CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-031/S-026

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-026

GlaxoSmithKline
Attention: Thomas F. Kline
Assistant Director, U.S. Regulatory Affairs
1250 S. Collegeville Rd.
P.O. Box 5089
Collegeville, PA 19426

Dear Mr. Kline:

Please refer to your supplemental new drug application dated April 28, 2000, received April 28, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil® (paroxetine hydrochloride) Tablets.

We acknowledge receipt of your submissions dated March 14, 2001 (revised draft labeling).

Your submission of March 14, 2001 constituted a complete response to our February 26, 2001 action letter.

This supplemental new drug application provides for the use of Paxil® (paroxetine hydrochloride) Tablets for the treatment of generalized anxiety disorder as a new indication.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted on March 14, 2001).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-031/S-026." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an

assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-031/S-026

APPROVABLE LETTER

NDA 20-031/S-026

GlaxoSmithKline
Attention: Thomas Kline
Assistant Director, U.S. Regulatory Affairs
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

Dear Mr. Kline:

Please refer to your supplemental new drug application dated April 28, 2000, received April 28, 2000 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil® (paroxetine hydrochloride) Tablets.

We acknowledge receipt of your submissions dated June 16, and October 4 and 13, 2000.

This supplemental new drug application provides for the use of Paxil® Tablets for generalized anxiety disorder (GAD).

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

Labeling

Accompanying this letter as an attachment is our proposal for the labeling of Paxil® Tablets for the generalized anxiety disorder indication. Please submit revised draft labeling identical in content to the enclosed labeling (text for the package insert). Explanations for our proposed changes are provided in the bracketed comments embedded within the proposed text. We would be happy to discuss these proposed changes in more detail through a teleconference if you wish.

Safety Update

Under 21 CFR 314.50(d)(vi)(b), we request that you provide a final safety update for Paxil® Tablets for GAD.

Regulatory Status Update

Please provide any new information on the worldwide regulatory status of Paxil® Tablets for GAD, including the status of all actions either taken or pending before foreign regulatory authorities.

World Literature Update

Prior to the approval of Paxil® Tablets for GAD, we will require an updated report on the world archival literature pertaining to the safety of this product for this indication.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

35 page(s) of revised draft labeling has been redacted from this portion of the review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-031/S-026

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	20-031 SE1-026-BZ
Sponsor:	GlaxoSmithKline Pharmaceuticals
Drug:	Paroxetine Hydrochloride
Indication:	General Anxiety Disorder
Dates of Submission:	Correspondence date: 3/14/01 Date received: 3/16/01
Materials Reviewed:	Supplemental NDA Amendment: Response to FDA Approvable Letter for Efficacy supplement SE1-026 for Paxil® tablets and treatment of generalized anxiety disorder. The following materials were included: • Proposed draft labeling • Safety Update • Regulatory Status Update • World Literature Update
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	March 28, 2001

The purpose of this review is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in making regulatory decisions regarding NDA 20-031 SE1-026 and SE1-026 BZ submissions.

I. Proposed Draft Labeling

The proposed draft labeling in this submission is almost identical to that proposed to the sponsor sent with the 2/26/01 approvable letter with some minor exceptions. These exceptions included minor editorial changes to enhance clarity, consistency, as well as some minor formatting or stylistic changes.

II. Safety Update

Only one new paroxetine study (Non-IND study 646, also briefly described in the original sNDA 20031 S026 submission, as ongoing) was completed since the original sNDA 20-031 S026 submission, entitled "A Study of the Maintained Efficacy and Safety of Paroxetine in Patients with Generalized Anxiety Disorder (GAD)." This study involved an 8-week single-blind paroxetine treatment phase (20-50 mg/day) followed by a 24-week double blind maintenance phase in which subjects (Ss) identified as treatment responders were randomized to placebo or paroxetine treatment. 652 Ss entered the single-blind treatment phase and 566 Ss were randomized to the maintenance phase (278 paroxetine Ss and 288 placebo Ss). The one death that occurred was in a placebo subject and is considered unrelated to the study drug (metastatic pulmonary carcinoma). None of

the reported serious adverse events and adverse dropouts were either of the following: unexpected, likely to be drug-related or not already included in the current labeling. The enumeration of these events is as follows:

- 10 serious adverse events (6 paroxetine Ss and 4 placebo Ss)
- 43 adverse dropouts (35 paroxetine and 8 placebo Ss)

16 post-marketing reports of adverse events (15 spontaneous and 1 from the literature) were revealed from a search (using search terms that included GAD, "general anxiety" and other similar search terms for the indication) of the SB Clinical Safety Database (AEGIS) for dates between 2/2/00 (the cut-off date used in the original submission) and 2/1/01.). None of the reported adverse events were either of the following: unexpected, likely to be drug-related or not already included in the current labeling. There were no reported deaths. One event met ICH criteria for a serious adverse event in which a 62 year old female was diagnosed with pulmonary fibrosis (confirmed by biopsy) after 20 months of paroxetine treatment. The etiology was considered to be idiopathic. The patient was also receiving lorazepam. No other medical history was provided. Pulmonary fibrosis is listed among events reported during the premarketing evaluation of Paxil® in the current labeling.

III. Regulatory Status Update

Marketing applications for the GAD indication were submitted to 30 countries of which 5 were approved and 24 are pending. [redacted] t is reported that paroxetine hydrochloride was never withdrawn from the market due to safety reasons.

IV. World Literature Update

A literature search was conducted regarding paroxetine treatment of GAD using various databases, which yielded 50 citations. "No important new safety findings" were revealed.

V. Conclusion and Recommendations

This amendment contains no new or unexpected safety information and the minor modifications in labeling from that provided with the 2/26/01 approvable letter appear acceptable.

/S/

Karen L. Brugge, ~~M.D.~~
Medical Review Officer, DNDP
FDA CDER ODE1 DNDP HFD 120

cc: IND
HFD 120
HFD 120/ P Andreason/ K Brugge/ A Homonnay/ T Laughren

3-30-01
I agree that this supplement can now be approved.
/S/

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	20-031
Sponsor:	SmithKline Beecham Pharmaceuticals
Drug:	Paroxetine Hydrochloride
Indication:	General Anxiety Disorder
Dates of Submission:	April 28, 2000
Materials Reviewed:	Efficacy supplement SE1-026 Inclusion of efficacy results from three 8-week double-blind, randomized trials on a total of 1,264 patients (studies 641, 642 and 637) comparing paroxetine (735 total patients) and placebo (529 total patients) for efficacy and safety for the treatment of generalized anxiety disorder.
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	December 14, 2000

Table of Contents

1.0 Material Utilized in Review 3

2.0 Background 3

3.0 Chemistry 4

4.0 Animal Pharmacology 4

5.0 Description of Clinical Data Source 4

6.0 Human Pharmacokinetics 5

7.0 Review of Sudies For Which Efficacy Claims Are Made 5

7.1 Study 641. A Randomized, Double-blind, Placebo Controlled, Fixed Dosage Trial to Evaluate the Efficacy and Tolerability of 20 and 40 mg/day Paroxetine in Patients with Generalized Anxiety Disorder; Study 29060/641. 5

7.2 Study 642. A Randomized, Double-blind, Placebo Controlled, Flexible Dosage Trial to Evaluate the Efficacy and Tolerability of 20 to 50 mg/day Paroxetine in Patients with Generalized Anxiety Disorder; 29060/642. 15

7.3 Study 637. A Randomized, Double-blind, Placebo Controlled, Flexible Dosage Trial to Evaluate the Eficiacy and Tolerability of 20 to 50 mg/day Paroxetine in Patients with GAD. 20

8.0 Integrated Safety Information 26

9.0 Labeling Review 41

10.0 Conclusions 41

11.0 Recommendations 42

Appendix 43

1.0 Material Utilized in Review

1.1 Materials from NDA/IND

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

Table 1.1.1 Documents Utilized in Clinical Review	
DATE	DESCRIPTION
April 28, 2000	NDA Efficacy Supplement 20-031 SE1-026, 22 volumes on CD-ROM and hard copy (23 volume) versions. Case Report Tabulations are provided as SAS transport files on CD-ROM.

1.2 Related Reviews

Please refer to NDA 20-031, in which Paxil® was approved for the indications of treating Depression, Obsessive Compulsive Disorder, and Panic Disorder. Also see the "Administrative History" section below.

2.0 Background. This review is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in making regulatory decisions regarding NDA 20-031 SE1-026.

2.1 Indication

Indication of Paxil® for treatment of Depression: the efficacy of Paxil® was demonstrated in placebo controlled studies of patients with "depression" that "corresponded closely to the DSM-III criteria for major depressive disorder". Studies showed a significantly greater efficacy with Paxil® treatment than with placebo on the following parameters: Hamilton Rating Scale, the Hamilton depressed mood item and the Clinical Global Impression-Severity of Illness. When patients responding to 8 weeks of open-label treatment with Paxil were continued on Paxil for one year, they showed a relapse rate of 15% compared to 39% of patients randomized to placebo treatment for a year. These results support the long-term maintenance efficacy claim of Paxil® for a period of up to one year.

Indication of Paxil® for treatment of Obsessive Compulsive Disorder (OCD): Two 12-week placebo controlled multicenter studies of patients with moderate to severe OCD (DSM-IIIR) were reported to demonstrate efficacy when using the Yale Brown Obsessive Compulsive Scale as the efficacy parameter.

Indication of Paxil® for treatment of Panic Disorder: efficacy was reported in three 10 to 12 week multicenter, placebo controlled studies in patients with panic disorder (DSM-IIIR) with or without agoraphobia.

Indication of Paxil® for treatment of Social Anxiety Disorder: this indication was based on three 12-week multicenter, placebo controlled studies of adults with social anxiety disorder (DSMIV). These studies showed a significant effect of Paxil® compared to placebo on response rate using criteria based on scores from the Liebowitz-Social Anxiety Scale and the Clinical Global Impression score or subscores.

2.2 Related INDs and NDAs

INDs:

IND 23,280 – Paroxetine Hydrochloride Tablets

IND 51, 171 – Paroxetine Hydrochloride Modified/Controlled-Release Tablets

NDAs:

NDA 20-031 – Paxil (paroxetine hydrochloride) Tablets

NDA 20-710 - Paxil (paroxetine hydrochloride) Oral Suspension

NDA 20-885 - Paxil (paroxetine hydrochloride) Capsules

NDA 20-936 - Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets

NDA 20-982 - Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets

2.3 Administrative History

Paroxetine hydrochloride is a selective serotonin reuptake inhibitor. The NDA for this drug was approved for the treatment of the following: Depression on 12/29/92, Obsessive Compulsive Disorder (OCD) on 5/7/96, and Panic Disorder in 1996. In May 6, 1998 a supplemental NDA 20-031/S-023 was submitted requesting approval for the addition of a new indication, Social Anxiety Disorder which was approved on May 11, 1999. Paxil Oral Suspension (NDA 20-710) and Paxil Capsules (NDA 20-885) are also marketed. A controlled release formulation Paxil CR (IND 51,171) was approved on 2/16/99 for treatment of "depression" (NDA 20-936) and for the treatment of panic disorder (NDA 20-982), which is currently under an "approvable" status.

2.4 Directions for Use

Depression: the recommended starting daily oral morning dose is 20 mg (with or without food) which can be increased by increments of 10 mg/day at intervals of at least one week, up to a maximum daily dose of 50 mg. The dose range employed in clinical trials was 20 to 50 mg daily.

OCD: the dosing recommendations regarding the starting dose and dose titration regimen are the same as those for depression. However, the recommended daily dose for treatment of OCD is 40 mg with a dose range of 20-60 mg/day employed in clinical trials. The dose is not to exceed a maximum of 60 mg/day.

Panic Disorder: a recommended starting dose of 10 mg/day that may be increased by 10 mg/day at intervals of at least one week to a target dose of 40 mg/day. The dose range employed in clinical trials was 10 to 60 mg/day. The maximum daily dose is recommended to be no greater than 60 mg.

Social Anxiety Disorder: the initial recommended dose is 20 mg/day. Although the safety of the drug has been assessed for a dose of up to 60 mg/day in patients with this disorder, "available information does not suggest any additional benefit for doses above 20 mg/day".

Elderly or Debilitated patients, and patients with Severe Hepatic or Renal Impairment: the recommended initial dose is 10 mg/day and the maximum dose is recommended to be no greater than 40 mg/day.

3.0 Chemistry

There are no chemistry issues to review in this submission.

4.0 Animal Pharmacology

There are no animal pharmacology/toxicology issues to review in this submission.

5.0 Description of Clinical Data Source

Three studies were reviewed employing a multi-center, randomized, double blind, placebo controlled parallel group design as indicated in the table below:

Clinical Studies Reviewed from this Submission

Protocol No	Study Design	Study Drug Dose, Route, Duration	N (ITT Pop.)
641	Titrated Fixed dose Conducted in the US and Canada	Daily oral doses of 20 mg or 40 mg of Paxil® (titrated from 10 mg/day to the randomly assigned dose) or placebo for 8 weeks	566
642	Flexible dose design Conducted in the US and Canada	Placebo or Paxil® with the start dose of 10 mg/day, increased by weekly increments of 10 mg/day, to a maximum dose of 50 mg/day	324
637	Flexible dose design Conducted in Europe	Placebo or Paxil® with the start dose of 20 mg/day, increased by weekly increments of 10 mg/day, to a maximum dose of 50 mg/day	364

5.1 Adequacy of Clinical Experience

The sponsor makes their claim for the efficacy of Paxil® in the treatment of generalized anxiety disorder (GAD) on the basis of three multicenter, placebo controlled studies involving approximately 1300 outpatients with GAD. This is adequate data to review.

