
-3 or less					2	1	6	3	9	4	12	6	16	8
-2			4	2	9	4	24	12	29	14	30	15	29	14
-1			38	19	56	27	49	24	52	25	54	26	51	25
0			136	67	112	55	98	48	84	41	79	39	77	38
+1 or greater			26	13	26	13	28	14	31	15	30	15	32	16

TABLE Trial 0012 - Grouped change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission) (continued)

Last observation carried forward analysis														
Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Quetiapine 25 mg BID														
Baseline severity scores														
moderate (4)	62	31												
marked (5)	85	43												
severe (6)	45	23												
most severe (7)	6	3												
Change from baseline														
-3 or less			1	1			3	2	5	3	7	4	10	5
-2			5	3	13	7	13	7	16	8	22	11	19	10
-1			23	12	46	23	60	30	55	28	49	25	52	26
0			148	75	110	56	88	44	85	43	81	41	78	39
+1 or greater			21	11	29	15	34	17	37	19	39	20	39	20
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.6130		0.1230		0.0790		0.0160		0.0070		0.0290	
150 mg TID vs 25 mg BID			0.2330		0.4140		0.1530		0.1800		0.3310		0.3440	
225 mg BID vs 150 mg TID			0.2260		0.4490		0.6520		0.0920		0.2140		0.4450	

TABLE Trial 0012 - Grouped change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission)

Observed case analysis														
Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Quetiapine 225 mg BID														
Baseline severity scores														
moderate (4)	51	26												
marked (5)	92	47												
severe (6)	44	23												
most severe (7)	8	4												
Change from baseline														
-3 or less			1	1	4	2	7	5	15	12	19	18	19	18
-2			8	4	16	9	22	16	16	13	18	17	20	19
-1			31	16	54	30	49	35	53	44	44	41	42	41
0			139	71	1	51	58	41	33	27	23	21	20	19
+1 or greater			16	8	15	8	6	4	4	3	4	4	2	2
Quetiapine 150 mg TID														
Baseline severity scores														
moderate (4)	54	26												
marked (5)	87	42												
severe (6)	58	28												
most severe (7)	6	3												
Change from baseline														
-3 or less					2	1	6	4	9	7	12	10	16	14
-2			4	2	9	5	23	16	28	21	28	23	26	23
-1			38	19	54	31	45	31	45	34	47	39	42	37
0			136	67	96	54	61	42	42	32	31	25	26	23
+1 or greater			26	13	16	9	10	7	9	7	4	3	4	4

TABLE Trial 0012 - Grouped change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission) (continued)

Observed case analysis														
Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Quetiapine 25 mg BID														
Baseline severity scores														
moderate (4)	62	31												
marked (5)	85	43												
severe (6)	45	23												
most severe (7)	6	3												
Change from baseline														
-3 or less			1	1			3	2	5	4	7	7	10	11
-2			5	3	11	6	12	9	14	12	20	20	17	18
-1			23	12	46	26	49	37	41	35	30	30	32	34
0			148	75	100	57	57	43	50	43	39	39	33	35
+1 or greater			21	11	18	10	13	10	7	6	4	4	2	2
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.5960		0.1480		0.1560		0.0230		0.0170		0.1110	
150 mg TID vs 25 mg BID			0.2230		0.5430		0.2110		0.0920		0.1530		0.2860	
225 mg BID vs 150 mg TID			0.2280		0.5590		0.8790		0.1070		0.4300		0.8370	

TABLE Trial 0012 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission) : Last observation carried forward analysis

Quetiapine Treatment Groups	Treatment week													
	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
225 mg BID	195	3.55	195	-0.37	195	-0.63	195	-0.79	195	-0.86	195	-0.92	195	-0.96
150 mg TID	204	3.52	203	-0.23	204	-0.47	204	-0.65	204	-0.68	204	-0.81	204	-0.86
25 mg BID	197	3.47	197	-0.25	197	-0.41	197	-0.53	197	-0.52	197	-0.61	197	-0.62
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.1445		0.0286		0.0194		0.0054		0.0157		0.0090	
150 mg TID vs 25 mg BID			0.7700		0.5862		0.2711		0.1708		0.1063		0.0649	
225 mg BID vs 150 mg TID			0.0780		0.0951		0.2054		0.1468		0.4066		0.4239	

TABLE Trial 0012 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission): Observed case analysis

Quetiapine Treatment groups	Treatment week													
	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
225 mg BID	195	3.55	195	-0.40	180	-0.78	141	-1.16	121	-1.43	108	-1.64	103	-1.79
150 mg TID	204	3.52	203	-0.25	177	-0.62	145	-1.07	133	-1.23	122	-1.55	114	-1.70
25 mg BID	197	3.47	197	-0.27	174	-0.58	134	-0.93	117	-1.13	100	-1.42	94	-1.49
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.1419		0.0532		0.0750		0.0339		0.1237		0.0476	
150 mg TID vs 25 mg BID			0.7932		0.7068		0.2737		0.4622		0.3529		0.1722	
225 mg BID vs 150 mg TID			0.0815		0.1176		0.4765		0.1460		0.5070		0.4994	

*Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

TABLE Trial 0012 - Mean change from baseline in SANS summary score (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
Quetiapine Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mcan	n	mean	n	mean	n	mcan	n	mcan	n	mean	n	mcan
225 mg BID	189	14.38	188	-0.52	189	-0.80	189	-1.15	189	-1.36	189	-1.53	189	-1.68
150 mg TID	197	14.69	194	-0.14	197	-0.76	197	-1.05	197	-1.32	197	-1.30	197	-1.37
25 mg BID	190	14.38	188	-0.10	190	-0.39	190	-0.81	190	-0.74	190	-0.81	190	-0.85
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.0553		0.1382		0.2647		0.0698		0.0415		0.0216	
150 mg TID vs 25 mg BID			0.8712		0.1764		0.4413		0.0829		0.1563		0.1425	
225 mg BID vs 150 mg TID			0.0768		0.8854		0.7220		0.9237		0.5212		0.3929	

TABLE Trial 0012 - Mean change from baseline in SANS summary score (adapted from sponsor's electronic submission)

Observed case analysis														
Quetiapine Treatment groups	Treatment week													
	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
225 mg BID	189	14.38	188	-0.59	176	-1.11	139	-1.89	119	-2.53	106	-3.02	100	-3.56
150 mg TID	197	14.69	194	-0.21	171	-1.19	138	-2.29	127	-3.01	117	-3.34	110	-3.73
25 mg BID	190	14.38	188	-0.16	166	-0.75	130	-1.76	116	-1.83	97	-2.66	93	-2.75
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.0524		0.2034		0.6984		0.0724		0.3929		0.0591	
150 mg TID vs 25 mg BID			0.8347		0.1276		0.1125		0.0023		0.0962		0.0212	
225 mg BID vs 150 mg TID			0.0807		0.7900		0.2195		0.2089		0.4121		0.6886	

APPENDIX TABLE 8.1.1.1 Deaths during or after trial treatment ended* (adapted from sponsor's electronic submission) Cutoff date: 3/1/96

Trial/center/ subject number	Age (y)	Sex	Dose [#] (mg/day)	Duration (days)	Cause of Death and Comments
Quetiapine					
0012/0023/2303	47	F	50	11	Suicide
0012/0091/9103	56	M	50	6	Progressive cerebral ischemic lesions consistent with a progressive basilar artery thrombosis, autopsy showed new basilar artery thrombus, severe cerebral atherosclerosis, and anencephalomalacia
0012OLE/0045/4502	56	M	500	52*	Cardiopulmonary arrest following several days of worsening angina
0012OLE/0062/6203	35	M	700	155*	Patient escaped hospital, stole car, died in Automobile accident
0012OLE/0080/8013	62	F	500	398	Died 3 days after a cerebrovascular accident; history of hypertension
0015OLE/0005/0514	56	M	300	700	Metastatic cancer from unknown primary
0048/0007/0703	92	M	150	191	Respiratory failure, Bronchopneumonia on autopsy (following transurethral resection of prostate)
0012OLE/0087/8702 ^{\$}	46	m	52 [@]	107	Committed suicide 11 weeks after d/c quetiapine
0048/0017/1703 [#]	81	m	50	15	Pneumonia after 15 days of quetiapine treatment; died 31 days after d/c quetiapine
0048/0007/0708	89	M	125	58	Aspiration Pneumonia; patient had Alzheimer's dementia and dysphagia
Placebo					
None	NA	NA	NA	NA	NA
Haloperidol					
0014/0043/4304	51	M	8	7	Sudden death, autopsy report: acute heart failure
Chlorpromazine					
None	NA	NA	NA	NA	NA
Blinded treatment**					
0031/0021/2104	50	M	UNK	55	Accidental drowning (autopsy: drowning)

*Additionally, two subjects (0014/0012/9002 and 0015/0012/9001) died (committed suicide) before randomization to trial treatment

^{\$} died more than 30 days after discontinuation of quetiapine treatment.

[#]The last full day's dose at time of death or withdrawal from the trial.

⁺Includes double-blind plus open-label treatment.

**Quetiapine or chlorpromazine

[@] mean daily dose

NA = Not applicable; UNK = Unknown

Table 8.1.1.1a Deaths that were not part of the NDA submission or safety update (From IND safety reports and interim IND safety summary presented in 9/20/96 submission) Note: case report forms or other detailed information were not available for these cases

Trial/center/ subject number	Age (y)	Sex	Dose (mg/day)	Dura- tion	Cause of Death and Comments
0402/015-003 Japan	40	m	Haloperidol		Found dead, possible water intoxication; no au- topsy
H-15-13 Japan 0201/013-001	27	f	blinded		suicide by hanging
0015 OLE No subject number listed	69	m	500	2 years	Hospitalized for treatment of deep vein thrombo- sis; found to have metastatic pancreatic cancer and died one month later (no autopsy)
0048/?/ 0310	77	m	500	295 d	Myocardial Infarction
0048 /0007/0712	64	m	100	205 d	Respiratory failure, aspiration in setting of progres- sive supranuclear palsy
0048/?/1306	65	f	175	328	Sepsis, esophageal cancer
0048/?/1310	81	f	75	190	Possible cardiopulmonary arrest

TABLE 8.1.1.2 Overall mortality in the integrated Phase II-III clinical program

	Number of subjects	Subject-years exposure ^a	Number of deaths ^b	Crude mortality rate	Mortality per 100 subject-years
Quetiapine	2387	865.3	8	0.34	0.92
Haloperidol	320	42.5	1	0.31	2.35
Chlorpromazine	100	9.2	0	0.00	0
Placebo	206	14.6	0	0.00	0

^aSubject-years is defined as the sum of all subjects' days on treatment (duration) divided by 365 days.

^bDeaths occurring within 30 days after trial treatment ended (excludes one death from Trial 0031, for which treatment assignment remains blinded).

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TABLE 8.1.5.3 Adverse events reported for at least 1% of quetiapine-treated subjects and for a higher percentage of quetiapine-treated subjects than subjects who received placebo in short-term, placebo-controlled Phase II-III trials (studies 0004, 0006, 0008, and 0013)
Adapted from sponsor's electronic ISS submission and draft labeling

Body system and COSTART Term	Number of subjects with adverse events (%)		p-value*
	Quetiapine (n = 510)	Placebo (n = 206)	
Whole body			
Headache	99 (19.4)	36 (17.5)	0.5150
Asthenia	18 (3.5)	6 (2.9)	0.7438
Abdominal pain	16 (3.1)	1 (0.5)	0.0236
Back pain	10 (2.0)	1 (0.5)	0.1928
Fever	8 (1.6)	2 (1.0)	0.5350
Chest pain	9 (1.8)	3 (1.5)	0.9053
Cardiovascular system			
Postural hypotension	36 (7.1)	5 (2.4)	0.0648
Tachycardia	36 (7.1)	10 (4.9)	0.3693
Hypertension	9 (1.8)	3 (1.5)	0.5763
Digestive system			
Constipation	44 (8.6)	10 (4.9)	0.0637
Dry mouth	33 (6.5)	6 (2.9)	0.0149
Dyspepsia	32 (6.3)	5 (2.4)	0.0816
Diarrhea	10 (2.0)	4 (1.9)	0.9926
GGT increased	8 (1.6)	1 (0.5)	0.0775
Hemic and lymphatic system			
Leukopenia	8 (1.6)	0	0.0938
Metabolic and nutritional disorders			
SGPT increased	31 (6.1)	3 (1.5)	0.0003
SGOT increased	18 (3.5)	2 (1.0)	0.0065
Weight gain	10 (2.0)	0	0.0471
Musculoskeletal system			
Myalgia	6 (1.2)	1 (0.5)	0.3714
Nervous system			
Somnolence	89 (17.5)	22 (10.7)	0.0005
Dizziness	49 (9.6)	9 (4.4)	0.0178
Anxiety	16 (3.1)	6 (2.9)	0.6636
Respiratory system			
Rhinitis	17 (3.3)	1 (0.5)	0.0680
Skin and appendages			
Rash	22 (4.3)	6 (2.9)	0.4106
Dry skin	6 (1.2)	2 (1.0)	0.7798
Special senses			
Ear pain	6 (1.2)	0	0.1371
Urogenital system			
Urinary tract infection	7 (1.4)	1 (0.5)	0.2799

*p-value from Cochran-Mantel-Haenszel test, adjusting for trial. NC = Not calculated
 Events for which the quetiapine incidence was equal to or less than placebo are not listed in the table, but included the following: pain, infection, hostility, accidental injury, hypotension, nausea, vomiting, agitation, insomnia, nervousness, akathisia, hypertonia, tremor, depression, paresthesia, pharyngitis, amblyopia.

TABLE 8.1.5.4

Other Events Observed During the Clinical Trial Evaluation of SEROQUEL: During its clinical trial assessment, multiple doses of SEROQUEL (quetiapine) were administered to 2162 patients in Phase 2 and 3 studies. The conditions and duration of exposure to SEROQUEL varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term and longer-term exposure.⁽¹³⁶⁾ In most studies, untoward events were obtained by spontaneous report and recorded by clinical investigators in terminology of their own choosing. Consequently, it is impossible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the listings that follow, spontaneously reported adverse events were classified using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) preferred terms. The frequencies presented, therefore, represent the proportion of the 2162 patients exposed to multiple doses of SEROQUEL who experienced an event of the type cited on at least one occasion while receiving SEROQUEL. All reported events are included except those already listed in the 1% table (appendix table 8.1.5.3), those events for which causality has not been established, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of descending frequency according to the following definitions: frequent adverse events are those reported in at least 1/100 patients; infrequent adverse events are those reported in 1/100 to 1/1000 patients; rare events are those reported in less than 1/1000 patients

Nervous System: *Frequent:* insomnia, agitation, nervousness, akathisia, hypertonia, tremor, depression, extrapyramidal syndrome, paraesthesia; *Infrequent:* abnormal dreams, thinking abnormal, vertigo, speech disorder, movement disorder, tardive dyskinesia, amnesia, dyskinesia, psychosis, cogwheel rigidity, confusion, hyperkinesia, dysarthria, hallucinations, hypokinesia, paranoid reaction, convulsion, dystonia, incoordination, libido increased, urinary retention, delusions, myoclonus, schizophrenic reaction, apathy, depersonalization, oculogyric crisis, personality disorder; abnormal gait, ataxia, catatonic reaction, drug dependence, hemiplegia, stupor; *Rare:* akinesia, buccoglossal syndrome, CNS neoplasia, delirium, euphoria, grand mal convulsion, libido decreased, manic reaction, neurosis aphasia, choreoathetosis, diplopia, emotional lability, facial paralysis, hypotonia, neuralgia, sleep disorder, subdural hematoma, torticollis, trismus

Body as a Whole: *Frequent:* pain, infection, accidental injury, flu syndrome, hostility; *Infrequent:* overdose, neck rigidity, neck pain, suicide attempt, cellulitis, malaise, pelvic pain, photosensitivity reaction, chills, intentional injury, abscess, cyst, face edema, sepsis; *Rare:* moniliasis, neuroleptic malignant syndrome, abdomen enlarged, accidental overdose, allergic reaction, cataract, granuloma, halitosis, hernia, injection site reaction, neoplasm.

Digestive System: *Frequent:* nausea, vomiting; *Infrequent:* increased salivation, anorexia, increased appetite, periodontal abscess, flatulence, rectal disorder, gastroenteritis, gingivitis, tooth disorder, gastritis, dysphagia, gastrointestinal disorder, stomatitis, thirst, rectal hemorrhage, tongue edema, tooth caries; *Rare:* fecal incontinence, glossitis, gum hemorrhage, melena, mouth ulceration, tongue disorder; biliary pain, cholecystitis, colitis, duodenal ulcer hemorrhage, hematemesis, hepatomegaly, intestinal obstruction, pancreatitis, peptic ulcer, ulcerative stomatitis.

Cardiovascular System: *Frequent:* hypotension, palpitation, syncope; *Infrequent:* vasodilatation, electrocardiogram abnormal, migraine, arrhythmia, cerebral ischemia; *Rare:* AV block first degree, bradycardia, deep vein thrombophlebitis, QT interval prolonged, ST segment elevated, supraventricular extrasystoles, angina pectoris, atrial fibrillation, bundle branch block, congestive heart failure, EKG abnormal, heart arrest, myocardial infarct, pallor, pericarditis, phlebitis, sinus bradycardia, T wave inverted, thrombophlebitis, ventricular extrasystoles

Respiratory System: *Frequent:* pharyngitis, cough increased, bronchitis; *Infrequent:* dyspnea, epistaxis, sinusitis, asthma, pneumonia; *Rare:* hiccup, hyperventilation, laryngitis, yawn.

Metabolic and Nutritional Disorders: *Frequent:* peripheral edema; *Infrequent:* weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, hypercholesterolemia; *Rare:* edema, gout, hyperglycemia, hypoglycemia, albuminuria, bilirubinemia, creatine phosphokinase increased, dehydration, healing abnormal, hyperkalemia, hypokalemia, lactic dehydrogenase increased, water intoxication.

Skin and Appendages: *Frequent:* sweating; *Infrequent:* pruritus, acne, fungal dermatitis, eczema, maculopapular rash, contact dermatitis, seborrhea; *Rare:* herpes simplex, herpes zoster, nail disorder, psoriasis, alopecia, cutaneous moniliasis, exfoliative dermatitis, furunculosis, hirsutism, pustular rash, skin discoloration, vesiculobullous rash.

Urogenital System: *Infrequent:* urinary incontinence, dysmenorrhea, impotence, vaginitis, dysuria, cystitis, metrorrhagia, urinary frequency, abnormal ejaculation, urination impaired; *Rare:* orchitis, polyuria, vaginal moniliasis, acute kidney failure, anorgasmia, anuria, bladder stenosis, breast abscess, breast carcinoma, breast enlargement, breast pain, cervical carcinoma, female lactation, gynecomastia, menstrual disorder, nocturia, pyuria, urine abnormality, vaginal hemorrhage, vulvovaginitis.

Special Senses: *Frequent:* amblyopia; *Infrequent:* conjunctivitis, cataract specified, otitis media, abnormal vision, dry eyes, blepharitis, otitis externa, taste perversion, tinnitus, eye pain; *Rare:* abnormality of accommodation, glaucoma, deafness, eye hemorrhage, hyperacusis, lacrimation.

Musculoskeletal System: *Infrequent:* pathological fracture, myasthenia, joint disorder, twitching, arthralgia, leg cramps, bone pain, arthritis; *Rare:* arthrosis, osteoporosis, ptosis, tendon disorder, tenosynovitis, tetany.

Hemic and Lymphatic System: *Infrequent:* leukocytosis, anemia, eosinophilia, ecchymosis, hypochromic anemia; *Rare:* cyanosis, hemolysis, lymphadenopathy, thrombocytopenia, iron deficiency anemia, petechiae, white blood cells abnormal

Endocrine System: *Infrequent:* hypothyroidism, diabetes mellitus; *Rare:* hyperthyroidism, thyroid disorder, thyroiditis

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TABLE 8.1.6.1 Clinical laboratory assessments by trial, Phase II-III trials (adapted from sponsor's electronic iss)

	Phase II-III trial										
	0004	0005	0006	0007	0008	0012	0013	0014	0015	0048	OLE
Hematology											
Hematocrit	X	X	X	X	X		X		X	X	US only
Hemoglobin	X	X	X	X	X	X	X	X	X	X	X
RBC	X	X	X	X	X		X		X	X	US only
Reticulocytes	X	US only									
WBC	X	X	X	X	X	X	X	X	X	X	X
Differential	X	X	X	X	X	X	X	X	X	X	X
Neutrophils	X	X	X	X	X	X	X	X	X	X	X
Bands	X										
Lymphocytes	X	X	X	X	X	X	X	X	X	X	X
Monocytes	X	X	X	X	X	X	X	X	X	X	X
Eosinophils	X	X	X	X	X	X	X	X	X	X	X
Basophils	X	X	X	X	X	X	X	X	X	X	X
Platelets	X	X	X	X	X	X	X	X	X	X	X
Chemistry											
Sodium	X	X	X	X	X				X	X	US only
Potassium	X	X	X	X	X				X	X	US only
Chloride	X	US only	X		US only				X	X	US only
Glucose	X	X	X	X	X				X	X	US only
BUN	X	X	X	X	US only				X	X	US only
Creatinine	X	X	X	X	X				X	X	US only
Phosphorus	X	US only	X		US only						
Calcium	X	US only	X		US only				X	X	US only
Cholesterol	X	US only	X		US only						
Triglycerides	X	US only	X		US only						
ALT (SGPT)	X	X	X	X	X	X	X	X	X	X	X
AST (SGOT)	X	X	X	X	X	X	X	X	X	X	X
GGT	X	X	X	X	X						
Alk phos	X	X	X	X	X	X	X	X	X	X	X
Total bilirubin	X	X	X	X	X	X	X	X	X	X	X
Total protein	X	X	X	X	X						
Albumin	X	X	X	X	X				X	X	US only