5.2 Data Quality and Completeness

Line listings of verbatim and preferred term texts were generally internally consistent and generally consistent with the narratives. This assessment is based on examination of most of the line listings for serious adverse events, a subset of line listings for adverse dropouts and a subset of line listings of subjects with safety parameters meeting criteria for "Clinical Concern". Minor discrepancies were noted when matching line listings with some of the narratives or with other line listings or data sources, such as for subject 637.017.03612. The serious adverse event (preferred term) listed on Table 26 of the Integrated Summary of Safety is "anxiety" while the line listing Appendix D.4 (which was made available upon request) indicates "psychotic depression" as the preferred term and "agitated depression" as the verbatim text.

Several narratives were found to be somewhat incomplete, such that additional information had to be requested. For example several narratives of subjects flagged as outliers on safety parameters (met predefined criteria for "Clinical Concern") indicated that the subject "completed the study as planned" but failed to provide sufficient clinical information pertaining to the diagnosis, clinical evaluation and follow-up of their abnormal laboratory test(s). Examples of these narratives containing insufficient information are as follows: 637.062.03804, 641.131.01559, 641.133.01610 and others (a fax was sent to the sponsor dated 8/7/00). However, the sponsor provided additional information upon request (the sponsor responded in a fax dated 8/31/00) or in some cases additional information was included in the Case Report Forms (CRFs). Some of these subjects are described in this review under sections on subjects flagged as outliers on various laboratory parameters.

6.0 Human Pharmacokinetics

There are no human pharmacokinetic issues to review with this submission.

7.0 Review of Studies For Which Efficacy Claims Are Made

Studies 637, 641, 642 are multicenter, randomized, double-blind, placebo controlled, parallel group efficacy studies conducted on outpatients with Generalized Anxiety Disorder (DSMIV). One study employed a fixed dose design (Study 641), and 2 studies employed a flexible dose design (Studies 642 and 637). Study 637 was conducted in Europe while the other two studies, Studies 641 and 642, were conducted in the US and Canada. These studies employed doses of Paxil® ranging from as low as 10 mg/day to as high as 50 mg/day given over an 8-week treatment phase followed by a taper phase of 2 or 3 weeks. Each study is described in detail below.

7.1 Study 641. A Randomized, Double-blind, Placebo Controlled, Fixed Dosage Trial to Evaluate the Efficacy and Tolerability of 20 and 40 mg/day Paroxetine in Patients with Generalized Anxiety Disorder; 29060/641.

7.1 A. Study 641. Investigators and Sites

See Table 7.1.1 A in the appendix for a listing of the fifty investigative centers located in the United States and Canada that participated in the study.

7.1 B. Study 641: Objectives

- The primary objective of the study was to determine the efficacy of paroxetine (20 mg and 40 mg) treatment compared to placebo treatment in patients with Generalized Anxiety disorder (GAD).

- The secondary objective was to evaluate safety and tolerability of paroxetine (20 and 40 mg) compared to placebo treatment in patients with GAD.

7.1 C. Study 641: Study Population

The study population consisted of 566 subjects (the randomized population) with GAD by DSM-IV criteria who had a Hamilton Anxiety Scale (HAM-A) score of at least 20. HAM-A subscores of at least 2 on item 1 (Anxious Mood) and item 2 (Tension) were additional inclusion criteria. The minimum age allowed for inclusion into the study was 18 years old. Subjects over 65 years old, who were included in the study, had to be "able to tolerate paroxetine starting dose of 10 mg/daily and be without evidence of significant renal or hepatic impairment", as assessed by liver and renal function tests.

In addition to the above criteria required at screening, subjects were required to meet additional criteria on a baseline visit that occurred following a one week placebo run-in phase of the study and prior to randomization into a treatment group for the treatment phase of the study. Eligibility for entry into the treatment phase required that subjects show the following scores on the baseline visit:

- ≥20 on the HAM-A and ≥2 on each of items 1 and 2 of the HAM-A.
- <18 on the Montgomery and Asberg Depression Rating Scale (MADRS) which was also required during the screening visit (Day –7, prior to onset of run-in phase).

Subjects meeting any of the following conditions were excluded from entering into the treatment phase of the study:

- Showed a reduction, from screening to baseline visits, on the HAM-A score of >20%.
- If the subject returned more than 20% of the expected amount of placebo run-in medication at the end of the run-in phase
- Patients with "unresolved" clinical findings were also excluded at this time.

Subjects with the following concomitant psychiatric illnesses (DSMIV) or conditions at screening or within 6 months of the trial were excluded from the study:

- Panic Disorder.
- Social Phobia.
- Agoraphobia.
- Post Traumatic Stress Disorder.
- Obsessive Compulsive Disorder.
- Eating Disorders.
- Substance Abuse or Dependence Disorder.
- Major Depressive Disorder.
- A score of 18 or greater on the MADRS at screening.
- Patients with dysthymia as a predominant condition at screening or within 6 months of the study.
- Patients with a history or a current diagnosis of Bipolar disorder, Cyclothymic Disorder, or psychotic disorder.
- Patients with current suicidal or homicidal risk.
- Patients with "clinically significant medical conditions" as judged by the investigator.

Patients with a history of not responding to SSRI treatment were also excluded from the study.

7.1 D. Study 641: Design

This double-blind, randomized, placebo controlled, multicenter, fixed dose, parallel group study involved an 8-week treatment phase. Subjects were randomized to one of three treatment groups (1:1:1 ratio): 20 mg or 40mg of paroxetine or placebo (the control group) and were administered a single tablet (over-encapsulated for blinding purposes) daily in the morning. Study assessments, including efficacy measures and some safety measures during the 8-week treatment phase, were scheduled for weeks 1, 2, 3, 4, 6 and week 8 or upon early withdrawal. A follow-up visit was conducted after one week of the taper phase (Taper Interim Visit), at the end of the taper phase (Taper End Visit) and 14 days after the last dose during which safety assessments were conducted. If a subject had an adverse event on this 14-day follow-up visit, an additional follow-up visit was required on post-treatment day 28 (14 days after the 14-day follow-up visit).

A single blind one-week placebo run-in phase was employed to eliminate "early placebo responders" and assess "suitability" for study entry. A two-week double-blind taper phase was also employed on subjects that participated in at least two weeks of the eight-week treatment phase of the study. The table below outlines the daily dose regimen for the three treatment groups during the treatment and taper phases of the study, as provided by the sponsor.

Medication Strength per Capsule

	Treatment Phase				Taper Phase	
	Week 1	Week 2	Week 3	Week 4 - 8	Week 9	Week 10
Paroxetine 20 mg	10 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Paroxetine 40 mg	10 mg	20 mg	30 mg	40 mg	30 mg	20 mg
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

Screening (Day –7) for entry into the run-in phase of the study consisted of the following:

- A history, psychiatric and physical exam.
- Clinical laboratory evaluation (thyroid function test, liver function tests, BUN, Cr, electrolytes, CBC with differential and urine dipstick, were among the tests, excluding glucose blood levels).
- Urine screen for benzodiazapines.
- Electrocardiogram (ECG).
- HAM-A, MADRS ratings and the Mini International Neuropsychiatric Interview (MINI).

Subjects meeting the inclusion/exclusionary criteria began the 1-week single blind placebo run-in phase. Following the run-in phase a baseline visit was conducted to assess subjects for eligibility for randomization into the treatment phase of the study.

7.1 E Study 641: Assessments Employed

See the schedule of assessments in Table 7.1.2 in the appendix, similar to that provided by the sponsor. The HAM-A was included for the primary efficacy measure.

To obtain secondary efficacy measures the following measures were employed:

- Subscales of the Hamilton Anxiety Rating Scale (HAM-A)
- COVI Anxiety Scale, Hospital Anxiety and Depression Scale (HAD)
- Montgomery and Asberg Depression Rating Scale (MADRS)
- Sheehan Disability Scale (SDS)
- Subscales of the Clinical Global Impression scale (CGI)
- EuroQol, and job attendance questionnaire (to determine total number of missed work days) EuroQol and job attendance was also obtained as pharmacoeconomic assessments in the study

7.1 F Study 641: Analysis Plan

Statistical analysis was performed on data from the "Intention-To-Treat" (ITT) efficacy population (subjects with at least one valid post-baseline efficacy assessment). The LOCF ITT dataset is that from which the sponsor proposed, *a priori*, to base their "primary inference". Analysis of data from the Per Protocol Population (see "Patient Disposition" section below) was also performed for only the primary efficacy variable. Additional analyses were conducted on the LOCF dataset using the last time-point when at least 70% of the subjects remained in the study (70% LOCF) and on an observed cases dataset (OC) at the 8 week endpoint. The endpoint measure occurred on week 8, more specifically defined as the measure obtained on days 51-64 of treatment.

Primary Efficacy Variable

The primary efficacy variable was defined as the mean change from baseline to treatment endpoint on the HAM-A total score. The baseline measure was defined as the measure on the baseline visit, which occurred on Days –4 to 0, with Day 1 being defined as the first day of treatment. If a subject missed a baseline evaluation for a variable, then the subject was not included in the analyses.

Secondary Efficacy Variables

The secondary efficacy variables included mean change (from baseline to treatment endpoint) on the additional scales or subscales:

- COVI Anxiety Scale
- Items 1 and 2 and Psychic and Somatic subcale scores on the HAM-A
- HAD
- MADRS
- Severity of Illness item score on the CGI
- SDS total score and Family, Social and Work item scores
- EuroQol score
- Job attendance

The percentages of responders on the HAM-A or CGI Global Improvement scales were determined for each treatment group. A responder was defined as a subject having a score of ≤10 on the HAM-A endpoint score or as having a score of ≤2 on the CGI Global Improvement Item endpoint score.

Statistical Tests Employed

The sponsor employed the general linear models (GLM) procedure, Statistical Analysis System (SAS) version 6.12 for the "change from baseline" on efficacy parameters. Type III sums of squares were used. Treatment, investigational site and treatment by site interaction effects were tested using a full model. Since a significant treatment by site interaction effect was not found, this interaction term was dropped from the model for the final analysis. Non-

parametric tests "were considered" because of "evidence of mild non-normality in the data". Instead, ANOVA was employed "due to sample sizes being reasonably large". However, non-parametric methods were employed for the CGI severity secondary efficacy variable. The CATMOD SAS (version 6.12) was employed for analyzing results on the secondary efficacy variables pertaining to patient response rates.

A p value of 0.10 was considered significant for interaction effects and a p value of 0.05 was considered significant for all other analyses, based on a two-sided hypothesis. Dunnet's multiple comparison procedure was employed when comparing the placebo group to each of the active treatment groups. This procedure resulted in a alpha level of 0.027 for each treatment group comparison, which was the alpha level employed for determining confidence intervals for a given dependent variable. The submission does not appear to include a correction of the alpha level for multiple tests employed over various time-points on the HAM-A total score, or on multiple tests employed on the various secondary efficacy variables.

7.1 G Study 641: Patient Disposition

842 patients were screened. 566 of these subjects were randomized into the treatment phase of the study in that they met criteria for entry into the run-in phase, successfully completed the run-in phase, and subsequently met eligibility criteria at the baseline visit. 276 patients failed the initial screening or failed the run-in phase of the study. The ITT Efficacy population (defined as requiring at least one HAM-A assessment during treatment) consisted of 565 subjects. The table below provides descriptive statistics regarding the disposition of the 566 subjects comprising the ITT Safety population, as provided by the sponsor.

Number (%) Subjects Completing or Withdrawing from the Study by Reason of Withdrawal (ITT Safety Population)			
Reason	**Placebo n=180 (%)**	**Paroxetine 20-mg n=189 (%)**	**Paroxetine 40-mg n=197 (%)**
Adverse Events[a]	12 (6.7)	20 (10.6)	24 (12.2)
Lack of efficacy	8 (4.4)	5 (2.6)	8 (4.1)
Deviation from Protocol[b]	9 (5.0)	3 (1.6)	4 (2.0)
Lost to Follow-up	8 (4.4)	13 (6.9)	9 (4.6)
Other Reasons[c]	3 (1.7)	5 (2.6)	9 (4.6)
Completed	140 (77.8)	143 (75.7)	143 (72.6)

[a] Includes serious adverse events.
[b] Includes non-compliant subjects.
[c] Includes subjects who withdrew consent (12 patients), difficulties in scheduling visits (2%), relocation (20 and family illness (1).

69 subjects in the ITT efficacy population were considered violators of the protocol (29 out of 180 of the ITT population in the placebo group, 21 out of 188 in the 20 mg paroxetine group, and 19 out of 197 in the 40 mg paroxetine group). These subjects were excluded from the per protocol population (PPP). Protocol violations were defined as "procedures excluded by the protocol that may have bearing on the effect of treatment on efficacy" and included noncompliance, comorbid Axis I disorder, incomplete HAM-A or MADRS ratings or total scores of <20 or ≥ 18, respectively, a positive benzodiazapine screen, or prohibited medications. 73% (50 subjects) of the total number of violators had used prohibited medications or showed "overall noncompliance" and were fairly evenly distributed across treatment groups.

7.1 H. Study 641. Baseline Demographics/Medical/Psychiatric Comorbidity and Baseline Efficacy Measures

Baseline Demographics. The treatment groups were similar on various demographic variables including mean age, age-group distribution, mean weight, gender and racial distribution. Upon examination of the demographic results the treatment groups show a predominance of Caucasians, women and subjects under 65 years old (only 2-5% of subjects were >65 y.o. among the treatment groups). The demographic results are summarized below:

- Mean (±SD) age of each treatment group: approximately 40 (± approximately 13) years.
- Mean weight and SD for each group: approximately 78 and ±18 kg.
- The distribution of subjects by race among the groups were similar with the range of percentages of subjects in each category of race among the groups were as follows:
  "Caucasians": 82 to 89%
  African American: 4-5%
  Asian: 5% or less were Asian
  "Other":13 to 20% were "other".
- Approximately 56 % of subjects were females in each treatment group.
- The range percentages of subjects in each age-group were the following (approximate figures):
  18-34 year old group: 37-38%
  35-64 year old group: 58-61%
  ≥ 65 year old group: 2-5%

Medical Comorbidity. Treatment groups are generally similar with respect to the percentage of subjects with various current/active or past ICD-9 medical diseases or conditions (73.9%, 79.4%, 73.6% with presenting conditions in the placebo, 20 mg and 40 mg paroxetine groups, respectively). Upon visual examination of the descriptive data, the treatment groups were also generally similar in the type of existing or past conditions/illnesses.

Psychiatric Comorbidity and Baseline Scores of Efficacy Rating Scales. The treatment groups had similar mean baseline scores on the various efficacy measures. The mean HAM-A score was approximately 23 to 24 and CGI severity score was 4.3 among the treatment groups. Mean duration of GAD symptoms was approximately 9 to 10 years with a mean age of onset of approximately 30 to 32 years among the treatment groups. The mean MADRS score was approximately 13 for each treatment group.

The proportion of subjects with history of psychiatric comorbidity was similar across the treatment groups for each of the various psychiatric disorders considered. Approximately 11% of subjects in all treatment groups had a history of a Major Depressive Episode and approximately 4% had a history of Dysthymia. Less than 3% had a history of alcohol or substance abuse/dependence disorder and less than 2% had a history of an additional anxiety disorder (Panic, Agoraphobia, social phobia, or others), suicidality, bulimia, or "other".

7.1 I. Study 641. Concomitant Medications

The number (percentage) of subjects reporting concomitant medication during the treatment phase of the study were similar among the treatment groups as follows: 150 (83.3%), 165 (87.3%) and 165 (83.8%) in the placebo, 20 and 40 mg paroxetine treatment groups, respectively. Furthermore, the groups do not appear to show substantial differences in either patterns of use, as well as in the total use of concomitant medication based on visual inspection of the descriptive data provided in the submission. Vitamins and analgesics were the most common concomitant medications, as reported in 16% to 35% of subjects across the treatment

groups for vitamins or for a given type of analgesic. Estrogen-like medications were third most common in which ethinylestradiol and/or conjugated estrogen use were reported in 6 to 11% or 5 to 7%, respectively, of subjects across the treatment groups. Medroxyprogesterone acetate was reported in 5% of subjects in the placebo group and approximately 3% of subjects in each of the paroxetine treatment groups. The following concomitant respiratory medications are also worth noting: dextromethorphan hydrobromide was reported in 2 to 5% of subjects, loratidine in 4 to 7%, pseudophedrine HCl in 6 to 9% of subjects across treatment groups. Levothyroxine Na was reported in 3 to 6% and caffeine was reported in 6 to 8% of subjects among the groups.

7.1 J. Study 641. Efficacy Results

Study 641. Primary Efficacy Variable:The mean change from baseline to treatment endpoint (in least square means) on the HAM-A total score.

Results provided by the sponsor: Each paroxetine group (-12.5±0.6, N=188 in the 20 mg group, -12.2±0.6, N=197 in the 40 mg group) showed significantly greater improvement ($p<0.001$ for each comparison) on the HAM-A total score than the controls (-9.6±0.7, N=180) for the LOCF ITT dataset. Similar results were obtained for the OC dataset and for the PPP in both LOCF and OC datsets (LOCF of the PPP: mean change of –9.8±0.7, N=151 in the placebo group, -12.5±0.6, N=167 with $p<0.01$, in the 20 mg paroxetine group, -12.1±0.7, N=178 with $p<0.01$ in the 40 mg group; OC of the PPP: $p<0.01$ for each pair-wise comparison). Table 7.1.3 A in the appendix shows the mean change from baseline of the HAM-A total score at each week for each treatment group of the ITT efficacy population for the LOCF and OC datasets.

The sponsor's statistical results on the primary efficacy variable were confirmed by an analysis of the raw data (provided by the sponsor) conducted by the Biometrics reviewer, Dr. Kallapa Koti.

Study 641. Secondary Efficacy Variables.

Results described below are those provided by the sponsor using methods described in the statistical methods section of the submission and also described in the corresponding section in this review.

Study 641. Results on Various Anxiety Rating Scales:

The mean change from baseline to treatment endpoint (least square means±SEM) on the HAM-A Items 1 (Anxiety Item) and 2 (Tension Item) and on the Psychic and Somatic Subscales: The 20 mg paroxetine group (-1.5±0.1, -1.4±0.1, respectively, N=188) and the 40 mg paroxetine group (-1.4±0.1, -1.4±0.1, respectively, N=197) showed a significantly greater improvement ($p<0.001$ for each comparison) than controls (-0.9±0.1, -0.9±0.1, respectively, N=180) on the mean change of Items 1 and 2 for the LOCF ITT dataset. Similar results were reported for the OC ITT dataset.

Trends for differences or significant differences were generally reported for comparisons between each paroxetine group and the control group on the mean change (from baseline to treatment endpoint) of Psychic (includes symptoms of anxious mood, tension, fears, insomnia, intellectual, depressed mood and behaviors at interview) and Somatic Subscales (includes muscular, sensory, cardiovascular, respiratory, gastrointestinal, genitourinary, and autonomic symptoms) of the HAM-A for the LOCF and OC datasets.

- **The mean change from baseline to treatment endpoint (least square means±SEM) on the COVI Anxiety Scale Score:** The 20 mg paroxetine group (-3.3±0.2, N=173) and the 40 mg paroxetine group (-3.2±0.2, N=179) showed a significantly greater improvement ($p<0.001$ for each comparison) than controls (-2.3±0.2, N=163) as reflected by the mean change of the COVI score. Table 7.1.4 A in the appendix provides the results of mean baseline and mean change

from baseline COVI scores in each treatment group for the weeks of treatment when the COVI Scale was administered (weeks 4 and 8).

- **The mean change from baseline to treatment endpoint (least square means±SEM) on the HAD Total Score:** Each paroxetine group showed a significantly greater ($p< 0.001$ for each comparison) mean improvement (-7.3±0.6, N=188 in the 20 mg group, -7.0±0.6, N=197 in the 40 mg group) than controls (-3.5±0.7, N=180) on the HAD Total Score when analyzing the LOCF dataset. Similar results were reported for the OC dataset.
- **A post-hoc analysis of results on the HAD Anxiety (the sum of all odd numbered items) and Depression (the sum of all even numbered items) subscales.** Each subscale consists of 7 items with scores/item ranging from 0 (not present) to 3 (severe) such that the score can range from 0 to 21. See below regarding results on the Depression subscale. The mean scores (least square means) of the treatment groups on the Anxiety subscale at baseline were similar: 12.4±0.3, N=180 in the placebo group, 12.0±0.3, N=188 in the 20 mg paroxetine group and 12.5±0.3, N=197 in the 40 mg paroxetine group. The mean change from baseline to treatment endpoint (least square means) on the Anxiety subscale score was significantly greater in the direction of improvement for each of the paroxetine groups compared to controls (mean change of –2.7±0.4, N=180 in the placebo group, -5.1±0.4, N=188 in the 20 mg paroxetine group, $p<0.001$ and –5.1±0.4, N=197 in the 40 mg group, $p<0.001$) for the LOCF dataset. The OC dataset showed similar results on the mean baseline score and mean change of the score in each treatment group ($p<0.001$ for each pair-wise comparison).

Study 641. Results on Rating Scales for Depressive Symptoms.

- **A post-hoc analysis of results on the HAD Depression Subscale were analyzed.** At baseline the mean Depression Subscale scores (least square means) of the treatment groups were similar (6.4±0.3, N=180 in the placebo group, 6.6±0.3, N=188 in the 20 mg paroxetine group, 6.0±0.3, N=197 in the 40 mg group). The mean change (least square mean) from baseline to treatment endpoint in the Depression Subcale score was significantly greater (reflecting greater improvement) in the paroxetine groups than in controls for the LOCF dataset (mean change of –0.7±0.3, N=180 in the placebo group, -2.1±0.3, N=188 in the 20 mg group with $p<0.001$ compared to controls, and –1.9±0.3, N=197 in the 40 mg group, $p<0.01$). Similar results were observed for the OC dataset ($p<0.01$ for each paroxetine group to placebo group comparison on the mean change in the score from baseline to treatment endpoint).
- **The mean change from baseline to treatment endpoint (Least Square Means±SEM) in the MADRS Score:** Comparisons between each paroxetine group and the control group revealed significantly greater improvements ($p<0.001$ for each comparison) in the paroxetine groups (-1.8±0.6, N=158 in the placebo group, -4.8±0.5, N=159 in the 20 mg group, -4.5±0.5, N=173 in the 40 mg group) for the LOCF dataset. Similar results were shown for the OC dataset ($p<0.001$ for each paroxetine group to placebo group comparison).

Study 641. Results on Scales of Overall Clinical and/or Functional Status.

- **Mean change from baseline to treatment endpoint (least square means±SEM) on the CGI Severity Illness Score:** Each paroxetine group showed a significantly greater mean improvement ($p<0.001$ for each comparison) than the controls for the LOCF dataset (-1.1±0.1, N=180 in the controls, -1.6±0.1, N=188 in the 20 mg paroxetine group, and –1.6±0.1, N=197 in the 40 mg group). Similar results were obtained for the OC dataset ($p<0.001$ for each paroxetine group to control group comparison).
- **Mean change from baseline to treatment endpoint (least square means±SEM) on the**

SDS Total, Work, Family and Social Items: A significantly greater improvement ($p<0.001$ for each comparison) was observed as reflected by the mean change of the SDS Total score in each paroxetine group (-6.1±0.6, N=164 in the 20 mg group, -6.6±0.6, N=175 in the 40 mg group) than that revealed in the controls (-3.0±0.7, N=155) for the LOCF dataset. The OC dataset revealed similar results. Group comparisons on the mean change of each of the SDS items generally revealed similar results with p values ranging from $p<0.021$ to 0.001 for the LOCF and OC datasets. However, there was one exception regarding a comparison between the placebo versus 20 mg paroxetine groups on the mean change on the Family Item of the OC dataset, which did not reach level of significance ($p=0.08$).

Study 641. Results on Proportion of Responders Based on the HAM-Total Score and the CGI Global Improvement Item Score.

- **The percentage of responders defined as a HAM-A total score of 10 or under at treatment endpoint.** Each paroxetine group had significantly more responders than that of the control group for the LOCF dataset (32.8% responders, N=180 in the placebo group, 48.9%, N=188 in the 20 mg paroxetine group with $p<0.01$ and 51.8%, N=197 in the 40 mg group with $p<0.001$). Upon visual inspection of Table7.1.5 A (in the appendix) the percentage of responders appears to increase with each incremental week of treatment for all three groups. However, these apparent weekly incremental increases appear to be greater in the paroxetine groups than in the control group, upon visual examination of Table7.1.5 A. Treatment group comparisons on the percentage of responders at treatment endpoint for the OC dataset revealed results similar to those for the LOCF dataset, described above.
- **The percentage of responders defined as having a score of 1 (very much improved) or 2 (much improved) on the CGI Global Improvement Item at treatment endpoint.** The percentage of responders was significantly greater in each paroxetine group (61.7%, N=188 in the 20 mg group with $p<0.01$, 68.0%, N=197 in the 40 mg group, with $p<0.001$) compared to controls (45.6%, N=180) at the treatment endpoint for the LOCF dataset. See Table 7.1.5 B in the appendix for mean baseline and weekly changes in the mean score for each treatment group. Similar results were revealed with the OC dataset, which are also shown in Table 7.1.5.B.

7.1 K Study 641. Conclusions

Overall, the results of Study 641 are positive. A statistical analysis of the raw data on the primary efficacy variable, conducted by the Biometrics Review, Dr. Kallapa Koti, confirms the statistical results described in the submission. The study shows significantly greater improvement with 8 weeks of paroxetine treatment than placebo on the primary efficacy measure, the total HAM-A score, in outpatients with GAD. However, the treatment effect does not appear to be dose dependent when comparing the 20 mg and 40 mg treatment groups. The sponsor reports that several secondary efficacy measures also demonstrate significantly greater improvement in the paroxetine groups compared to controls. However, these results must be interpreted with caution given that lack of a correction for the multiple tests employed. Regardless, several secondary efficacy variables were highly significant such that with correction (such as a Bonferoni correction) the treatment group differences might still be considered significant.