TABLE
Clinical laboratory assessments by trial (continued)

	0004	0005	0006	0007	0008	0012	0013	0014	0015	0048	OLE
Chemistry (cont)											
Total T ₄	X	X	X	X	X		X		X		
Total T ₃	X	X	X	X	X		X		X		
Free T ₄						X	X	X	X	X	X
TSH	X	X	X	X	X	X	X	X	X	X	X
TBG							X		X		
Reverse T ₃							X		X		
Prolactin		X	X	X	X	X	X	X	X		
Urinalysis											
Specific gravity	X	X	X		US only					X	
pH	X	X	X		US only					X	
RBC	X		X		US only					X	
WBC	X		X		US only					X	
Glucose	X		X		US only					X	
Protein										X	
Albumin	X		X		US only						
Ketones	X		X		US only					X	
Casts	X		X		US only					X	

Table 8.1.6.3.1a Mean change from baseline for hematology values, short term placebo controlled trials (reproduced from sponsor's electronic submission)

	SERQUEL								PLACEBO							
	NUMBER OF PATIENTS*	BASELINE		END OF TREATMENT		CHANGE		NUMBER OF PATIENTS*	BASELINE		END OF TREATMENT		CHANGE			
		MEAN	SD	MEAN	SD	MEAN	SD		MEAN	SD	MEAN	SD	MEAN	SD		
WHITE CELL COUNT (X10 ⁹ /L)	479	7.81	2.26	7.60	2.40	-0.21	2.14	195	7.74	2.71	7.86	2.79	0.12	2.08		
NEUTROPHILS (X10 ⁹ /L)	472	4.75	1.91	4.60	1.96	-0.15	1.90	194	4.72	2.22	4.82	2.42	0.11	1.91		
NEUTROPHILS SEGS (%)	472	59.63	9.88	59.24	10.07	-0.24	9.66	192	59.24	10.71	59.48	11.20	0.25	9.56		
NEUTROPHIL BANDS (X10 ⁹ /L)	8	0.01	0.04	0.00	0.00	-0.01	0.04	4	0.00	0.00	0.00	0.00	0.00	0.00		
NEUTROPHIL BANDS (%)	8	0.10	0.49	0.00	0.00	-0.10	0.49	4	0.00	0.00	0.00	0.00	0.00	0.00		
LYMPHOCYTES (X10 ⁹ /L)	472	2.20	0.79	2.25	0.77	-0.05	0.50	194	2.26	0.77	2.42	0.82	0.06	0.64		
LYMPHOCYTES (%)	472	20.28	9.05	20.64	9.00	0.27	8.25	192	21.81	9.43	22.12	9.74	0.21	8.25		
MONOCYTES (X10 ⁹ /L)	472	0.45	0.22	0.44	0.20	-0.01	0.20	194	0.29	0.17	0.23	0.19	-0.01	0.17		
MONOCYTES (%)	472	6.06	2.91	6.04	2.60	-0.02	2.59	192	5.41	2.20	5.12	2.27	-0.28	2.04		
EOSINOPHILS (X10 ⁹ /L)	469	0.24	0.22	0.22	0.20	-0.01	0.14	192	0.20	0.19	0.19	0.15	-0.02	0.15		

EOSINOPHILS (%)	468	2.12	2.47	2.14	2.49	0.02	1.95	191	2.76	2.40	2.45	2.27	-0.20	1.91
BASOPHILS (X10 ⁹ /L)	467	0.06	0.05	0.06	0.05	0.00	0.00	191	0.06	0.05	0.06	0.05	0.00	0.05
BASOPHILS (%)	466	0.79	0.67	0.85	0.61	0.06	0.30	190	0.82	0.68	0.82	0.62	0.01	0.67
RED CELL COUNT (X10 ¹² /L)	480	4.87	0.47	4.81	0.46	-0.06	0.22	195	4.87	0.42	4.83	0.45	0.00	0.22
HEMOGLOBIN (G/DL)	480	14.65	1.21	14.47	1.25	-0.19	0.91	195	14.75	1.24	14.77	1.28	0.02	0.85
RETICULOCYTE COUNT (X10 ⁹ /L)	8	61.42	28.71	62.21	20.08	1.79	24.04	4	42.40	20.21	61.15	15.84	18.75	24.12
HEMATOCRIT (%L FRACTION)	475	0.44	0.05	0.42	0.05	-0.01	0.04	192	0.45	0.04	0.44	0.04	-0.00	0.04
PLATELET COUNT (X10 ⁹ /L)	479	260.45	66.91	264.50	66.78	4.05	47.82	194	262.09	67.88	261.26	62.78	-1.82	42.95

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Table 8.1.6.3.1b Mean Change from Baseline for chemistry values, short term placebo controlled trials (reproduced from sponsor's submission)

	SEROUVEL							PLACEBO						
	NUMBER OF PATIENTS*	BASELINE		END OF TREATMENT		CHANGE		NUMBER OF PATIENTS*	BASELINE		END OF TREATMENT		CHANGE	
		MEAN	SD	MEAN	SD	MEAN	SD		MEAN	SD	MEAN	SD	MEAN	SD
CALCIUM (NBOL/L)	166	2.27	0.30	2.26	0.12	-0.01	0.12	110	2.29	0.10	2.23	0.10	-0.01	0.10
PHOSPHORUS INORGANIC (NBOL/L)	166	1.27	0.19	1.27	0.21	-0.00	0.20	110	1.28	0.19	1.23	0.22	-0.05	0.26
UREA NITROGEN (NBOL/L)	226	4.42	1.71	4.54	1.50	0.12	1.45	145	4.55	1.20	4.50	1.51	-0.06	1.46
CREATININE (NBOL/L)	226	87.94	15.70	86.26	15.94	-1.59	11.28	145	87.59	16.00	85.94	17.26	-1.74	12.64
GGT (U/L)	225	29.98	21.58	22.09	22.00	2.11	17.84	145	21.82	22.17	29.85	20.85	-2.97	12.28
AST/ASOT (U/L)	484	22.26	10.97	26.16	20.17	2.90	19.26	196	22.94	11.40	26.57	20.21	2.72	29.06
ALT/ASPT (U/L)	483	27.88	21.71	25.24	40.59	7.26	28.22	194	28.94	22.45	26.85	30.71	5.91	77.66
PROTEIN TOTAL SERUM (G/L)	226	70.47	5.82	70.54	5.95	0.06	5.26	146	71.25	5.20	71.27	5.17	0.02	4.81
ALBUMIN (G/L)	222	42.67	2.21	42.42	2.51	-0.24	2.20	144	44.05	2.11	44.16	2.55	0.11	2.22
BILIRUBIN TOTAL (NBOL/L)	484	9.97	2.47	8.74	2.50	-0.22	2.49	195	9.00	4.16	9.21	4.09	0.21	2.11

ALKALINE PHOSPHATASE (U/L)	481	100.88	44.21	100.29	45.62	-0.51	22.95	195	112.85	62.15	106.96	57.12	-5.39	22.79
GLUCOSE (NBOL/L)	220	5.44	1.24	5.61	1.56	0.18	1.47	142	5.21	1.22	5.22	1.19	0.02	1.21
CHOLESTEROL TOTAL (NBOL/L)	166	5.02	1.22	5.59	1.22	0.58	0.92	110	5.18	1.08	5.14	1.07	-0.04	0.91
TRIGLYCERIDES (NBOL/L)	166	1.94	1.28	2.27	1.51	0.23	1.12	110	2.12	1.09	1.87	0.99	-0.25	1.05
SODIUM (NBOL/L)	225	140.88	2.07	140.92	2.84	0.04	2.53	145	140.89	2.88	141.17	2.28	0.28	2.15
POTASSIUM (NBOL/L)	226	4.25	0.40	4.21	0.45	-0.04	0.50	146	4.23	0.45	4.27	0.25	-0.11	0.52
CHLORIDE (NBOL/L)	166	101.49	2.18	101.10	2.88	-0.29	2.61	110	101.89	2.16	101.28	2.78	0.29	2.21
TOTAL T4 (THYROXINE) RIA (NBOL/L)	442	106.79	25.96	85.68	24.07	-21.11	27.52	184	105.49	22.28	102.67	25.48	-1.82	21.84
TOTAL T2 (TRIiodOTHYRONINE) (NBOL/L)	422	2.07	0.44	2.00	0.47	-0.07	0.45	178	2.07	0.44	2.11	0.49	0.04	0.29

TSH HIGHLY SENSITIVE (NBOL/L)	441	1.71	2.25	1.80	4.74	0.09	5.12	181	1.61	1.27	1.49	1.27	-0.12	1.24
PROLACTIN RIA (NBOL/L)	202	21.05	21.12	11.94	12.26	-10.01	28.75	122	24.82	20.82	14.02	17.22	-10.80	25.10
T2 UPTAKE (UPTAKE)	8	0.20	0.05	0.20	0.05	0.00	0.00	4	0.25	0.06	0.25	0.06	0.00	0.00
FREE T4 (PBOL/L)	212	22.41	7.62	18.95	6.52	-4.26	5.41	44	22.12	4.59	21.26	4.81	-0.86	5.18
THYROXINE-BINDING GLOBULIN (NBOL/L)	212	26444.2	6021.11	26925.9	7418.12	491.72	7099.15	45	27027.0	6220.84	26741.0	6240.85	-286.00	6165.45
REVERSE T2 (NBOL/L)	199	0.22	0.09	0.17	0.09	-0.04	0.11	45	0.22	0.08	0.22	0.10	0.00	0.12

Table 8.1.6.3.1c Mean change from baseline for urinalysis values, short term placebo controlled trials (reproduced from sponsor's submission)

	SERONEL								PLACEBO							
	NUMBER OF PATIENTS*	BASELINE		END OF TREATMENT		CHANGE		NUMBER OF PATIENTS*	BASELINE		END OF TREATMENT		CHANGE			
		MEAN	SD	MEAN	SD	MEAN	SD		MEAN	SD	MEAN	SD	MEAN	SD		
SPECIFIC GRAVITY	102	1.02	0.01	1.02	0.01	0.00	0.01	109	1.02	0.01	1.02	0.01	0.00	0.01		
REACTION PH	102	5.56	0.65	5.52	0.70	-0.02	0.02	109	5.56	0.59	5.48	0.82	-0.07	0.09		