Secondary efficacy measures showing greater improvement with paroxetine treatment compared to placebo that were highly significant (based on the sponsor's statistical analyses) included another anxiety rating scale, the COVI, and the Tension and Anxiety Items of the HAM-A. Significant treatment effects were also found on measures of overall clinical and/or functional status, the CGI Severity Illness score and the SDS Total score. Finally, a significant

treatment effect was shown on the percentage of responders defined by using a treatment endpoint cut-off score on either the HAM-A Total score or the CGI Global Improvement Item score. Results on the primary and secondary efficacy variables for the LOCF dataset were similar to those when analyzing the OC dataset. The dataset from the PP population was analyzed for potential treatment group effects on the primary efficacy variable and revealed significantly greater paroxetine treatment effects than that observed in the placebo group.

The above effects were demonstrated at both of the daily dose regimens (20 and 40 mg daily oral doses) of paroxetine employed when each treatment group was compared to controls. However, the paroxetine groups showed similar magnitudes of effect on the various efficacy measures, such that a dose-dependent effect was not demonstrated in the study. The group receiving the higher 40 mg dose regimen had a few more subjects classified as responders than the group on the lower dose regimen but the group difference on the percentage of responders was only 3 to 6%, which was not shown to be significant. One possible interpretation for failure to show dose-dependent effects may be that the peak in the dose response curve occurs at doses of 20 mg or possibly less. Another possible consideration might be regarding the sensitivity of the HAM-A score in detecting differences between the low and high dose paroxetine groups. Other factors to consider may be possible group differences in drop out rates or adverse events between the groups, among other potential confounding variables. However, the percentage of subjects with adverse events and the percentage of subjects completing the study were similar among the various treatment groups, as shown in the table in the "Patient Disposition" section of this review. Therefore, these potential factors do not appear to be playing role based on these findings. When groups are compared on adverse events categorized by the "Preferred Term", the high dose paroxetine group shows at least trends for greater AE's for asthenia, abnormal ejaculation and constipation, as noted in the safety section of this review. Hence, a greater incidence of these adverse events in the high dose group may secondarily mask a potential dose-dependent effect on the primary efficacy variable.

The duration of the treatment phase of Study 641 and the study population appear adequate for demonstrating potential efficacy of paroxetine for treatment of GAD. The 8 week duration of treatment employed by the sponsor appears sufficient, given that GAD is a chronic disorder in which a 6 month duration of symptoms is required for a DSMIV diagnosis of GAD can be made. The population under investigation in Study 641, appears to be fairly representative of that expected of the patient population with GAD. Furthermore, the treatment groups were similar on various demographic variables and baseline measures.

One concern with the interpretation of the results of this study may be that the treatment effects could be reflecting antidepressant effects rather than an anxiolytic effect, independent of potential antidepressant effects. Antidepressant effects in the GAD population may be anticipated for several reasons. One is that paroxetine is known to have antidepressant effects at least in other patient populations. Indeed the subjects on paroxetine showed significantly greater improvement on the MADRS score compared to controls in the present study, based on the statistical analyses performed by the sponsor. However, the MADRS contains several items that overlap with the symptoms listed as DSM-IV criteria for GAD. Highly significant treatment effects were demonstrated on both of the HAD Depression and Anxiety subscales, according to the sponsor, supporting the hypothesis that paroxetine showed both antidepressant and anxiolytic effects in the study.

The challenge in teasing out antidepressant versus anxiolytic effects of a drug in patients with GAD is also problematic due to some overlap in some of the symptomatology between

GAD and Major Depressive disorder, including those listed in the DSMIV. Comorbidity for these two psychiatric disorders is not uncommon. Major Depressive disorder is reported to occur in as high as approximately 40 % of the GAD population. However, subjects were screened for a Major Depressive episode occurring within 6 months of the study. The majority of the population (almost 90%) was found to have no history of Major Depressive disorder. Only 4% of the subjects had a history of Dysthymia. The sponsor also included other inclusion/exclusion criteria as an effort to ensure that subjects would have minimal depressive symptoms and predominant anxiety symptoms. The inclusion/exclusion criteria included a maximum cut-off score on the MADRS, a minimum cut-off score of 20 on the HAM-A and minimum of 2 on the Anxiety and Tension Items on the HAM-A. Consequently, the ITT population had a mean baseline score of only 13 out of a possible maximum score of 60 on the MADRS, while their mean baseline score on the HAM-A was 23 to 24 out of a possible maximum score of 56. Furthermore, analysis conducted by the sponsor of results on the HAD Anxiety subscale revealed a paroxetine treatment effect on improvement of anxiety symptoms compared to controls, as described above. These results support those obtained from the two anxiety scales employed, the HAM-A and the COVI, as wells as those of the Tension and Anxiety Items on the HAM-A, which showed significantly greater improvement in the paroxetine compared to control groups, as stated above. Consequently, Study 641 represents a positive study.

7.2 Study 642. A Randomized, Double-blind, Placebo Controlled, Flexible Dosage Trial to Evaluate the Efficacy and Tolerability of 20 to 50 mg/day Paroxetine in Patients with Generalized Anxiety Disorder; 29060/642.

7.2 A. Study 642. Investigators and Sites

Table 7.1.1 B in the appendix shows a listing of the 35 investigative centers that participated in the study, as provided by the sponsor. These sites were located in the US and Canada, as in Study 641 described above.

7.2 B. Study 642. Objectives

The objectives of this study are the same as those for the above described study, which were to determine the efficacy, safety and tolerability of paroxetine treatment compared to placebo treatment in patients with GAD. However, this study employed a flexible design involving a daily oral dose ranging from 20 to 50 mg of paroxetine.

7.2 C. Study 642. Study Population

331 male and female subjects (randomized population) ages 18 years and older, with GAD (DSM-IV) participated in the study. The inclusion and exclusion criteria for this study are the same as those employed in Study 641.

7.2 D. Study 642. Design

The design of Study 642 was the same as that employed in Study 641, except for the dose regimen employed which was a flexible dose design with two treatment groups as follows: 20-50 mg paroxetine and placebo. A one-week run-in phase and an 8 week treatment phase was employed. The starting dose of paroxetine during the first week of the treatment phase was 10 mg/day, and was increased by weekly increments of 10 mg/day. The dose of paroxetine was increased upon the "discretion of the investigator, according to clinical response and tolerability". Subjects could be increased to a maximum daily dose of 50 mg for a maximum period of 4 weeks, given the incremental dose regimen employed. A dosage reduction was permitted during the treatment phase, as deemed necessary in a subject experiencing an adverse event. During the double blind study, the various daily dose regimens were referred as dosage

levels as follows: level 0 (10 mg), level 1 (20mg), level 2 (30 mg), level 3 (40mg) and level 4 (50mg).

Study assessments including efficacy measures and some safety measures during the 8-week treatment phase were scheduled for weeks 1, 2, 3, 4, 5, 6 and week 8 or upon early withdrawal. The taper phase occurred over a 3-week period. Assessments were conducted at the end of the taper phase (an Interim Taper visit was not conducted) and follow-up visits. The table below provides the dosing regimen employed during the taper phase, as provided in the submission.

Double- Blind Study Medication Dosing Instructions During the Taper Phase

Dose Level at End of Treatment Phase	Paroxetine-Equivalent Dosage (mg)	Capsules/Day by Taper Phase Week		
		Week 1	Week 2	Week 3
Level 1	20	No taper phase medication dispensed		
Level 2	30	2	No medication dspensed	
Level 3	40	3	2	None dispensed
Level 4	50	4	3	2

a One bottle of taper phase medication was dispensed at week 8 visit or early withdrawal and contained either 70 paroxetine 10 mg capsules or 70 placebo capsules.

7.2 E. Study 642. Assessments

Assessments conducted for this study were identical to those employed in Study 641. Refer to Table 7.1.2 in the appendix for the assessment schedule.

7.2 F. Study 642. Analysis Plan

The primary and secondary efficacy variables, as well as the statistical methods employed for this study were the same as those employed for Study 641.

7.2 G. Study 642. Patient Disposition

531 patients were screened and 331 of them met criteria for entry into the run-in phase of the study, as well as successfully completing the run-in phase and meeting eligibility criteria for randomization into the treatment phase of the study. The total number of screening and run-in failures was 200 patients. The ITT Efficacy population (required at least one HAM-A assessment during treatment) consisted of 324 subjects. The table below provides descriptive statistics provided by the sponsor regarding the disposition the 326 subjects of the ITT Safety population.

Number (%) Patients Completing or Withdrawing from Study by Reason for Withdrawal (ITT Safety Population)

Reason	Placebo (N=164) N (%)	Paroxetine (N=162) N (%)
Adverse Events[a]	6 (3.7)	17 (10.5)
Lack of efficacy	9 (5.5)	3 (1.9)
Deviation from Protocol[b]	5 (3.0)	3 (1.9)
Lost to Follow-up	6 (3.7)	8 (4.9)
Other Reasons[c]	6 (3.7)	6 (3.7)
Completed	132 (80.5)	125 (77.2)

a Includes SAEs

b Includes patients who withdrew consent (8 patients), difficulties in scheduling visits (2), financial concerns (1), incorrectly admitted to study (1)

Data source, according to the sponsor: Table 11.2.4, Section 12; Listing B. 3, Appendix B.

Forty-nine out of the 331 randomized subjects were identified as protocol violators (25 in the placebo group and 24 in the paroxetine group), as defined by criteria also employed in Study 641 described above. The majority of protocol violations were due to use of prohibited medications (17 in the placebo group and 10 in the paroxetine group). The remaining 39 violations were due to one or a combination of the following violations: overall noncompliance (4, 8 violations in the placebo and paroxetine groups, respectively), positive benzodiazapine screen (3,3), incomplete/inappropriate HAM-A Score (3,4) and/or MADRS Score (2,0).

7.2 H. Study 642. Baseline Demographics/Severity of Illness

Demographic Characteristics. The placebo and paroxetine groups were similar in mean age (41.2±12.2 and 39.7±12.0 years, respectively), weight (75.1±18.2 and 77.1±17.8, respectively) and height. The groups also had a similar distribution of subjects by age-group, race and gender. The majority of subjects were female (65.9% and 61.1% in the placebo and paroxetine groups, respectively), and were under 65 years old (4.3% and 2.5% were 65 years and older in each respective treatment group). The subjects were also primarily Caucasian (81.7% and 85.2% in the placebo and paroxetine groups, respectively) with about 4% African American subjects and 1% Asian subjects in each group, while the remainder subjects were categorized as "other" (10-13% in the two groups).

Medical Comorbidity. Treatment groups were generally similar on the number subjects with past medical disorders/conditions, as well as on the type of conditions. The percentage of subjects with current disorders/conditions appeared to be slightly greater in the placebo group (82.3%) compared to the paroxetine group (74.6%). However, the groups were generally similar in the types of current conditions reported.

Psychiatric Comorbidity and Baseline Scores of Efficacy Rating Scales.

The treatment groups were comparable in reported psychiatric comorbidity, in mean scores on baseline efficacy measures, in mean age of onset, and mean years of duration of the primary diagnosis of GAD. The mean total HAM-A score was approximately 24 and the mean CGI Severity score was 4.2 for each treatment group. The mean MADRS Score was 12.8 and 12.9 for the placebo and paroxetine groups, respectively. The mean duration of GAD was 10.2 and 11.1 years and mean age of onset was 31.3 and 29.2 years in the placebo and paroxetine treatment groups, respectively. The proportion of subjects with history of psychiatric comorbidity was similar across the treatment groups for each of the various psychiatric disorders considered. A history of Major Depressive Episode was reported in 9% and 11% of subjects in the placebo and paroxetine groups, respectively, a history of Panic disorder was reported in 2% of subjects in each treatment group, Dysthymia was reported in 4 and 6% of placebo and paroxetine subjects, respectively, a history of alcohol abuse/dependence was reported in 2% of subjects in each treatment group and a history of drug abuse/dependence was reported in 2% or less in each treatment group. Sucidality was reported in 3% of controls and 1% of paroxetine subjects. Less than 2% of subjects of each group reported a history of other specified psychiatric illnesses (other specific anxiety disorders or subtypes such as agoraphobia, social anxiety disorder, and other psychiatric categories such as bulimia). The remaining subjects (approximately 8% in each group) were in the "other" category of psychiatric history.

7.2 I. Study 642. Concomitant Medications

The number (percentage) of subjects reporting concomitant medications during the treatment phase of the study was 133 (81.1%) and 140 (86.4%) of subjects in the placebo and paroxetine groups, respectively. These percentage rates are similar to those observed in study 641, as well as the types of the most commonly reported concomitant medications which were analgesics (paracetomol, Ibuprofen, acetylsalicylic acid) and vitamins. Ethinylestradiol was also one of the most commonly reported medications as reported in 12.8% and 11.1 % of control and paroxetine groups. Pseudoephedrine HCl was reported in 6.1% and 13.0% in each treatment group, respectively.

7.2.J Study 642. Efficacy Results

Study 642. Primary Efficacy Variable: the mean change from baseline to treatment endpoint (least square means±SEM) on the total HAM-A score.

Results provided by the sponsor: The paroxetine group showed a significantly greater improvement than controls for both the LOCF ITT dataset (-11.8±0.7, N=161 in the paroxetine group, -9.5±0.7, N=163 in the placebo group, $p<0.01$) and the OC ITT dataset (-13.3±0.8, N=127 and –10.7±0.8, N=133, respectively, $p<0.01$). See Table 7.1.3 B in the appendix showing the mean baseline scores and mean change at weekly intervals during the 8 weeks of treatment for each group. These statistical results were confirmed by an analysis of the raw data (provided by the sponsor) conducted by the Biometrics reviewer.

Analysis of the per protocol population on the primary efficacy variable revealed trends for greater improvement in the paroxetine group compared to controls for the LOCF dataset (mean change of –9.5±0.8, N=140 in controls, -11.0±0.8, N=138 in the paroxetine group, $p=0.125$) and for the OC dataset (-11.0±0.8, N=114 in controls, -12.7±0.8, N=105 in the paroxetine group, $p=0.095$).

Study 642. Secondary Efficacy Variables

Results described below are those provided by the sponsor.

Study 642. Results on Various Anxiety Rating Scales:

- **The mean change from baseline to treatment endpoint (least square means±SEM) on the HAM-A Items 1 (Anxiety Item) and 2 (Tension Item) and on the Psychic and Somatic Subscales:** The paroxetine group showed a significantly greater improvement compared to controls on the mean change of the Item 1 score (-1.3±0.1, N=161 in the paroxetine group, -0.9±0.1, N=163 in controls, $p=0.001$) and on the mean change on the Item 2 score (-1.2±0.1, N=161, -0.9±0.1, N=163, respectively, $p<0.01$) for the LOCF dataset. Similar results were revealed with the OC dataset.

A significantly greater improvement ($p<0.01$) was observed in the paroxetine group compared to controls on the mean change of the Psychic Subscale score for the LOCF dataset (-6.6±0.5, N=161 in the paroxetine group, -4.9±0.4, N=163 in the placebo group). Similar results were observed for the OC dataset. Results on the Somatic Subscale revealed only a trend for greater improvement in the paroxetine group compared to controls (-5.1±0.4, N=161 and –4.5±0.4, N=163 in paroxetine and control groups, respectively).

- **The mean change from baseline to treatment endpoint (least square means±SEM) on the COVI Anxiety Scale Score:** The paroxetine group (-3.1±0.3, N=152) showed a trend for greater mean improvement ($p=0.058$) than controls (-2.5±0.2, N=155) on the mean change of the COVI score for the LOCF dataset. When analyzing the OC dataset the observed treatment group difference (mean change of –3.5±0.3, N=125 in the paroxetine group and –2.8±0.3, N=133 in the placebo group) had a p value of 0.027. The COVI scale was administered on weeks 4 and 8 of

treatment with results of mean baseline and mean change from baseline scores shown for each group in Table 7.1.4 B in the appendix.

- **The mean change from baseline to treatment endpoint (least square means±SEM) on the HAD Total Score:** The paroxetine group showed a significantly ($p< 0.001$) greater mean improvement (-6.9±0.7, N=161) than controls (-4.2±0.7, N=162) on the HAD Total Score when analyzing the LOCF dataset. Similar results were reported for the OC dataset.
- **Results on the scores from the Anxiety and Depression Subscales of the HAD were analyzed by the sponsor.** Results of the Depression Subscale scores are described in the section below. A significantly greater improvement ($p<0.001$) on the mean change (least square means) from baseline to treatment endpoint on the Anxiety Subscale score was revealed for the LOCF dataset (-3.2±0.4, N=162 in the placebo group, -5.2±0.4, N=161 in the paroxetine group) and for the OC dataset ($p<0.001$).

Study 642. Results Rating Scales for Depressive Symptoms.

- **Results from the Depression Subscale scores on the HAD were analyzed.** The paroxetine group showed a trend for greater improvement compared to controls ($p=0.071$) on the mean change (least square means) from baseline to treatment endpoint of the Depression subcale score (mean change of –1.7±0.4, N=161 in the paroxetine group, -0.9±0.4, N=162 in the controls) for the LOCF dataset. Similar results were found with the OC dataset.
- **The mean change from baseline to treatment endpoint (Least Square Means±SEM) in the MADRS Score:** Comparisons between the paroxetine and the control groups revealed a trend for a greater improvement in the paroxetine group (-1.4±0.7, N=148 in the placebo group, -2.9±0.7, N=144 in the paroxetine group, $p=0.087$) for the LOCF dataset. Similar results were shown for the OC dataset in which the p value was 0.037 when comparing the groups (a mean change of –2.5±0.7, N=133 in the placebo group, -4.3±0.7, N=126 in the paroxetine group).

Study 642. Results on Scales of Overall Clinical and/or Functional Status.

- **Mean change from baseline to treatment endpoint (least square means±SEM) on the CGI Severity Illness Score:** The paroxetine group showed a significant ($p=0.042$) greater mean improvement of –1.2±0.1 (N=161), compared to controls which had an improvement of –1.0±0.1 (N=163) when analyzing the LOCF dataset, according to that provided in the submission. The sponsor considered this a significant treatment group effect for an alpha equal to 0.05. Analysis of the OC dataset revealed a p value of 0.02 when comparing the treatment groups (mean change of -1.5±0.1, N=127 in the paroxetine group and –1.2±0.1, N=133 in the control group).
- **Mean change from baseline to treatment endpoint (least square means±SEM) on the SDS Total, Work, Family and Social Items:** A significantly greater improvement ($p<0.001$) on the SDS Total score was observed in the paroxetine group (-5.2±0.6, N=152) compared to controls (-2.8±0.6, N=155) in the LOCF dataset with similar results revealed with the OC dataset. Group comparisons on the mean change of the SDS Work item failed to show significant differences (mean change of –1.7±0.3, N=152 in the paroxetine group, -1.3±0.3, N=155 in the control group, p=338) of the LOCF dataset. Significantly greater improvement in the paroxetine group compared to controls was revealed for the Family ($p<0.01$) and Social ($p<0.001$) items. The OC dataset showed similar results.

Study 642. Results on Proportion of Responders Based on the HAM-Total Score and the CGI Global Improvement Item Score.

- **The percentage of responders defined as a HAM-A total score of 10 or under at treatment endpoint.** The paroxetine group had significantly more responders than the control group for the LOCF dataset (37.4 % responders, N=163 in the placebo group, 54,7%, N=161 in

the paroxetine group with p<0.01). Upon visual inspection of Table 7.2.1.A (in the appendix) the percentage of responders generally appears to increase with each incremental week of treatment for both paroxetine and control groups, but the magnitude of the weekly increments of % responders appears to be, upon visual examination, greater in the paroxetine group than that of the control group. A comparison of the treatment groups on this efficacy measure using the OC dataset revealed similar results.

- **The percentage of responders defined as having a score of 1 (very much improved) or 2 (much improved) at treatment endpoint.** The percentage of responders was significantly greater (p<0.01) in the paroxetine group (62.1%, N=161) compared to controls (47.2%, N=163) at the treatment endpoint for the LOCF dataset as shown in Table 7.2.1 B in the appendix. Similar results were revealed with the OC dataset, as shown in Table 7.2.1 B.

7.2 K. Study 642 Conclusions

According to the sponsor's statistical results, Study 642 generally replicated the findings reported by the sponsor for Study 641, although the treatment group effect on the primary efficacy variables appeared to be less robust in the present study. While Study 641 employed a parallel group fixed dose design (daily doses of 20 or 40 mg in the paroxetine groups) with about 190 or more subjects in each group, Study 642 employed a flexible dose design (20-50 mg daily dose) with about 160 subjects per group. Perhaps these differences contributed to failure of some of the observed trends to reach a level of significance on some of the secondary efficacy measures in Study 642. The methods of the two studies were otherwise generally the same and the ITT populations were similar on various baseline measures and demographic characteristics. The magnitude of the effect of paroxetine treatment compared to controls on improvement of symptoms reflected by various efficacy measures, including the primary efficacy measure, was small (such as a mean difference of about 2 to 3 units between paroxetine groups and controls on improvement on the HAM-A total score). According to the sponsor's analyses, group differences were generally highly significant, particularly on the primary efficacy measure. Furthermore, the two studies showed that paroxetine treatment was associated with approximately 15 to 22% more responders than that observed for placebo groups.

7.3 Study 637. A Randomized, Double-blind, Placebo Controlled, Flexible Dosage Trial to Evaluate the Efficacy and Tolerability of 20 to 50 mg/day Paroxetine in Patients with GAD.

7.3 A. Study 637. Investigators and Sites

The multi-center study was conducted in 50 European sites (UK, Ireland, France Germany, Austria, and Italy). Four sites, which screened at least one patient, failed to enroll any subjects. A listing of the sites and investigators, as provided in the submission, is included in the appendix as Table 7.1.1 C.

7.3 B. Study 637. Objectives

The primary and secondary objectives are to examine efficacy and safety/tolerability, respectively, of paroxetine versus placebo in the treatment of GAD.

7.3 C. Study 637. Study Population

374 subjects (the randomized population) met the exclusion/inclusion criteria for entry into the treatment phase of the study. The inclusion/exclusion criteria employed were almost identical to those of Studies 641 and 642.

7.3 D. Study 637. Design

The study employed a double-blind, randomized, placebo controlled flexible dosage trial design in which subjects were either randomized into a placebo group or a paroxetine group (daily oral dose of 20 to 50 mg). The methods employed in this study were the same as those employed in

Study 642. One exception is that the starting dose in the paroxetine group during the treatment phase of Study 637 was higher (20 mg/day, instead of 10 mg/day). Therefore, subjects could reach a maximum daily dose of 50 mg one week sooner than in Study 642 and have a maximum possible duration for receiving the 50 mg daily dose of 5 weeks instead of 4 weeks.

7.3 E. Study 637. Assessments

Assessments conducted for this study were almost identical to those employed in Studies 641 and 642, as shown in the assessment schedule (Table 7.1.2 in the appendix) similar to that provided by the sponsor.

7.3 F. Study 637. Analysis Plan

The primary and secondary efficacy variables, as well as the statistical methods employed for this study were the same as those employed for Studies 641 and 642.

7.3 G. Study 637. Patient Disposition

415 patients were screened, of which 41 failed the screening or eligibility criteria for entry into the treatment phase (run-in failures), leaving 374 subjects who were randomized into the treatment phase of the study. The table below provides descriptive statistics regarding the disposition of subjects in the ITT Safety population, as provided by the sponsor.

The Number (%) of Randomized Patients who Completed the Study or were Withdrawn by the Reason for Study Withdrawal : ITT Population Treatment Group

	Treatment Group	
	Placebo	Paroxetine
	(N = 185)	(N = 187)
Study Conclusion Reason	**n (%)**	**n (%)**
Completed Study**	163 (88.1)	153 (81.8)
Withdrawal Reason:		
Adverse experience*	2 (1.1)	18 (9.6)
Lack of efficacy	5 (2.7)	0 (0.0)
Deviation from protocol***	5 (2.7)	6 (3.2)
Lost to Follow- up	2 (1.1)	3 (1.6)
Other Reasons+	8 (4.3)	7 (3.7)
Total Withdrawn	22 (11.9)	34 (18.2)

*Includes SAEs.

**Completed all visits up to the end of Week 8.

***Including non-compliance.

+Other Reasons: 7 paroxetine and placebo subjects were unwilling to continue the study. 5 paroxetine and placebo subjects withdrew consent. One paroxetine subject withdrew due to worsening anxiety. One patient (placebo) was withdrawn at the sponsor's request as this patient had been enrolled after the LPE date. A paroxetine subject withdrew due to a positive benzodiazepine test. This patient should be listed as a protocol violator rather than withdrawn due to "other reasons".

7.3 H. Study 637. Baseline Demographics/Severity of Illness

The treatment groups were similar in mean age (45.4±15.0 and 46.5±14.9 years in the placebo and paroxetine groups, respectively), mean weight (approximately 70 kg for each group) and mean height (approximately 166 cm for each group). The percentages of women in the control and paroxetine groups were 66.5% and 74.3%, respectively. The racial and age distributions were similar among the 2 treatment groups in which the majority of subjects were under 65 years old (86% and 84% in the placebo and paroxetine groups respectively) and were Caucasian (98.9% and 100%, respectively).

Medical Comorbidity

The treatment groups were similar in incidence and pattern of distribution for medical comorbidity. 64.7% of the paroxetine subjects and 66.5% of the controls reported medical illness in which the most common illnesses were hypertension (11.8%, 10.3% in each group, respectively), Parkinson's disease (7%, 8.6%), menopausal state (5.9%, 3.8%), and back pain (5.3%, 6.5%).

Psychiatric Comorbidity and Baseline Scores of Efficacy Rating Scales

The treatment groups were comparable in reported psychiatric comorbidity, mean age of onset and years of duration of GAD and in mean baseline scores on the various efficacy rating scales. The mean total HAM-A score was approximately 26 and the mean CGI Severity of Illness score was 4.1 for each group. The mean MADRS score was 12.4 and 12.8 for the placebo and paroxetine groups, respectively. The mean age of onset of GAD was approximately 39 years for each group and the mean duration of GAD was 6.8±7.7 and 7.8±8.5 years in the placebo and paroxetine groups, respectively.