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TABLE 8.1.6.3.2 Definition of clinically significant clinical laboratory values (adapted from sponsor's electronic ISS)

Hematology parameter	Significant value
Hematocrit	males $\leq 0.37 \geq 0.50$ vol fraction; females $\leq 0.32 \geq 0.55$ vol fraction
Hemoglobin	males ≤ 11.5 g/dl; ≥ 18.5 g/dl; females ≤ 9.5 g/dl; ≥ 16.5 g/dl
RBC	$\leq 3 \times 10^{12}$ cell/L ; $\geq 6 \times 10^{12}$ cell/L
Platelet count	$\leq 75 \times 10^9$ cells/L $\geq 700 \times 10^9$ cells/L
WBC	$\leq 2.8 \times 10^9$ cells/L; $\geq 16.0 \times 10^9$ /L
Neutrophils - percent	$\leq 15\%$
- absolute	$\leq 1.5 \times 10^9$ cells/L
Eosinophils	$\geq 10\%$
Basophils	$> 3\%$
Lymphocytes	$\leq 10\%$
Monocytes	$> 20\%$
Chemistry parameter	Significant value
SGPT/ALT	≥ 165 U/L
SGOT/AST	≥ 150 U/L
Alkaline phosphatase	$\geq 3 \times$ ULN
GGT	females ≥ 135 U/L; males ≥ 195 U/L
LDH	≥ 1125 U/L
CPK	$\geq 3 \times$ ULN
Total bilirubin	≥ 34.2 mol/L (2 mg/dl)
Uric acid	f ≥ 505.58 μ mol/L (8.5 mg/dl); m ≥ 624.54 μ mol/L (10.5 mg/dl)
Albumin	≤ 25 g/L
Total protein	≤ 50 g/L
Calcium	≤ 1.7465 mmol/L (7 mg/dl); ≥ 2.994 mmol/L (12 mg/dl)
Phosphorus	≤ 0.4833 mmol/L (1.5 mg/dl); ≥ 1.7759 mmol/L (5.5 mg/dl)
Sodium	≤ 129 mmol/L; ≥ 160 mmol/L
Glucose	≤ 2.4979 mmol/L (45 mg/dl); ≥ 13.8775 mmol/L (250 mg/dl)
BUN	≥ 10.68 mmol/L (30 mg/dl)
Creatinine	≥ 176.8 μ mol/L (2 mg/dl)
Potassium	$< 0.9 \times$ LLN; $> 1.1 \times$ ULN
Chloride	$< 0.9 \times$ LLN; $> 1.1 \times$ ULN
CO	$< 0.9 \times$ LLN; $> 1.1 \times$ ULN
Triglycerides	$< 0.5 \times$ LLN; $> 2 \times$ ULN
Cholesterol	$< 0.5 \times$ LLN; $> 2 \times$ ULN
Total T ₄ , Total T ₃ , Free T ₄ , TSH, Reverse T ₃ , and TBG	$< 0.8 \times$ LLN; $> 1.2 \times$ ULN
Prolactin	> 100 ug/L
Urinalysis parameter	Significant value
Specific gravity	≤ 1.001 ; ≥ 1.035
pH	≤ 4.6 ; > 8
RBC	males > 1 /hpf; females > 5 /hpf
WBC	> 5 /hpf
Protein	increase of ≥ 2 units
Glucose	increase of ≥ 2 units
Casts	increase of ≥ 2 units
Ketones	$\geq 2+$
Bilirubin	$\geq 2+$
Nitrite	$\geq 2+$
Leukocyte esterase	$\geq 2+$

Table 8.1.6.3.2a Hematology: proportion of patients meeting clinically significant criteria, short term placebo controlled trials

Variable	Quetiapine				Placebo				CS low value		CS high value	
	n	Number (%) with CS low values	n	Number (%) with CS high values	n	Number (%) with CS low values	n	Number (%) with CS high values	p-value*	Odds ratio	p-value*	Odds ratio
Hematocrit	469	16 (3.4)	361	56 (15.5)	192	1 (0.5)	161	22 (13.7)	0.0576	5.056	0.3429	0.756
Hemoglobin	478	1 (0.2)	480	1 (0.2)	194	0 (0.0)	194	1 (0.5)	0.6547	NC	0.8229	0.689
Red cell count	480	0 (0.0)	474	6 (1.3)	195	0 (0.0)	194	3 (1.5)	NC	NC	0.9270	0.925
Platelet count	478	1 (0.2)	479	0 (0.0)	194	0 (0.0)	194	0 (0.0)	0.6554	NC	NC	NC
White cell count	479	3 (0.6)	478	8 (1.7)	195	0 (0.0)	191	5 (2.6)	0.1989	NC	0.4659	0.611
Neutrophils - percent	472	2 (0.4)	NA	NA	193	0 (0.0)	NA	NA	0.2158	NC	NA	NA
Neutrophils - absolute	470	12 (2.6)	NA	NA	191	2 (1.0)	NA	NA	0.2415	2.480	NA	NA
Eosinophils	NA	NA	458	14 (3.1)	NA	NA	185	5 (2.7)	NA	NA	0.8566	0.896
Basophils	NA	NA	464	4 (0.9)	NA	NA	188	2 (1.1)	NA	NA	0.9808	1.022
Lymphocytes	469	9 (1.9)	NA	NA	192	1 (0.5)	NA	NA	0.2041	4.537	NA	NA
Monocytes	NA	NA	471	1 (0.2)	NA	NA	193	0 (0.0)	NA	NA	0.4679	NC

CS Clinically significant

NA Not applicable

NC Not calculated

*CMH test

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Table 8.1.6.3.2b Chemistry: proportion of patients meeting clinically significant criteria, short term placebo controlled trials

Variable	Quetiapine				Placebo				CS low value		CS high value	
	n	Number (%) with CS low values	n	Number (%) with CS high values	n	Number (%) with CS low values	n	Number (%) with CS high values	p-value*	Odds ratio	p-value*	Odds ratio
SGPT/ALT	NA	NA	483	29 (6.0)	NA	NA	194	3 (1.5)	NA	NA	0.0051	5.533
SGOT/AST	NA	NA	484	6 (1.2)	NA	NA	196	1 (0.5)	NA	NA	0.4467	2.290
Alkaline phosphatase	NA	NA	482	1 (0.2)	NA	NA	195	0 (0.0)	NA	NA	0.6534	NC
GGT	NA	NA	234	3 (1.3)	NA	NA	145	0 (0.0)	NA	NA	0.2150	NC
Total bilirubin	NA	NA	484	0 (0.0)	NA	NA	195	0 (0.0)	NA	NA	NC	NC
Uric acid												
Albumin	232	0 (0.0)	NA	NA	144	0 (0.0)	NA	NA	NC	NC	NA	NA
Total protein	236	0 (0.0)	NA	NA	146	1 (0.7)	NA	NA	0.1573	0.000	NA	NA
Calcium	166	0 (0.0)	166	0 (0.0)	110	0 (0.0)	110	0 (0.0)	NC	NC	NC	NC
Phosphorus	166	0 (0.0)	163	6 (3.7)	110	0 (0.0)	110	2 (1.8)	NC	NC	0.4975	1.806
Sodium	234	2 (0.9)	235	0 (0.0)	145	0 (0.0)	145	0 (0.0)	0.2211	NC	NC	NC
Glucose	230	5 (2.2)	230	3 (1.3)	143	2 (1.4)	143	0 (0.0)	0.4202	1.920	0.2174	NC
Urea	NA	NA	232	1 (0.4)	NA	NA	145	1 (0.7)	NA	NA	0.8214	0.686
Creatinine	NA	NA	236	0 (0.0)	NA	NA	145	1 (0.7)	NA	NA	0.3220	0.000
Potassium	236	0 (0.0)	236	6 (2.5)	146	0 (0.0)	145	0 (0.0)	NC	NC	0.0458	NC
Chloride	166	0 (0.0)	166	0 (0.0)	110	0 (0.0)	110	0 (0.0)	NC	NC	NC	NC
CO ₂												
Triglycerides	166	0 (0.0)	152	40 (26.3)	110	0 (0.0)	98	8 (8.2)	NC	NC	0.0002	4.323
Cholesterol	166	0 (0.0)	165	0 (0.0)	110	0 (0.0)	110	0 (0.0)	NC	NC	NC	NC
Total T ₄	441	20 (4.5)	440	2 (0.5)	183	1 (0.5)	183	2 (1.1)	0.0093	8.791	0.3428	0.433
Total T ₃	429	7 (1.6)	429	4 (0.9)	177	1 (0.6)	177	3 (1.7)	0.2968	3.010	0.5781	0.685
TSH	427	24 (5.6)	434	4 (0.9)	174	10 (5.7)	177	1 (0.6)	0.8741	1.063	0.6373	1.712
Free T ₄	209	14 (6.7)	209	0 (0.0)	44	0 (0.0)	44	0 (0.0)	0.0779	NC	NC	NC
TBG	209	4 (1.9)	211	3 (1.4)	45	2 (4.4)	45	0 (0.0)	0.3116	0.420	0.4220	NC
Reverse T ₃	199	0 (0.0)	185	3 (1.6)	45	0 (0.0)	42	5 (11.9)	NC	NC	0.0011	0.122
Prolactin	NA	NA	286	0 (0.0)	NA	NA	118	0 (0.0)	NA	NA	NC	NC

CS Clinically significant
 NC Not calculated
 NA Not applicable

*CMH test

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Table 8.1.6.3.2c Urinalysis: proportion of patients meeting clinically significant criteria, short term placebo controlled trials

Variable	Quetiapine				Placebo				CS low value		CS high value	
	n	Number (%) with CS low values	n	Number (%) with CS high values	n	Number (%) with CS low values	n	Number (%) with CS high values	p-value*	Odds ratio	p-value*	Odds ratio
Specific gravity	162	1 (0.6)	161	6 (3.7)	109	0 (0.0)	108	3 (2.8)	0.3126	NC	0.6215	1.445
Reaction pH	162	0 (0.0)	162	1 (0.6)	109	1 (0.9)	109	1 (0.9)	0.3220	0.000	0.6000	0.429

CS Clinically significant
 NC Not calculated

*CMH test

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Table 8.1.7.1 Vital signs and weight assessments by trial (integrated Phase II-III trials)
Reproduced from sponsor's electronic ISS

	Phase II-III trials											
	0004	0005	0006	0007	0008	0012	0013	0014	0015	0048	OLE	
Pulse	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressures	X	X	X	X	X	X	X	X	X	X	X	X
Respiratory	X	X	X		X							
Temperature	X	X	X	X	X		X		X	X		US only
Weight	X	X	X	X	X	X	X	X	X	X	X	X

- * All measures were taken while subjects were seated.
- ^a Unless otherwise noted, readings were taken for both supine and standing systolic and diastolic blood pressures.
- ^c Only supine readings were taken for Trials 0002, 0007, 0025, and 0026.
- ** Respiration readings were taken while subjects were in the supine position unless otherwise noted.

Table 8.1.7.3.2 Definitions of clinically significant vital signs and weight (reproduced from sponsor's electronic ISS)

Vital sign	Criterion value	Change from baseline
Systolic blood pressure	≥ 180 mmHg	increase ≥ 20 mmHg
Diastolic blood pressure	≤ 90 mmHg ≥ 105 mmHg	decrease ≥ 20 mmHg increase ≥ 30 mmHg
Pulse	≤ 50 mmHg 120 bpm	decrease ≥ 20 mmHg increase ≥ 15 bpm
Temperature	50 bpm	decrease ≥ 15 bpm
Weight	≥ 38.3°C	change ≥ 1.11°C
	—	change ≥ 7% body weight
Orthostatic changes		
Systolic blood pressure	decrease ≥ 30 mmHg from supine to standing	
Diastolic blood pressure	increase ≥ 30 mmHg from supine to standing	
Pulse	increase ≥ 20 bpm from supine to standing	
Combined	decrease ≥ 30 mmHg in systolic blood pressure from supine to standing and increase ≥ 20 bpm in pulse from supine to standing	

Table 8.1.7.3.1 Mean and mean change values for vital signs variables at baseline and end of treatment with quetiapine or placebo in the Phase II-III short-term, placebo-controlled trials (adapted from sponsor's electronic ISS)

Variable	Quetiapine				Placebo			
	Number of subjects*	Base-line mean (±SD)	End-of- treatment mean (±SD)	Change mean (±SD)	Number of subjects*	Base-line mean (±SD)	End-of- treatment mean (±SD)	Change mean (±SD)
Systolic BP								
Supine (mmHg)	474	119 (16)	119 (15)	-0.2 (16)	186	121 (15)	119 (14)	-2.1 (14.5)
Standing (mmHg)	466	117 (16)	117 (15)	-0.1 (16.5)	180	118 (15)	117 (15)	-1.1 (14.9)
Diastolic BP								
Supine (mmHg)	474	75 (11)	76 (11)	0.8 (11.4)	186	78 (12)	76 (11)	-1.8 (13.6)
Standing (mmHg)	466	78 (11)	78 (11)	0.3 (12.1)	180	79 (11)	78 (11)	-0.8 (12.9)
Pulse								
Supine (bpm)	466	81 (12)	84 (12)	3.3 (14.5)	183	79 (12)	80 (13)	0.8 (14.9)
Standing (bpm)	447	88 (14)	92 (15)	3.9 (16.8)	179	87 (13)	88 (15)	1.6 (15.2)
Temperature (C)	450	36.5 (0.4)	36.5 (0.5)	-0.0 (0.6)	179	36.5 (0.5)	36.5 (0.5)	0.0 (0.6)
Weight (kg)	391	78 (16)	80 (17)	2.3 (3.9)	178	78 (16)	78 (16)	0.1 (3.1)
Postural changes:								
Systolic BP (mmHg)	448	-1.9 (11.7)	-1.9 (10.4)	-0.1 (13.9)	176	-2.4 (11)	-1.7 (9)	0.7 (12.6)
Diastolic BP (mmHg)	448	2.3 (8.8)	1.9 (8.6)	-0.4 (11.2)	176	1.8 (10)	2.4 (9)	0.6 (13.2)
Pulse (bpm)	430	7.5 (11.2)	8.1 (11.1)	0.6 (14.1)	174	7.5 (11)	8.4 (12)	0.9 (13.8)

*Number of subjects is based on number of subjects with both baseline and end-of-treatment assessments.

*This table presents supine-to-standing values; the T Tables present standing-to-supine values; therefore the positive and negative signs will be opposite to that presented in the intent tables.

SD = Standard deviation

BP = Blood pressure

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Table 8.1.7.3.2b Vital signs: proportion of patients meeting clinically significant criteria, short term placebo controlled trials

Variable	Quetiapine				Placebo				CS high value		CS low value	
	n	Number (%) with CS high values	n	Number (%) with CS low values	n	Number (%) with CS high values	n	Number (%) with CS low values	p-value*	Odds ratio	p-value*	Odds ratio
Supine systolic blood pressure	495	4 (0.8)	487	77 (15.8)	202	1 (0.5)	198	26 (13.1)	0.7300	1.507	0.1671	1.403
Supine diastolic blood pressure	492	16 (3.3)	490	50 (10.2)	197	8 (4.1)	201	14 (7.0)	0.5451	0.746	0.1588	1.551
Standing systolic blood pressure	489	4 (0.8)	470	96 (20.4)	197	2 (1.0)	190	30 (15.8)	0.8916	1.121	0.1351	1.421
Standing diastolic blood pressure	488	37 (7.6)	486	44 (9.1)	193	12 (6.2)	197	13 (6.6)	0.5625	1.232	0.2631	1.439
Supine pulse rate	489	28 (5.7)	491	4 (0.8)	201	5 (2.5)	201	2 (1.0)	0.1042	2.295	0.5450	1.641
Standing pulse rate	472	101 (21.4)	482	4 (0.8)	195	23 (11.8)	196	1 (0.5)	0.0036	2.116	0.2352	2.952
Temperature	482	4 (0.8)	NA	NA	200	1 (0.5)	NA	NA	0.7151	1.542	NA	NA
Weight	391	89 (22.8)	391	11 (2.8)	178	11 (6.2)	178	9 (5.1)	0.0000	4.301	0.0855	0.457
	n	Number (%) with CS values		n	Number (%) with CS values			p-value*	Odds ratio			
Orthostatic pulse	415	256 (61.7)		165	93 (56.4)			0.2335	1.262			
Orthostatic diastolic blood pressure	484	16 (3.3)		195	8 (4.1)			0.9160	0.951			
Orthostatic systolic blood pressure	482	34 (7.1)		194	13 (6.7)			0.7091	1.134			
Orthostatic pulse/systolic blood pressure	473	15 (3.2)		194	5 (2.6)			0.5325	1.369			
CS Clinically significant	*CMH test											
NA Not applicable												

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Table 8.1.8.1 Electrocardiogram assessments by trial (integrated Phase I and Phase II-III trials) (adapted from sponsor's electronic ISS)

	Phase I trials																
	0002	0007	0008	0016	0017	0018	0019	0020	0024	0025	0026	0027	0029	0035	0045	0046	0047
Heart rate					X			X	X	X	X	X		X	X	X	X
PR					X			X	X		X	X		X	X	X	X
QRS					X			X	X	X	X	X		X	X	X	X
QT					X			X	X	X	X	X		X	X	X	X
QT _c					X			X	X	X	X	X		X	X	X	X
PQ										X							

	Phase II-III trials										
	0004	0005	0006	0007	0008	0012	0013	0014	0015	0048	OLE
Heart rate	X	X	X	X	X		X		X	X	US only
PR	X	X	X	X	X		X		X	X	US only
QRS	X	X	X	X	X		X		X	X	US only
QT	X	X	X	X	X		X		X	X	US only
QT _c	X	X	X	X	X		X		X	X	US only

Table 8.1.8.3.2a Zeneca-defined electrocardiogram (ECG) abnormalities considered clinically significant (adapted from sponsor's electronic submission)

Heart rate	> 120 bpm and an increase of \geq 15 bpm from the baseline value < 50 bpm and a decrease of \geq 15 bpm from the baseline value
PR	\geq 0.210 sec
QRS	\geq 0.150 sec \leq 0.050 sec
QT	\geq 0.500 sec \leq 0.200 sec
QT _c	\geq 0.450 sec \geq 0.4

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TABLE 8.1.8.3.1 Mean and mean change values for electrocardiogram variables at baseline and end of treatment with quetiapine and placebo in the short-term (\leq 6 weeks), placebo-controlled Phase II-III clinical trials (adapted from sponsor's electronic ISS)

Variable	Quetiapine				Placebo			
	Number of subjects*	Baseline mean (\pm SD)	End of treatment mean (\pm SD)	Change mean (\pm SD)	Number of subjects*	Baseline mean (\pm SD)	End of treatment mean (\pm SD)	Change mean (\pm SD)
Ventricular rate (bpm)	405	79 (14)	86 (14)	7 (15)	158	79 (15)	81 (16)	1 (16)
PR interval (sec)	405	0.15 (0.02)	0.15 (0.03)	-0.00 (0.03)	160	0.15 (0.02)	0.15 (0.02)	-0.00 (0.02)
QRS interval (sec)	405	0.09 (0.01)	0.09 (0.01)	-0.00 (0.01)	160	0.08 (0.01)	0.08 (0.01)	-0.00 (0.01)
QT interval (sec)	395	0.36 (0.04)	0.35 (0.03)	-0.01 (0.03)	155	0.36 (0.04)	0.36 (0.04)	-0.01 (0.04)
QT _c interval (sec)	393	0.41 (0.03)	0.41 (0.03)	0.00 (0.03)	153	0.41 (0.04)	0.41 (0.03)	-0.00 (0.04)

*Based on number of subjects with both baseline and end-of-treatment assessments.

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Table 8.1.8.3.2b ECG: proportion of patients meeting clinically significant criteria, short term placebo controlled trials

Variable	Quetiapine				Placebo				CS high value		CS low value	
	n	Number (%) with CShigh values	n	Number (%) with CS low values	n	Number (%) with CS high values	n	Number (%) with CS low values	p-value*	Odds ratio	p-value*	Odds ratio
Heart rate												
Atrial	403	4 (1.0)	401	1 (0.2)	159	1 (0.6)	157	0 (0.0)	0.6411	1.542	0.4980	NC
Ventricular	403	4 (1.0)	401	1 (0.2)	157	1 (0.6)	155	0 (0.0)	0.6513	1.524	0.5026	NC
PR	402	1 (0.2)	406	0 (0.0)	160	1 (0.6)	160	0 (0.0)	0.3802	0.234	NC	NC
QRS	405	0 (0.0)	403	3 (0.7)	160	0 (0.0)	159	2 (1.3)	NC	NC	0.5808	0.592
QT	395	0 (0.0)	393	1 (0.3)	154	0 (0.0)	154	0 (0.0)	NC	NC	0.4924	NC
QT _c	377	18 (4.8)	393	0 (0.0)	144	5 (3.5)	153	0 (0.0)	0.4817	1.473	NC	NC

CS Clinically significant
 NC Not calculated

*CMH test

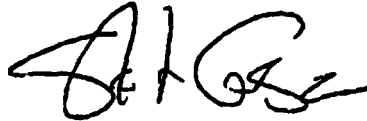
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February 5, 1997

**Report: Neutropenic Episodes Associated With the Use
of Seroquel™ (Quetiapine) in Clinical Trials by Stanton
L Gerson, MD, Professor of Medicine, Division of
Hematology/Oncology, BRB 3-West, 10900 Euclid
Avenue, Cleveland, OH 44106-4937.**

**Stanton L. Gerson, MD
Professor of Medicine
Chief, Division of Hematology/Oncology
Associate Director for Clinical Research,
CWRU/Ireland Cancer Center**

A handwritten signature in black ink, appearing to read 'S. L. Gerson', written in a cursive style.