The treatment groups showed a similar proportion of subjects with history of psychiatric comorbidity. A history of Major Depressive Episode was reported in 4.3% and 8.0% in the control and paroxetine groups, respectively, suicidality was reported in 1.6% and 3.2%, respectively. Panic disorder was reported in no controls and 3.2% of the paroxetine group. Less that 1.1% of subjects had other psychiatric disorders such as alcohol dependence/abuse, other anxiety disorders among others.

7.3 I. Study 637. Concomitant Medications

70.6% of paroxetine subjects and 63.8% of controls reported use of concomitant medications during the treatment phase of the study. The commonly reported medications were the analgesic; Paracetamol (13.5 and 9.6% in controls and paroxetine subjects), hormonal agents; ethinylestradiol (7.6 and 9.1%, respectively), levonorgestrel (6.5 and 5.3%, respectively) and dopamine agonists; levodopa (8.6 and 7.0%, respectively) and benserazide HCl (a dopamine carboxylase inhibitor, 7.6% and 5.3%, respectively).

7.3 J. Study 637. Efficacy Results

Study 637. Primary Efficacy Variable: the mean change from baseline to treatment endpoint (least square means±SEM) on the total HAM-A score.

Results provided by the sponsor: The paroxetine group showed a trend for greater improvement than controls for the LOCF ITT dataset on the primary efficacy variable (-12.4±0.8, N=181 in the paroxetine group, -11.3±0.8, N=183 in the placebo group, p=0.171). Analysis of the OC ITT dataset showed greater improvement in the paroxetine group (-14.8±0.8, N=149) than controls (-12.5±0.8, N=163) that reached a level of significance (p<0.01). See Table 7.1.3 C in the appendix showing the mean baseline scores and mean change at weekly intervals during the 8 weeks of treatment for each group.

Analysis of the per protocol population on the primary efficacy variable revealed a mean change (least square means) of –13.9±0.9, N=124 in the paroxetine group and of –11.7±0.8 in the placebo group (p=0.017) for the LOCF dataset. The mean scores (least square means) at baseline were 26.0±0.5 and 25.8±0.5 in the paroxetine and placebo groups respectively. Analysis of the OC dataset revealed a similar results (p<0.01).

The sponsor's statistical results on the primary efficacy variable were confirmed by an analysis of the raw data (provided by the sponsor) conducted by the Biometrics reviewer, Dr. Kallapa Koti.

Study 637. Secondary Efficacy Variables

The results described below are those provided by the sponsor.

Study 637. Results on Various Anxiety Rating Scales:

- **The mean change from baseline to treatment endpoint (least square means±SEM) on the HAM-A Items 1 (Anxiety Item) and 2 (Tension Item) and on the Somatic and Psychic Subscales:** The paroxetine group showed a significantly greater improvement compared to controls on the mean change of the Item 1 score (-1.3±0.1, N=181 in the paroxetine group, -1.1±0.1, N=183 in controls, p=0.011) and a trend for an improvement on the mean change of the Item 2 score (-1.3±0.1, N=181, -1.1±0.1, N=183, respectively, p=0.071) for the LOCF dataset. Analyses of the OC dataset revealed significantly greater improvement in the paroxetine group than that of controls for both Items 1 and 2 scores ($p<0.01$ for each comparison).

No significant group differences were observed for mean change in the Somatic subscale score for the LOCF dataset, with a trend ($p<0.087$) for greater improvement in the paroxetine group compared to controls on this efficacy measure for the OC dataset. The paroxetine group showed a significantly greater ($p<0.01$) mean change (least square mean) in the Psychic Subscale score of –8.0±0.5 (N=149) and the controls showed a mean change of –6.5±0.4 (N=163) for the OC dataset. Similar results were obtained for the LOCF dataset but the p value for comparing the treatment groups was 0.029.

- **The mean change from baseline to treatment endpoint (least square means±SEM) on the COVI Anxiety Scale Score:** The paroxetine group (-3.1±0.3, N=175) showed a trend for greater mean improvement (p=0.059) than controls (-2.6±0.3, N=178) on the mean change of the COVI score for the LOCF dataset. When analyzing the OC dataset the observed treatment group difference (mean change of –3.5±0.3, N=149 in the paroxetine group and –2.9±0.3, N=163 in the placebo group) had a p value of 0.027. The results of the mean baseline score and mean change from baseline scores for treatment weeks 4 and 8 are shown for each group in Table 7.1.4 C in the appendix.
- **The mean change from baseline to treatment endpoint (least square means±SEM) on the HAD Total Score:** The paroxetine group showed a significantly ($p< 0.01$) greater mean improvement (-7.7±0.8, N=180) than controls (-5.5±0.8, N=182) on the HAD Total Score when analyzing the LOCF dataset. Similar results were reported for the OC dataset ($p<0.01$).
- **A post-hoc analysis of results on the mean change on the HAD Anxiety Subscale from baseline to treatment endpoint was analyzed.** This analysis showed significantly ($p<0.01$) greater improvement in the paroxetine group compared to controls (-5.1±0.4, N=180 in the paroxetine group, -3.7±0.4, N=182 in the placebo group). Similar results were found for the OC dataset ($p<0.01$).

Results on Rating Scales for Depressive Symptoms.

- **A post-hoc analysis of results on the mean change on the HAD Depression Subscale from baseline to treatment endpoint was analyzed.** A trend for greater improvement in the paroxetine group (-2.7±0.4, N=179) than in controls (-1.8±0.4, N=182) was observed (p=0.058) for the LOCF dataset. Similar results were observed for the OC dataset, in which the p value was equal to 0.034 (considered significant by the sponsor using an alpha of $p<0.05$).
- **The mean change from baseline to treatment endpoint (Least Square Means±SEM) in the MADRS Score:** The paroxetine group showed a mean improvement of –4.2±0.5 (N=169), while the placebo group showed an improvement of –3.0±0.5 (N=173) for the LOCF dataset. The difference between treatment groups on this variable was reported in the submission as statistically significant with a p value equal to 0.023. When the OC dataset was analyzed, the

paroxetine group showed a significantly ($p<0.001$) greater improvement than controls of this efficacy variable (-5.2±0.5, N=149, -3.5±0.5, N=163, respectively).

Study 637. Results on Scales of Overall Clinical and/or Functional Status.

- **Mean change from baseline to treatment endpoint (least square means±SEM) on the CGI Severity Illness Score:** The paroxetine group showed a trend ($p=0.027$) for a greater mean improvement (–1.5±0.1, N=181), than controls (-1.2±0.1, N=183). This group difference was considered significant by the sponsor. Analysis of the OC dataset revealed a significant treatment group difference (mean change of –1.7±0.1, N=149 in the paroxetine group, -1.3±0.1, N=163 in the placebo group, $p<0.01$).
- **Mean change from baseline to treatment endpoint (least square means±SEM) on the SDS Total, Work, Family and Social Items:** The paroxetine group showed an improvement on the mean SDS Total Score of –5.0±0.8 (N=139) and the controls showed an improvement of –3.2±0.8 (N=139) for the LOCF dataset. These groups are described in the submission as being significantly different on this parameter ($p=0.037$). Group comparisons on the mean change of each of the SDS items generally showed trends for greater improvement in the paroxetine group than in the controls (p values ranged from 0.44 to 0.020).

Study 637. Results on Proportion of Responders Based on the HAM-Total Score and the CGI Global Improvement Item Score.

- **The percentage of responders defined as a HAM-A total score of 10 or under at treatment endpoint.** The paroxetine group had 49.7% responders (N=181), while the control group had 46.4% responders (N=183) at the treatment endpoint when analyzing the LOCF dataset. The groups were not significantly different on this efficacy measure at any weekly time-point throughout treatment. Similar results were observed for the OC dataset. Although, there were trends for more responders in the paroxetine group compared to the controls on several time-points during treatment (57% responders out of the total N=149 in the paroxetine group and 49.7% responders, N=163, in the control group at the treatment endpoint, $p=0.19$). Table 7.3.1 A (in the appendix) shows the percentage of responders in each group, at weekly intervals during treatment.
- **The percentage of responders defined as having a CGI Global Improvement Item score of 1 (very much improved) or 2 (much improved) at treatment endpoint.** The percentage of responders was significantly greater ($p=0.011$) in the paroxetine group (63.0%, N=181) compared to controls (49.7%, N=183) at the treatment endpoint for the LOCF dataset as shown in Table 7.3.1.B. in the appendix. Similar results were revealed with the OC dataset, which are also shown in Table 7.1.3.B.

7.3 K. Study 637. Conclusions

This study which employed almost identical methods as those employed in Study 642, failed to show a significantly greater improvement on the primary efficacy measure, mean change on the HAM-A total score compared to controls when analyzing the LOCF dataset of the ITT Efficacy population. The statistical results described in the submission regarding the primary efficacy variable were confirmed by an analysis of raw data conducted by the Biometrics reviewer, Dr. Kallapa Koti. The LOCF ITT dataset is the dataset from which the sponsor, *a priori*, proposed to make their primary inference. A trend for greater improvement in the paroxetine group was observed with this dataset. The sponsor's analysis of the OC ITT dataset, which was not, *a priori*, the dataset from which the sponsor based their "primary inference", did reveal significantly greater improvement in the paroxetine group compared to controls ($p<0.01$). An analysis conducted by the sponsor of the per protocol dataset also revealed significant effects of

paroxetine compared to placebo treatment on the primary efficacy measure when analyzing either the LOCF or OC dataset.

Measures of overall clinical or functional status as reflected by the CGI Severity of Illness score or the SDS total score showed trends for greater improvement in the paroxetine group compared to controls. The sponsor considered a p value of less than 0.05 significant. However, given the multiple pair-wise comparisons performed on the data, this reviewer is not considering the observed p values of 0.027 and 0.037, as significant. The only significant comparison revealed was when analyzing the OC dataset on the mean change on the CGI Severity Illness Score.

The study also failed to show significant effects of paroxetine treatment, but showed a small trend for an effect on the percentage of responders, based on the HAM-A total score. However, the paroxetine group showed significantly more responders than the control group based on the sponsor's analysis of the CGI Global Improvement Item treatment endpoint score. Scales for assessing depressive symptoms, the MADRS and the HAD Depression Subscale, revealed trends for a paroxetine group effect compared to controls on mean improvement, but the groups were not significantly different.

Overall Study 637 failed to support the sponsor's efficacy claim when considering only the results of the primary efficacy measure for the LOCF dataset of the ITT efficacy population. However, trends for an effect or significant effects were observed for other datasets or for some of the secondary efficacy measures. Failure to show a significant effect on either, the MADRS score or the HAD Depression subscale, is not surprising given that the primary symptoms of the population were anxiety symptoms and that the subjects were patients with GAD. It is not clear why Study 637 failed to convincingly replicate results of Studies 641 and 642. The methods of Study 637 were almost identical to those of Study 642, except that the daily starting dose of paroxetine was 20 mg rather than 10mg. As a consequence to a higher starting dose subjects reaching the higher doses up to a maximum of 50 mg could potentially be maintained on the higher dose levels a week longer than subjects in Study 642. Hence, a longer duration of exposure at higher dose levels would not explain failure to demonstrate a robust and/or significant treatment effect observed in Study 642.

Demographic and baseline characteristics of the ITT population of Study 637 (the European study) show several differences when compared to those of the ITT populations of the other two studies (US/Canadian studies, Studies 641 and 642). The subjects of the European study had a mean age of 45 or 46 years old in the treatment groups with approximately 15% of the subjects being 65 years and older. The mean age of subjects in the US/Canadian studies were approximately 40 years old with only 4 to 9% of subjects being 65 years or older. The mean weight of subjects in the European study was 69 to 70 kg, while in the US/Canadian studies it was 75 to 79 kg. Another observation is that only 2 out of 370 subjects of Study 637 (European study) were not Caucasian while 11 to 20% of subjects in the various treatment groups of the other two studies were non-Caucasian.

Another critical factor to consider is that 7 to 9% of subjects in each treatment group of Study 637 had Parkinson's disease with a similar percentage of subjects receiving dopamine agonists. Therefore, the screening of subjects in the European study (Study 637) did not seem to reflect the methods described in the protocol of the sponsor's submission. The submission indicates that patients with the following clinically findings were to be excluded from the study: "clinically significant abnormalities on … or physical examination at screening which had not resolved prior to the baseline visit", or a "clinically significant condition which in the opinion of

the investigator would have rendered the patient unsuitable for the study...". The inclusion of Parkinson's patients is not only likely to confound measures of anxiety, depression, functional and clinical status, but is also not representative of the patient population with GAD. The inclusion of Parkinson's patients may also account for the higher percentage of subjects 65 and older that were observed in the ITT population of Study 637 in contrast to that observed for ITT populations in Studies 641 and 642. Given the observed differences between the study populations of Study 637 and of Studies 641 and 642, along with the inclusion of patients with Parkinson's disease in the former study, the efficacy results of Study 637 are difficult to interpret.