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Summary

Quetiapine has been administered to 2,387 patients who have accumulated over 865 patient years of exposure. A total of 88 neutropenic and 43 leukopenic episodes have been recorded, including episodes of severe neutropenia. A number of these episodes were reported as adverse events requiring cessation of therapy by the physician. Review of these episodes indicates that most are transient, some oscillating in nature but none progressive and none leading to a severe episode of agranulocytosis. There is no clear pattern in onset or duration and in most instances, patients were continued on quetiapine without symptoms related to neutropenic or leukopenic events. Thus, it appears that although neutropenia is observed in patients receiving quetiapine, it can be safely administered without an expectation of progression of the neutropenia to more severe neutropenia or to episodes of agranulocytosis. Nonetheless, given the relatively small patient base of exposures, a rare episode of agranulocytosis could possibly occur in a much larger exposed population.

Database

Zeneca Pharmaceuticals asked for my review of the cumulative episodes of reported and recorded neutropenia and leukopenia. I reviewed this data first in the integrated summary of safety hematology values for the phase II and III clinical trials program, including the controlled and uncontrolled, short-term placebo controlled, short-term comparator controlled trials and the long-term controlled clinical trials. This data was originally provided in June of 1996 with an update in November of 1996 consisting of the 4 month safety update of the previous trials. I also had the opportunity to review other significant adverse hematology values, such as leukocytosis thrombocytopenia and eosinophilia. Given the nature of the case identification, adverse event reportings and clinically significant values were identified. Comprehensive patient summaries were not provided and I did not have access to concurrent drug lists or intercurrent illnesses in the patient base.

Case Definitions

Standard definitions were used:

Leukopenia	(<	3.0	X	10 ⁹ cells per L
Neutropenia				
Agranulocytosis	(<	0.5	(X 10 ⁹ cells per L) with symptoms)	
Severe Neutropenia	(<	0.5	(X 10 ⁹ cells per L) without symptoms)	
Moderate Neutropenia	(≥	0.5 and	< 1.0 (X 10 ⁹ cells per L))	
Mild Neutropenia	(≥	1.0 and	< 1.5 (X 10 ⁹ cells per L))	

These values reflect convention for reporting clinically significant values of neutropenia.

It appears that the laboratory reporting included the WBC and neutrophil, segs (for segmented neutrophils) for each individual patient. In most, if not all instances, the data was recorded and reported as absolute values and not as percent neutrophils. This reduces the probability of erroneous reports, although there are apparently some episodes suggesting irregularity by the reporting laboratory.

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APPENDIX A

Listings of abnormal ANC and WBC values

A1 to A

	Number of patients with abnormal WBC and ANC values					
	Quetiapine (n=2387)		Placebo (n=206)		Active control (n=420)	
	transient n (%)	Persistent N (%)	transient n (%)	Persistent N (%)	transient n (%)	Persistent N (%)
Neutropenia						
agranulocytosis (<0.5 with symptoms)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
severe neutropenia (<0.5 without symptoms)	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
moderate neutropenia (≥ 0.5 and <1.0)	15 (0.6)	4 (0.2)*	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
mild neutropenia (≥ 1.0 and <1.5)	59 (2.5)	6 (0.3)	2 (1.0)	1 (0.5)	6 (1.4)	0 (0.0)
Leukopenia						
severe leukopenia ($<3.0 \times 10^9$ cells/L)	37 (1.6)	5 (0.2)†	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)

Units for neutrophil and leukocyte counts are $\times 10^9$ cells/L

*These 4 patients had persistent mild neutropenia with an occasional data point falling into the moderate neutropenic range.

†Three of the 5 patients had treatment values that were similar to baseline values.

**Case Distribution
Patients in Quetiapine Clinical Trials with Neutropenia or Leukopenia**

APPENDIX A

1 Quetiapine

1.1 Agranulocytosis A

None

1.2 Severe neutropenia. A

1.2.1 Transient severe neutropenia

Patient 0006/0008/0814

Patient 0005/0017/0002

Patient 0012/0011/1106

Patient 0012/0045/4508 A

1.2.2 Persistent severe neutropenia

None A

1.3 Moderate neutropenia A

1.3.1 Transient moderate neutropenia

Patient 0008/0044/1701

Patient 0007/0017/0002

Patient 0007/0017/0003

Patient 0015/0018/1815

Patient 0005/0017/0001

Patient 0005/0018/0001

Patient 0048/0002/0210

Patient 0012/0089/8943

Patient 0012/0035/3504

Patient 0012/0039/3901

Patient 0012/0047/4712

Patient 0014/0044/4405

Patient 0014/0067/6707

Patient 0015/0005/0502

Patient 0015/0005/0507 A

1.3.2 Transient moderate neutropenia with persistent mild neutropenia

Patient 0048/0015/1504

Patient 0014/0001/0141

Patient 0013/0004/0402

Patient 0015/0027/2706 A

1.3.3 Persistent moderate neutropenia

None

- 1.4 Persistent mild neutropenia A
 - Patient 0007/0004/0006
 - Patient 0007/0030/0005
 - Patient 0012/0005/0508
 - Patient 0013/0007/0711
 - Patient 0014/0001/0103
 - Patient 0015/0034/3408 A
- 1.5 Severe leukopenia... A
 - 1.5.1 Transient severe leukopenia
 - None
 - 1.5.2 Transient severe leukopenia with persistent mild to moderate leukopenia
 - Patient 0012/0036/3609
 - Patient 0015/0034/3409 A
 - 1.5.3 Persistent severe leukopenia
 - Patient 0007/0030/0005
 - Patient 0012/0005/0508
 - Patient 0012/0042/4203
 - Patient 0013/0004/0402
 - Patient 0014/0045/4508 A
- 2. Placebo A
 - 2.1 Agranulocytosis A
 - None
 - 2.2 Severe neutropenia. A
 - 2.2.1 Transient severe neutropenia
 - None
 - 2.2.2 Persistent severe neutropenia
 - None
 - 2.3 Moderate neutropenia A
 - 2.3.1 Transient moderate neutropenia
 - None

NUMBER OF PATIENTS WITH ABNORMAL WBC AND ANC VALUES
While on Quetiapine
SEVERE NEUTROPENIA
TRANSIENT SEVERE NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0006/0008/0814	2.8	0.28	2	Disproportionately low single value of ANC. Followup preceding and followup values at 7 and 28 days were normal. No neutropenic symptoms. Not clinically significant.
0005/0017/0002	6.4/7.6	0.51/0.48	3/4	Laboratory evidence of severe neutropenia on 2 occasions with no mention of symptoms. Disproportion between the WBC and ANC suggests abnormality in ANC measurement and the real possibility of laboratory error. There are no followup values. It is very unusual to have no change in the WBC with sudden onset of drug associated neutropenia. Doubt an association with drug use.
0012/0045/4508	3.1	0.43	6	Single low value with preceding and post values of WBC and ANC normal. Downward trend in WBC pre and post nadir are noted, but are within the range of subsequent values. Patient had 2 infections remote to the time of the reported neutropenia, unassociated with the neutropenic episode. This is possibly associated with drug use, but may well have been some other intercurrent process. Non progressive, asymptomatic single reported abnormal value.
0012/0011/1106	2.4	0.27	3	Single low value with normal values the week before and the week after in both WBC and ANC could represent significant severe neutropenia. No evidence of symptoms. Nonprogressive and resolved spontaneously. Could be intercurrent illness, concomitant drug use or laboratory error.

MODERATE NEUTROPENIA
TRANSIENT MODERATE NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0008/0044/1701	5.4	0.76	2	Surprising drop in ANC without significant change in WBC associated with numerous unrelated complaints. Nonprogressive, asymptomatic.
0007/0017/0002	3.4, 3.3, 4.1	1.0, 0.79, 1.44	1,2,5	Repeated mild to moderate neutropenia. Nonprogressive. No apparent symptoms. Moderately low WBC to start with proportionate ANC/WBC percentages. This is probably drug related case of neutropenia which resolved while on treatment.
0007/0017/0003	3.4, 2.5	1.09, 0.95	1, 2	Patient discontinued for leukopenia 4 days later. Had a WBC of 4.0 an ANC of 3.1. Possibly drug related since it resolved quickly off drug. Clinically asymptomatic.
0015/0018/1815	3.3/3.7	0.92/1.10	2	Repeated value showing low ANC 2 days after first value shown suggesting represents probable drug related neutropenia resolving spontaneously without symptoms.
0005/0017/0001	5.7, 6.4	0.58, 0.73	0, 1	Asymptomatic moderate neutropenia continued on treatment for 4 weeks subsequent WBCs all normal, no differentials after week 2. Not drug related and atypical because of the disproportionately low ANC/WBC ratio.
0005/0018/0001	2.8/3.0	0.9/1.3	4/5	Final value on study. WBC 3.1 ANC 1.9 appears to represent mild to moderate neutropenia resulting spontaneously, not associated with symptoms. May be drug related.
0048/0002/0210	5.5	0.88	24	Single value at apparent end of study in an elderly individual who had normal WBC and ANC throughout the first 20 weeks of treatment. In the absence of a change in WBC, the low ANC may represent artifact. This episode is not associated with symptoms and in this age group suggests perhaps an intercurrent illness or concomitant medication. Of doubtful clinical significance.

MODERATE NEUTROPENIA
TRANSIENT MODERATE NEUTROPENIA (CONT.)

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0012/0089/8943	2.9/3.4	1.02/1.98	20/24	A 23 y/o male on study for 55 weeks two episodes of leukopenia and neutropenia. No apparent symptoms, non progressive and maintained on drug with recovery period, possible drug related process.
0012/0035/3504	9.5	0.66	13	Repeat value the next day: WBC 6.4, ANC 4.35; laboratory artifact.
0012/0039/3901	2.5	0.91	1	A 24 y/o male on study 4 weeks. Subsequent week, values normal. Nonprogressive, no associated symptoms, unlikely clinical significance, possible drug related.
0012/0047/4712	3.2; 3.1, 3.3	1.2, 1.27, 0.94	1, 16, 17	Oscillating neutropenia with moderately low WBC and ANC. Nonprogressive process with recurrent episodes of mild to moderate neutropenia occurring at the beginning and end of study. Possible drug related.
0014/0044/4405	2.7	0.75	8	Single episode week 7, week 10 values normal. Most likely intercurrent event or concomitant drug lab abnormality is also possible. No evidence of progression. Clinically insignificant, possible drug related.
0014/0067/6707	4.2	0.67	2	Mild drop in WBC at occurrence of ANC nadir. Transient nonprogressive, possible drug related. Note: suicide attempt by overdose of valium plus quetiapine without evidence of neutropenia.
0015/0005/0502	2.5	0.60	61	Leukopenia observed one month later with a WBC of 3.0 and an ANC of 2.01. Since two low values were observed in this 64 y/o female, this is probably drug related. Of note is the diagnosis of breast cancer on the 44th week of treatment and a variety of other intercurrent illnesses which could account for the neutropenic event. The question is raised whether this woman was on systemic therapy for breast carcinoma, such as adjuvant chemotherapy or had received radiation therapy as a result of her initial diagnosis. Given these facts, it is unlikely to be quetiapine related.