Overall Conclusion Regarding Studies 641, 642 and 637. The sponsor provides results from Study 641 showing evidence supporting the proposed claim for paroxetine as an indication for treatment of GAD. According to the sponsor's statistical analyses of the LOCF ITT dataset these findings were replicated by a second study (Study 642), although effects observed in the latter study appeared to be less robust, at least on some of the secondary efficacy measures. Study 637 failed to show a significant treatment group effect on the primary efficacy variable when analyzing the LCOF ITT dataset from which the sponsor, *a priori*, was to base their primary inference.

Both studies, 641 and 642, were conducted in the US and Canada and examined ITT populations that appeared to be representative of the GAD population of North America and the US. However, the results of Study 637 are difficult to interpret given the demographic and baseline characteristics of the ITT population which did not appear to be representative of the GAD population in the US. Therefore, the overall conclusion regarding the three studies described in the submission is that the two US/Canadian studies were adequately controlled multi-center studies that provide evidence supporting the sponsor's efficacy claim for treating GAD patients with Paxil®.

8.0 Integrated Safety Information

The sponsor provides safety information for primarily the completed studies (Study 637, 641, and 642) described in the submission. The submission briefly describes an ongoing long-term study being conducted in non-US countries (Study 646). Any deaths and serious adverse events (SAE's) reported to occur during Study 646 were also provided in the submission and are described below.

8.1.1 Deaths

Studies 637, 641, and 642: There were no deaths in the completed studies (Studies 637, 641, 642) during the treatment or taper phases or at 14 days after the last dose. Patients with an adverse event on their Day 14 follow-up visit were required to return for an additional follow-up visit 14 days later (28 days after their last dose). No deaths were reported for the 28 day follow-up period in these patients, as well.

Ongoing Study 646: This long term study involves 8 weeks of single blind treatment of placebo or paroxetine (20-50 mg/day with a flexible dose design) followed by 24 weeks of double blind treatment of either placebo treatment or paroxetine (20-50 mg/day flexible dose regimen) treatment. As of 2/1/00, 663 patients were enrolled and 476 of them have completed the 8 week single-blind treatment phase and were randomized to the 24 week double blind treatment phase.

One death was reported in Study 646. The patient who died (646.107.05093) was a 52 year old female with pulmonary carcinoma with multiple metastases who received 74 days of

blinded medication. The patient died 24 days after last dose. It is unlikely that the cancer and death were drug related.

8.1.2 Serious Adverse Events

Studies 637, 641 and 642: Out of 1264 subjects of the ITT Safety population, 9 paroxetine treated subjects and 7 placebo treated subjects were reported to have nonfatal SAE's. A listing for these subjects, as provided by the sponsor, is included as Table 8.1.1.A. in the appendix. Narratives were provided for these subjects. None of the SAE's were drug-related or unexpected events. The following are noted regarding SAE's among selected individual paroxetine treated subjects.

Description of Selected Individual Paroxetine Subjects:

Subject 637.092.03458 was a 51 year old female who required hospitalization for "gastritis/abdominal pain". The study drug was stopped and a diagnosis of "erosive gastritis" was given, which was believed to be associated with an increase in the dose of the patient's concomitant medication, meloxicam. This change in the dose regimen was reportedly self-initiated by the patient without prior consultation with her physician and/or the study investigator. While the increase in meloxicam may have been related to this AE, a possible paroxetine related or interaction effect cannot be ruled out. Gastritis, abdominal pain, among other gastrointestinal symptoms, are described in the Paxil® product labeling.

Subject 637.052.03711 experienced anxiety as a SAE in which the patient "stopped eating, sleeping and ceased to go out" on Day 39 in the treatment phase of the study. This patient was hospitalized and treated with benzodiazapines. One day later the dose of the study drug was increased from 30 mg to 40 mg p.o. Q.D. The patient reportedly "recovered" from this SAE 8 days later. Given the reported recovery following an increase in the dose of paroxetine, it is unlikely that this SAE was drug related.

Another subject (637.017.03612) was also reported to experience anxiety as a SAE that occurred one day after stopping the study drug for a non-serious AE, "agitated depression". This non-serious AE resulted in the subject withdrawing from the study. The anxiety described as an "acute anxiety reaction" was reportedly associated with a "personal stressor". The patient was referred to a psychiatric consultant. A few days later (3 days after the last dose of study drug) the patient was hospitalized after appearing "depressed" with "very odd fluctuations in mood". The patient was diagnosed as having an "Adjustment Reaction" and recovered after approximately 2 months from the onset of this SAE. Given the patient's underlying psychiatric condition, the presence of an environmental stressor and the diagnosis of "Adjustment Reaction", it is unlikely that this event was drug-related.

Subject (642.225.04217) was a 37 y.o. female with no history of psychotic disorders as reported at baseline, complained of visual hallucinations ("bubbles coming out of walls") after 2 days on the study drug. The study drug was discontinued and 6 days later the patient required hospitalization. The patient also reported to have auditory hallucinations, suicidal ideations and "severe anxiety". She received fluoxetine and risperdal for depressive and psychotic symptoms. Clonazepam was later administered. This SAE was reported to resolve after 14 days following the initial report of hallucinations and after stopping the study drug. While the event was considered drug related, the patient was reported to have later (during her hospitalization) indicated that the intermittent hallucinations, including visual hallucinations began one week prior to starting the study drug. If the onset of the hallucinations was prior to exposure to the study drug, it suggests a pre-existing condition that may have resulted in the onset of the

hallucinations during the study. However, corroborating evidence, which the narrative does not include, would be needed to confirm the patient's latter report, particularly given the patient's inconsistent reports regarding the onset of her symptoms. Hallucinations are included in the labeling for Paxil® as an infrequent event (occurring in 1/100 to 1/1000 patients) reported during the premarketing evaluation of Paxil® but were not reported as "necessarily caused" by the drug.

Subjects 641.120.00972 and 637.031.03396 required hospitalization for chest pain. In the former patient, who was 63 y.o. female on Estroderm®, the episode was associated with dyspnea and blood pressure of 190/100. This SAE resolved in two days and was considered by the investigator to be "probably related to heat". No other information was provided. The other subject with chest pain was a 27 y.o. male with a history of chest pain associated with GAD. The patient was hospitalized and showed a "minimal" ST elevation in the II, III, I and VF leads on EKG. A non-steroidal anti-inflammatory agent was administered and the patient "recovered" six days later. The investigator considered this SAE to be associated with patient's underlying GAD. No other information was provided. It is unlikely that the events were drug related.

Subject 642.150.02452 experienced trauma associated with a car accident (he was hit by another driver), which was unlikely to be drug-related.

Ongoing Study 646: SAE's were reported in a total of 8 out of 663 enrolled subjects. 5 subjects were receiving paroxetine during the initial single blind 8 week treatment phase and 3 subjects were receiving blinded treatment during the double blind 24 week treatment phase. A listing for these subjects are provided in Table 8.1.1.B. in the appendix, which is the table provided in the submission. Note that subject 646.151.04531 was a 39 female who had a grand mal seizure after 30 days of single blind paroxetine treatment and was successfully treated after cessation of paroxetine and administration of anticonvulsant agents. Whether or not this event was potentially drug-related remains unclear. Nevertheless, "convulsions" are listed in the labeling of Paxil® under "Other Events Observed During the Premarketing evaluation of Paxil" as a "rare" event (occurs in less than 1/1000 patients).

Another patient (646.307.05113) with history of gastric ulcer disease experienced gastritis and bronchitis (had a smoking history) after 29 and 37 days, respectively of single-blind paroxetine treatment. Paxil® is associated with abdominal pain and dyspepsia, among other gastrointestinal adverse events, as indicated in the labeling. Gastritis in this patient could have been partly related to paroxetine treatment. However, the patient's history of gastritis is likely to be major factor, such that the event could have occurred independent of drug treatment. A possible interaction effect between a previous history of gastritis or vulnerability to gastrits and drug treatment cannot be ruled out. An overdose with benzodiazapines occurred 2 days after paroxetine treatment in a 32 year old female (646.153.04604) and considered to be drug-related. However, the rationale for why this SAE was considered as drug related was not provided. Given the patients underlying psychiatric condition it is possible that this SAE was not drug-related, but the information provided in the submission is limited.

8.1.3 Dropouts due to Adverse Events in Completed Studies (Studies 637, 641 and 642)

A total of 79 subjects (10.7%) in the paroxetine group and 20 subjects (3.8%) in the placebo group withdrew due to an Adverse Event (AE) after randomization. Narratives were provided for all of these patients. Three subjects with AE's leading to withdrawal experienced AE's that were classified as serious (see above section) of which 2 subjects were in the paroxetine group. The SAE's reported in the paroxetine subjects were hallucinations (subject 642.225.04217) and abdominal pain/gastritis (subject 637.092.03458). Since these events were SAE's they were

previously described in the above section on SAE's. The table below provides the number and percentages of adverse dropouts among the randomized subjects (ITT Population) in each treatment group.

The Number (%) of Randomized Subjects (ITT Population) Withdrawn Due to an AE in Each Treatment Group of Each Study

Study	Placebo Group	Paroxetine Group
641	12 (6.7%)	**20 mg group:** 20 (10.6%) **40 mg group:** 24 (12.2%)
642	6 (3.7%)	17 (10.5%)
637	2 (1.1%)	18 (9.6%)

The following table is a composite of Tables 28 and 29 provided in the submission. The table summarizes AEs leading to withdrawal that occurred in at least 1% of subjects in a given treatment group with a frequency of at least twice that of placebo. AE's leading to withdrawal of two or more subjects, including those occurring in less than 1% of subjects in each treatment group are shown in Table 8.1.2 in the appendix, as provided in the submission. Some discrepancies or "irregularities" were described in the submission regarding the dataset summarized in these tables and are briefly described below (also see the footnotes in the tables). The following reasons for data irregularities were described in the submission: the AE was not provided by the investigator in 1 placebo treated subject and 7 paroxetine treated subjects, the AE was recorded as leading to withdrawal despite prior termination of drug treatment in 3 placebo subjects and 3 paroxetine subjects, and gingivitis was recorded as an AE leading to withdrawal in a paroxetine treated subjected who had already completed the study. The sponsor attempted to resolve data issues by matching the date recorded for the time of withdrawal in a given subject to the time that an AE was reported for that subject. By this method, the sponsor identified AE's presumably associated with the reason for withdrawal in 12 out of the 14 subjects in question. The revised data are summarized in the "Revised Summary" sections of the table below and in the Table 8.1.2 in the appendix, as provided by the sponsor.

Summary of Treatment Phase Emergent Adverse Experiences Leading to Withdrawal (>= 1.0% and Twice Placebo) By Body System and Preferred Term –Studies 637, 641 and 642 (ITT Population)

Body Systems Preferred Terms	**n**	**Placebo N =529 (%)**	**n**	**Paroxetine N =735 (%)**	**n**	**Placebo N =529 (%)**	**n**	**Paroxetine N =735 (%)**
	Revised Summary+				**Data Source Summary++**			
Body as a Whole Asthenia	1	(0.2)	13	(1.8)	1	(0.2)	11	(1.5)
Digestive System Nausea	1	(0.2)	15	(2.0)	1	(0.2)	13	(1.8)
Nervous System								
Dizziness	1	(0.2)	7	(1.0)	1	(0.2)	7	(1.0)
Somnolence	1	(0.2)	15	(2.0)	1	(0.2)	14	(1.9)
Skin and Appendages								
Sweating	1	(0.2)	8	(1.1)	1	(0.2)	7	(1.0)
Urogenital System								
*Abnormal Ejaculation	1	(0.5)	7	(2.5)	1	(0. 5)	6	(2. 1)

+ Includes AEs from patients identified as having a data issue (as described in the submission and in the text above), ++ For one placebo patient and 7 paroxetine patients, AE leading to withdrawal not identified; for 3 placebo and 3 paroxetine patients AE leading to withdrawal was reported to occur after stopping study medication. (See above text) *% corrected for gender. ** One patient, gingivitis lead to temporary stoppage

8.1.4 Specific Search Strategies

Taper Phase Emergent AE's: The table below summarizes results on AE's occurring during the Taper Phase of the combined studies (Studies 637, 641 and 642). A total of 327 placebo treated subjects and 444 paroxetine treated subjects among the three completed studies entered the Taper Phase. None of the AE's shown in the table occurred with an incidence of ≥5%. These numbers do not include subjects receiving the lowest daily dose of paroxetine (20 mg/day) during the treatment phase of the flexible dose studies, as they did not undergo a taper phase according to the protocol. However, subjects in the fixed dose study (Study 641) that were in the 20 mg/day paroxetine group were continued on paroxetine (20 mg/day) during the taper phase for a period of two weeks. Other subjects not included in the above totals had withdrawn from the study because of the following reasons: lack of efficacy, AE including intercurrent illness, deviation from the protocol, including non-compliance, lost to follow-up or other reasons (see previous sections regarding disposition of subjects).