MODERATE NEUTROPENIA
TRANSIENT MODERATE NEUTROPENIA (CONT.)

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0015/0005/0507	3.4, 3.1, 2.0	1.29, 1.1, 0.94	8, 22, 27	34/35 y/o male with no clear symptoms associated with episodic neutropenia and associated with leukopenia. Most WBC counts are less than 5,000, suggesting a chronic leukopenic process not likely to be drug related. Nonprogressive, asymptomatic.

MODERATE NEUTROPENIA
TRANSIENT MODERATE NEUTROPENIA WITH PERSISTENT MILD NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0048/0015/1504	3.5-2.7	1.0, 0.82, 1.13	-5-40	Chronic persistent leukopenia and neutropenia in a 78 y/o woman appears to have preceded the onset of quetiapine therapy. Not drug related.
0014/0001/0141	2.6-4.5	0.86-1.17	2-18	A 30 y/o male with chronic persistent leukopenia and neutropenia while on therapy. Had numerous repeat values verifying the presence of neutropenia. Since this patient did not have followup it is difficult to determine whether this is drug related but with the information obtained since the baseline WBC (5.5) or, ANC (2.48) for normal. This is likely drug related. Note, however, drug dependency, use of cannabis and alcohol. Suggesting alcohol as a comorbid condition and perhaps etiology of the persistent neutropenia and leukopenia.
0013/0004/0402		1.35, 0.84 (nadir), 1.13	7-115	A 39 y/o man with recurrent gastritis, gastroenteritis, periodontal abscess, E or I skin ulcers. Treated successfully for 113 weeks without progressive neutropenia. It may well be that other intercurrent illnesses in this individual were responsible for the low ANC and WBC. However, drug effect needs to be considered since the WBC and ANC were in the normal range for the first 6 weeks of treatment. There is no followup to define whether the WBC normalizes with this continuation of quetiapine.
0015/0027/2706	4.0, 3.5-4.0	1.27, 1.31, 1.25, 0.72, 1.50	2, 12-24	A 30 y/o male with a normal WBC/ANC at baseline with repeated mild neutropenic values in one neutropenic episode at week 20, which resolved on week 24. However, all WBC/ANC values are at the low end of the normal range, suggesting preexisting cause for mild leukopenia/neutropenia. Only one transient episode at week 20 and note the accidental inhalation of javex on week 21, suggests the possibility of other concurrent medications or drug abuse as the cause of this transient episode. Not likely drug related.

MODERATE NEUTROPENIA
PERSISTENT MILD NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0007/0004/0006	3.5-0.9	1.35-1.31	0-4	Leukopenia at baseline. No associated symptoms, nonprogressive. Unlikely to be drug related since present at baseline.
0007/0030/0005	2.9-3.0	1.18-1.26	1-3	34 y/o female, no baseline value. Nonprogressive asymptomatic. Possible drug related, although no baseline value available. No followup available either. For posttreatment normalization. Nondrug relationship.
0012/0005/0508	2.7-2.9	1.23-1.20	9-30	25 y/o female. Oscillating mild neutropenia with some normal values. All values including at baseline (WBC 3.5) are below a WBC of 5.0. Nonprogressive oscillating neutropenia taken off study on week 3 for ANC of 1.07 on repeat value 2.9 with a WBC with an ANC of 1.2. Possibly drug related, but given baseline low values, this could be a chronic neutropenia due to another cause.
0013/0007/0711	3.6-3.2	1.5-1.15	2-9	43 y/o male. Persistent mild neutropenia, nonprogressive. No other cause of neutropenia, likely drug related.
0014/0001/0103	3.7-5.1	1.34-1.10 (nadir), 1.73	1-22	30 y/o male. Nonprogressive mild neutropenia. Baseline values 4.9 WBC, 2.63 ANC. Numerous other medical complaints. Nonprogressive mild neutropenia. Of note, week 18 is the only time with repeated values, WBC 3.8, 4.3; ANC 1.0, 2.02. Mild neutropenia no clinical symptoms, nonprogressive. Possible drug related.
0015/0034/3408	4.5-2.8 (week 75)- 3.1	1.5-1.19 (nadir)- 1.35	-1-85	Chronic persistent neutropenia preceding drug onset not associated with symptoms or progression. Unlikely to be related to drug as it appears to be preexisting.

SUMMARY OF NEUTROPENIC CASES

Of the total of 88 neutropenic episodes, none are progressive, none were associated with symptoms and none led to neutropenic febrile episodes. There is no pattern in onset, which ranged from week 1 to 61. Given the number of patients exposed, however, most episodes occurred in less than 6 weeks, strongly biased by the duration at exposure. Many episodes are probably not drug related, and only a few (6 cases, underlined) appear to be associated with drug use in a clear fashion and only some of these appear to be persistent. Furthermore, there is no evidence that therapy exacerbates baseline neutropenia. Thus the conclusion can be drawn that quetiapine has a low incidence of nonprogressive transient neutropenia, infrequent episodes of persistent neutropenia and no episodes of progressive neutropenia leading to agranulocytosis.

SEVERE LEUKOPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0012/0036/3609	2.8	1.86	12	Transient episode of severe leukopenia with persistent mild to moderate leukopenia. This is nonprogressive. Had associated lymphopenia. Not clinically significant.
0015/0034/3409	2.9	1.6	72	Chronic persistent mild leukopenia, nonprogressive in a patient on drug for 78 weeks. Clinically asymptomatic. Possibly related.
0007/0030/0005	2.9-3.0	1.18-1.26	1-3	No baseline values. Severe leukopenia with mild neutropenia. Nonprogressive. Unlikely to be drug associated in a 34 y/o female and no followup. Not clinically significant.
0012/0005/0508		1.23, 1.07	9, 30	Chronic persistent mild to moderate leukopenia with episodes of severe leukopenia and 3 episodes of mild neutropenia. Nonprogressive. Note that this occurred in a 24 y/o woman with a baseline WBC 3.5, ANC 1.77 probably unrelated to drug exposure on a background of chronic mild leukopenia.
0012/0042/4203	2.9	1.33	14	34 y/o female on drug for 14 weeks who reported adverse events of leukopenia and neutropenia at week 14, based on a single value. Followup 6 days later at an ANC of 2.58 and WBC of 3.5. This is possibly drug related, occurring late and nonprogressive and rapidly reversible. No other etiology to the leukopenia and neutropenia.
0013/0004/0402	2.9	1.1-1.7	85, 91, 95	39 y/o male on drug for 115 weeks with chronic intermittent recurrent leukopenia and neutropenia. Patient reported to have multiple bacterial infections, LFT abnormalities suggesting a variety of intercurrent illnesses to explain the mild to moderate leukopenia.
0014/0045/4508	2.5	1.10	7	Patient developed chronic leukopenia and neutropenia while on quetiapine. Repeat values during week 7 showed an episode of moderate to severe leukopenia. Adverse event was reported and the patient was taken off study. There was no evidence of progression. The WBC recovered to 5.1, 14 days off drug, suggesting that this may well have been a drug related episode of lymphopenia and mild neutropenia.

This group of individuals represents patients with severe leukopenia, some of which is persistent and associated with mild to moderate neutropenia. Some of these events appear to be drug related (3 cases) because there is no other obvious etiology. Etiology of leukopenia without neutropenia can be obscure but is rarely clinically significant in the absence of severe lymphopenia with immunodeficiency as with HIV infection. Otherwise, isolated leukopenia is usually not clinically significant.

Adverse events reports of neutropenia and leukopenia.
The following cases were also adverse reports:

0007/0017/0003
0007/0017/0002
0012/0039/3901
0015/0005/0507
0015/0027/2706

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APPENDIX B

Listings of adverse events classified as neutropenia or leukopenia (COSTART Term Leukopenia) related to abnormal ANC and WBC values B1 to B

Summary of adverse events and withdrawals classified by severity

	Quetiapine			
	Patients with adverse events because of leukopenia*		Withdrawn for adverse events of leukopenia*	
	transient*	persistent*	transient*	persistent*
Neutropenia				
agranulocytosis (<0.5 with symptoms)	0	0	0	0
severe neutropenia (<0.5 without symptoms)	0	0	0	0
moderate neutropenia (≥0.5 and <1.0)	5	0	1	0
mild neutropenia (≥1.0 and <1.5)	10	2	4	1
Leukopenia				
severe leukopenia (<3.0)	6	0	3	0
mild to moderate leukopenia (≥3.0 and <4.0)	18	0	5	0
Normal or ANC >1.5 and WBC >4.0		7		

*The incidences (14) of withdrawal because of the adverse event of leukopenia are included in the columns describing patients with adverse events of leukopenia.

Units for neutrophil and leukocyte counts are x 10⁹ cells/L.

ADVERSE REPORTS OF TRANSIENT MILD NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0012/0035/3506		1.4	3	Asymptomatic mild.
0012/0064/6406		1.32	8	Transient mild neutropenia.
0012/0065/6503		1.12	26	Mild leukopenia. Transient with mild leukopenia.
0014/0031/3101	3.7, 3.6, 3.2	1.9, 1.6, 1.2	3, 18-26	Intermittent neutropenia on both haloperidol and on quetiapine. Moderate leukopenia and mild neutropenia that may be drug related despite its mild nature.
0014/0051/5101	4.1	1.41	3	Nonprogressive mild neutropenia.
0012/0005/0502	2.4	1.4	6	Single episode of transient neutropenia on week 6. Noncumulative transient cytopenia etiology.
0013/0021/2119	3.0	1.27	3	Two values of mild neutropenia on week 3 and 4. Nonprogressive asymptomatic.
0013/0022/2206	4.0-3.6	1.44, 1.32, 1.27	5-11	Mild persistent neutropenia with mild leukopenia.
0014/0004/0401	3.1	1.27	32	Repeat 3 weeks later, normal. Transient leukopenic episode unclear etiology.
0015/0029/2912	3.3	1.9	50	Repeat on week 51, normal. Single episode of transient leukopenia and neutropenia. Unclear etiology associated with dermatitis in a 36 y/o female. Possible comorbid condition.

ADVERSE REPORTS OF PERSISTENT MILD NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0012/0005/0508	3.2, 2.7, 2.9	1.23, 1.07, 1.20	9, 13, 30	Repeat value on week 30 confirmed mild leukopenia, persistent mild leukopenia. This led to withdrawal of the patient with repeat value 10 days later showing WBC 5.0, ANC 2.8. Probable association with drug administration, late onset persistent neutropenia.
0014/0001/0103	2.9-3.9	1.1-1.48	1, 4, 6, 7, 10, 18	Persistent mild leukopenia without progression associated with a low normal neutrophil count. Presence on week 1 suggests prior abnormality.

ADVERSE REPORTS OF SEVERE LEUKOPENIA WITHOUT NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0013/0022/2212	2.7-3.7	1.52-2.57	1-8	Asymptomatic mild leukopenia noted repeatedly as an adverse event, not apparently associated with any abnormality.
0012/0062/6205	2.9	1.7	16	Single episode of mild leukopenia widely fluctuating WBC and ANC, no evidence of progression or symptoms.
0013/0014/1401	2.8-3.7	1.54-1.68	7-9, 14, 15	Nonprogressive, tolerated continued therapy. Not drug related.
0012/0036/3609				See above review.
0012/0042/4203				See above review.
0014/0045/4508				See above review.

**MILD TO MODERATE LEUKOPENIA
TRANSIENT MILD TO MODERATE LEUKOPENIA LEADING TO WITHDRAWAL**

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0008/0008/0007	3.7		3	Transient episode found 2 days after a WBC of 5.0 leading to withdrawal, repeat 3 days later. WBC 6.7. Possible drug effect.
0012/0044/4404	3.4		3	Transient, repeat 7 days later, WBC 5.1. Unclear drug association.
0005/0003/0010	3.6		3	Withdrawal, no followup values. Unclear drug etiology.
0013/0019/1909	3.0	1.7	18	Associated with URI. Transient nonprogressive, probably nonrelated.
0014/0006/0005	3.4		14	Terminated on week 15, 5 days later WBC 3.9. Unrelated to drug given baseline WBC of 4.0.

PLEASE NOTE: Patient Number 0014/0006/0005 is a typographical error. This Patient Number is 0014/0006/0605.

TRANSIENT MILD TO MODERATE LEUKOPENIA NOT LEADING TO WITHDRAWAL

Patient Number	Comments
0008/0001/0018	<p>Episodes of transient mild to moderate leukopenia or mild nonprogressive. Most occurred early with very minimal changes in WBC and not associated with neutropenic episodes. In most instances, the WBC fell from less than 6,000 to greater than 3,000. Most patients had WBCs in the range of 4,000-5,000 persistently. None of these can be ascribed to be progressive symptomatic or indicative of definitive drug effect.</p>
0008/0001/0032	
0008/0015/0009	
0013/0007/0701	
0005/0011/0005	
0014/0001/0144	
0012/0036/3604	
0012/0050/5002	
0013/0019/1904	
0013/0022/2203	
0013/0022/2207	
0014/0035/3506	
0014/0035/3507	

Summary of adverse drug events

Many of these adverse drug events could be classified as severe neutropenias or mild to severe leukopenias and could be used to generate an overall incidence of episodes. There is no characteristic which separates the reported adverse events from those not reported in terms of absolute values or progression of WBC and ANC.

In summary, quetiapine has an association of episodes with mild to severe nonprogressive asymptomatic neutropenia and no cases of agranulocytosis. No patients were removed for adverse events due to symptomatic neutropenia and the breadth of the data does not indicate any clinically significant adverse outcome due to the presence of neutropenia. It appears that this drug can be safely administered and there is no population at risk for development of sustained and neutropenic episodes including those patients with benign neutropenia or leukopenia at the time of onset of treatment.

**Medical Officer's Review of NDA 20-639
Ophthalmology Consult**

**NDA # 20-639
Consult**

**Submission: 7/29/96
Consult Request: 2/3/97
Review completed: 3/9/97**

Name: Seroquel (quetiapine fumarate tablets)

Applicant: Zeneca Pharmaceuticals
1800 Concord Pike
Wilmington, DE 19850-5437

Proposed Indication(s): For the management of the manifestations of psychotic disorders

Reviewer's Comments: Comments in this review are limited to areas of ophthalmic concern.

Non-clinical: (From Integrated Summary of Safety, Vol 285, page 53)

"The lens was the principal organ affected by quetiapine in the dog. Opacities were first noted after 3 months of dosing at 100 mg/kg/day with posterior subcapsular triangular cataracts appearing after 6 months. These did not progress to diffuse cataracts. Histologic changes included anterior and posterior fiber swelling and variations in staining intensity."

Reviewer's Comments: *Based on the animal studies, quetiapine fumarate should be considered potentially cataractogenic in man until studies are performed to demonstrate otherwise.*

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Clinical:

(From Integrated Summary of Safety, Vol 286, page 6-10)

Number and percent of subjects with unchanged, improved, or worsened LOCS III scores from baseline to final evaluation during treatment with quetiapine in trials 12, 13 and 15.

	Number of patients		
	Improved	No Change	Worsened
Cortical cataract	5	77	8
Posterior subcapsular	0	86	4
Nuclear opalescence	15	57	17
Nuclear color	15	60	15

Reviewer's Comments:

The number of patients demonstrating a worsening was higher than the number of patients demonstrating improvement. If the changes were due to observational mis-classification, the groups would be expected to be balanced. The small number of subjects in the haloperidol and placebo groups makes their use of limited value.

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Number and percent of subjects with no change, improved, or worsened LOCS III scores from baseline to final evaluation during treatment with quetiapine in uncontrolled trials including open label extension of trials 12, 13 and 15.

	Number of patients		
	Improved	No Change	Worsened
Cortical cataract	6	45	9
Posterior subcapsular	0	54	6
Nuclear opalescence	13	27	19
Nuclear color	8	39	13

Reviewer's Comments:

The number of patients demonstrating a worsening was higher than the number of patients demonstrating improvement. If the changes were due to observational mis-classification, the groups would be expected to be balanced.

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Patients with clinically significant changes [From Volume 1.171, pages 132-139]

007/00702 34 ♀	Seroquel 75 mg	Normal baseline, clinically significant change in right eye at week 12	Cataract unusual for this age
013/01308 43 ♂	Seroquel 75 mg	Normal baseline and week 12. Lens changes at week 24.	Cataract unusual for this age
013/01309 43 ♀	Seroquel 300 mg	Normal baseline, lens changes at week 12 and continuing. Visual acuity loss from 20/15 to 20/25.	Cataract unusual for this age
023/02301 23 ♂	Seroquel 600 mg	Normal baseline, posterior subcapsular cataracts noted at week 12.	Cataract unusual for this age
029/02902 51 ♀	Seroquel 600 mg	Normal baseline and week 12. Central lens opacity at week 24.	Cataract
006/00601 24 ♂	Seroquel 75 mg	Posterior subcapsular opacities with decreased vision during study	Decreased vision

Reviewer's Comments: *Cataracts in patients under the age of 50-60 is very unusual.*

From Consultant's Report [Volume 1.178, pages 62-67]:

"Study 5077IL/0015 -Relapse Prevention Clinical Trial

The requirement for retro-illumination photography of the crystalline lens was removed from the protocol on October 23, 1994. This technique had been included to allow a small group of cataract graders, masked to visit, drug status, and other parameters, to grade in a standardized manner all of the photographs after the trial was completed. Its omission means that cataract classification will be done at the slit-lamp by several graders, and that there will be less likelihood that cataract classification criteria will be employed uniformly to all instances lens specification and cataracts."

Reviewer's Comments: *The deletion of retro-illumination photography specifically undermines the ability to detect the development of cataracts.*

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"Patients completing the trial:

'... the overall proportion of patients who completed the trial was low.' 16%-34% in the Seroquel and Haloperidol groups. This inevitably reduces the power of the study to detect significant adverse effects of Seroquel on the lens."

Reviewer's Comments: *Concur.*

"On page 102 are the specific data for the ophthalmologic and slit-lamp examinations and LOCS III data for the 139 U.S. and 21 Canadian patients.

In the narratives on p 103 one can read the specific ophthalmologic problems observed. It should be noted however that the protocol does not attempt to standardize either the observational methods used to examine the lens or the terminology used to describe the lens findings. Therefore the precise meaning of the terms used below is unknown. Also whether or not the examiner was describing a normal age-related change or finding in the lens is not clear."

Reviewer's Comments: *The methods used also undermine the ability to detect the development of cataracts. Many of the patients failed to have both visual acuity measurements and slit lamp examinations.*

"(Canadian Data) 4/21 Canadian patients had normal baseline and at least one abnormal exam of the ocular lens. Three of these 4 were deemed to be clinically significant (in the Seroquel) group. It is not possible to draw any conclusions about the effect of Seroquel on the lens from such a small sample."

Reviewer's Comments: *Disagree. This represents a 15% rate of clinically significant changes and is unusual for any trial.*

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Applicant's Summary:

Overall, the results of the slit-lamp examinations of the ocular lens support the view that Seroquel has no clinically relevant effect on the ocular lens. Ocular changes noted were of a very minor nature, were noted in all treatment groups, and were not related to the dose of Seroquel administered. The LOCS III data support the slit lamp examination results, that Seroquel had no clinically relevant effect on the ocular lens.

Reviewer's Comments:

The applicant's summary should be regarded as either false or very misleading. Few patients had complete examinations, abnormal findings were dismissed even when listed as clinically significant and tests to detect cataract changes were deleted from the protocols.

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Reviewer's Conclusions:

The non-clinical study results are suggestive of a drug product which is capable of increasing the development of cataracts. The applicant has had the opportunity to study the issue, but failed to adequately follow patients and/or perform the necessary examinations. The ocular adverse experiences which have been observed, have been inappropriately minimized by the applicant and are not balanced between groups (higher in the Seroquel groups).

Reviewer's Recommendations:

1. If the application is approved, the package insert should include a statement in the WARNINGS section that "Seroquel has the potential to increase the development of cataract formation. Periodic slit lamp examinations (approximately every 6 months) are recommended."
2. Prior to any modifications of the above warning, an additional study should be performed to further evaluate the cataract potential of Seroquel. The study should be controlled, include at least 300 patients on treatment for at least 12 months with standardized slit lamp examinations and best corrected distance visual acuity measurements performed at baseline, months 3, 6, 9 and 12. Retro-illumination photography would be helpful, but alternative standardized grading systems are also acceptable.


Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 20-639
HFD-120
HFD-120/Mosholder
HFD-105
HFD-550/Consult File
HFD-550/Chambers