A Summary of Results (Incidence) on Taper Phase Emergent Adverse Events[+]

	Paroxetine N=444	**Placebo N=327**
Adverse Event (AE):	**%**	**%**
Gender Non-Specific	27.9	14.7
AE's occurring in Paroxetine subjects with at least twice the rate of Placebo subjects:		
Dizziness	2.7	0.6
Abnormal Dreams	2.0	0
Anxiety	2.0	0.3
Diarrhea	2.0	0.6
Respiratory disorder	2.0	0.9
AE's occurring in at least 1% of subjects in a treatment group:		
Headache	3.6	2.1
Insomnia	1.6	1.2
Nervousness	1.6	0.9
Somnolence	1.1	0.9
Infection	1.1	0.3
Trauma	1.1	0.6
Nausea	1.1	0.6
Gender Specific* in Females	1.1	1.0
Gender Specific in Males	0.6	0.8

[+] Results are from Table 31 of the Integrated Summary of Safety of the submission.
*Gender Specific AE's included abnormal ejaculation in men and dysmenorrhea in women in the paroxetine groups.

Most of the Taper Phase (TP) AE's were considered to be mild or moderate in intensity. AE's considered as severe in intensity were reported in 2.7% of the paroxetine group (12 out of 444 subjects) and 1.5% of the placebo group (5 out 327 subjects) among subjects that entered the

Taper Phase. These subjects were fairly evenly distributed among the specific "Preferred Term" categories (less than 1% of subjects per treatment group for a given specific category).

Follow-up Phase Emergent AE's. Dizziness was reported in 6.2% of paroxetine subjects and 1.3% of placebo subjects. No other AE's occurred at a rate of >5% and ≥ 2 times placebo. The overall incidence of gender non-specific AE's in paroxetine and placebo subjects was 25.5% and 14.4%, respectively.

Most of the reported AE's during the follow-up phase of the studies were mild to moderate in intensity with less than 1% of subjects per group having an AE, within a given specific "Preferred Term" category, that was considered severe in intensity.
466 placebo treated subjects and 627 paroxetine treated patients underwent at least one follow-up visit out of the 529 controls and 735 paroxetine treated patients, respectively, that had entered the treatment phase of the study in which they participated. A follow-up visit was required of all subjects on Day 14 following completion of the Taper Phase of the study or following the last dose of treatment (in the case of early withdrawal is subjects completing at least 2 weeks of study medication). If a given subject had an AE on this visit, an additional visit was required 14 days later in Studies 641 and 642 or 28 days later in Study 637.

Serious AE's On Day 56 or Later in the Study.
The Integrated Safety Summary provided by the sponsor does not explicitly distinguish SAE's occurring during the taper phase or after cessation of drug, from SAE's occurring during the treatment phase of the study. However, the sponsor provides the "Days of Study at Event Onset". Since the treatment phase of the study was for 8 weeks, which is 56 days, then this section summarizes SAE's reported to occur on or after Day 56 of the study for the three completed studies, combined. These SAE's are also discussed in the above section on SAE's of this review. Only 4 paroxetine treated subjects were reported to have SAE's on Day 56 or later in the study and 5 paroxetine treated subjects had SAE's between Study Days 3 and 39. The reported SAE's occurring on Day 56 or later were as follows (the number of "Days on Study at Event Onset" and "Total Days on Dbl-Blind Study Drug", respectively, are indicated in the parentheses below, as provided by the sponsor which is shown as Table 8.1.1.A. in the appendix):

- Chest pain in two subjects (68 days in the Study, 62 days on study drug in one subject, 61 days, 60 days, respectively in the other subject)
- Trauma-car accident in 1 subject (69 days, 56 days)
- Pneumonia in one subject (83 days, 56 days)

These events are not unexpected or were not likely to be drug related and are described in the labeling for Paxil®.

8.1.5 Adverse Events
At least one treatment phase emergent adverse event (TP AE's) was reported by 588 of 735 subjects (80%) receiving paroxetine 588 (80%) and in 335 (63%) of 529 subjects receiving placebo. The following table enumerates spontaneously reported TP AE's by subjects in the three completed studies (Studies 637, 641 and 642, combined), similar to that provided in the submission, but only includes commonly reported AE's (occurring in at least 5% of paroxetine subjects) with an incidence of at least twice that of placebo subjects.

Treatment Phase Emergent Adverse Experiences Occurring in 5% (rounded off) or More of the Paroxetine Group and Twice that of Placebo subjects– Studies 637, 641 and 642 (ITT Population)				
Body System Preferred Term	**Placebo N = 529**		**Paroxetine N = 735**	
	n	(%)	n	(%)
Body As a Whole				
Asthenia	34	(6.4)	105	(14.3)
Infection	18	(3.4)	41	(5.6)
Digestive System				
Constipation	9	(1. 7)	77	(10. 5)
Decreased Appetite	6	(1. 1)	38	(5. 2)
Dry Mouth	25	(4.7)	80	(10.9)
Nausea	28	(5.3)	148	(20.1)
Nervous System				
Libido Decreased	8	(1.5)	69	(9.4)
Somnolence	24	(4.5)	113	(15.4)
Tremor	4	(0.8)	34	(4.6)
Skin and Appendages				
Sweating	8	(1.5)	46	(6.3)
Urogenital				
*Abnormal Ejaculation	4	(2. 0)	70	(24. 7)

* Percentage corrected for gender

When only considering the US/Canadian studies (Studies 641 and 642) the following additional TP AE's met criteria for being considered as "commonly occurring": female genital disorders (incidence of 6.4% and 1.0%, in paroxetine and placebo groups, respectively) and yawning (incidence of 5.5% and 0.3%, respectively). In contrast to these studies, the European study (637) had no additional TP AE's that were reported at a rate meeting the "commonly occurring" AE criteria. However, the sample size of this study was smaller than that of the two US/Canadian studies, combined.

Visual inspection of Table 8.1.3 in the appendix (the enumeration of TP AE's in US/Canadian or European study populations, as provided by the sponsor) reveals that the percentage of TP AE's among treatment groups of the European study were generally less than that observed in the North American study. The placebo groups compared to the paroxetine groups of the European versus the combined US/Canadian study populations generally show a similar pattern of TP AE's. Therefore, the sponsor indicates that "the attributable risk which takes into account incidences of an event in the paroxetine groups relative to that of placebo group supports that most of the common AE's are similar in the North American and European studies". However, the magnitude of the difference in the incidence of each TP AE between the placebo and paroxetine groups, generally appears to be greater in the Northern American population compared to that observed in the European study population (based on visual inspection of Table 8.1.3, as provided by the sponsor).

A coding error is noted in the submission for one of the reported AE's in Study 642 regarding a female patient with history of anorgasmia, reported anorgasmia on day 9 of

paroxetine treatment. Because this AE was incorrectly coded as a male AE and the ADECS dictionary term "produced the preferred term of abnormal ejaculation". Hence, this event was not included in the summary tables provided by the sponsor and in this review.

Dose Dependent Relationship of Treatment Emergent Adverse Events. The table below shows the incidences of AE's that appeared to show a dose-dependent relationship between the 20 mg and 40 mg paroxetine groups in the fixed dose parallel group study (Study 641). These AE's were among AE's provided in Table 33 for Study 641 in the submission, with an incidence of at least 5% in paroxetine groups and of at least twice that of controls.

Incidence of Selected Adverse Events Occurring in at Least 5% of Paroxetine Subjects in Study 641

Adverse Event	Placebo Group	20 mg Paroxetine Group	40 mg Paroxetine Group
Asthenia	3.9	10.6	19.3
Constipation	3.3	8.5	14.2
Abnormal Ejaculation	2.5	17.4	36.0

Data Source: Table 33, page 000096 in the safety results section for Study 641 in the submission.

Similar results were revealed when examining incidences AE's considered to be severe that also occurred in at least 5% of either the paroxetine groups and with an incidence of at least twice that of placebo. The severe AE's that appeared to be dose dependent were asthenia (0%, 1.1%, and 2.5% in the placebo, 20 and 40 mg paroxetine groups, respectively) and constipation (0%, 0.5%, and 1.5% for each respective group).

The number of SAE's in the fixed dose study (Study 641) was insufficient to compare the low and high dose groups on the incidence of SAE's. The table below (derived from Table 42 in the safety results section for Study 641 of the submission) shows the incidence of those AE's associated with treatment cessation that at least revealed a trend for greater incidences in the high dose compared to the low dose groups. None of these AE's were common (occurred in ≥5% of a given paroxetine group).

Adverse Experiences Which Lead to Withdrawal in at Least Two Patients in Any Treatment Group and Showed at Least a Trend for a Greater Incidence in the High Dose Paroxetine Group compared to the Low Dose Paroxetine Group (see above text)

Adverse Experience+ by Preferred Term	Placebo N = 180		Paroxetine 20 mg N = 189		Paroxetine 40 mg N = 197	
	n	(%)	n	(%)	n	(%)
Asthenia	0	(0.0)	1	(0.5)	5	(2.5)
Insomnia	1	(0.6)	1	(0.5)	3	(1.5)
Amnesia	0	(0. 0)	0	(0. 0)	2	(1. 0)

+ "For three patients in the 20 mg paroxetine regimen and three in the 40 mg regimen, the AE leading to withdrawal was not identified. In addition, for one placebo patient and two paroxetine patients in the 20 mg regimen, the investigators reported that the AE leading to withdrawal occurred 1- 3 days after stopping medication. AE information from these nine patients is not included in Table 42 or Data Source Table 13.3.4, Section 13 (see Section 3.14 for details)."

Data source: "Tables 13.3.4 and 13.3.4x, Section 13; Listing D. 5 in Appendix D"

Gender, Age-group and Racial-group Analysis of AE's. An analysis of results on the incidence of AE's of the combined three studies by gender revealed results similar to that described in the product labeling. Interpretation of AE results analyzed by age-group or race is difficult, since the size of the subgroups were small and insufficient for an adequate analyses. The sample sizes of the placebo and paroxetine subgroups of subjects over 65 years old were 36 and 47 subjects, respectively. The number of non-Caucasian subjects was also small for each treatment group (N=65 and N=80 in the placebo and paroxetine groups, respectively.
AE's During Post-Marketing. A total of 5 SAE's and 24 non-serious AE's were described in the submission. No unlabeled SAE's were reported.

8.1.6 Laboratory Findings
8.1.6.1 Analysis of Central Tendency
The mean changes in various laboratory parameters were not clinically significant in magnitude. Upon visual inspection of Tables 8.1.5 and 8.1.6 in the appendix, as provided by the sponsor, the treatment groups showed similar mean changes in the various parameters. A list of the laboratory tests and the schedule of assessments that were performed may be found in Table 7.1.2 in the appendix. Tables 8.1.4 A in the appendix also provides a list of assessments, as well as the criteria for meeting "Potential Clinical Concern".

Tables 8.1.5 and 8.1.6 in the appendix summarize results on the mean laboratory values at baseline and the mean change from baseline to endpoint for the 3 completed studies (combined), as provided by the sponsor. The results summarized in these tables show that the paroxetine and placebo groups were similar in mean changes in the various laboratory parameters. The range of these mean changes was 0 to ± a few units and remained within the normal reference range for each parameter. However, the variance or standard deviations for the mean changes are generally several-fold to 10 fold larger in magnitude than the value for the mean change for each respective parameter.

The sponsor provides the following observations regarding the mean change in laboratory values when expressed as a percentage (the mean change at endpoint/mean baseline value x 100%). The percent change observed in each treatment group for each of the following blood chemistry values is less than 5%: BUN, Creatinine, potassium and sodium levels. The paroxetine and placebo groups showed 16 and 14% changes, respectively, in total bilirubin levels. The percent change in the liver function tests, alkaline phosphatase, AST and ALT ranged from 5 to 10% in the paroxetine group and from 0.4 to 1.6% in the placebo group.

8.1.6.2 Analysis of Outliers

Tables 8.1.4 A and B in the appendix provides the "potential clinical concern" (PCC) criteria for each laboratory measure monitored. The following table summarizes the number of subjects meeting criteria for PCC, as provided by the sponsor. With the exception of eosinophilia, the incidence of all other laboratory values meeting PCC criteria within each treatment group was less than 1%.

Clinical Laboratory Values Meeting Sponsor- Defined Potential Clinical Concern Criteria - Studies 637, 641 and 642 (ITT Population)						
			Placebo		Paroxetine	
			N = 529		N = 735	
Parameters	**Lab Units**		**n**	**(%)**	**n**	**(%)**
Aspartate Aminotransferase	IU/ L	H	0	(0.0)	2	(0.3)
Blood Urea Nitrogen	MMOL/ L	H	4	(0.8)	6	(0.8)
Creatinine	UMOL/ L	H	0	(0.0)	3	(0.4)
Potassium	MMOL/ L	H	0	(0.0)	2	(0.3)
Thyroid Stimulating	MU/ L	H	1	(0.2)	0	(0.0)
Hormone						
Total Bilirubin	MMOL/ L	H	1	(0. 2)	6	(0. 8)
Eosinophils	10^ 9/ L	H	5	(0.9)	14	(1.9)
Hematocrit	%	L	2	(0.4)	5	(0.7)
Hemoglobin	G/ L	L	1	(0.2)	1	(0.1)
Monocytes	10^ 9/ L	H	2	(0.4)	3	(0.4)
Platelets	10^ 9/ L	L	2	(0.4)	0	(0.0)
White Blood Cell Count	10^ 9/ L	L	0	(0.0)	2	(0.3)

Hematological results: There were no reported cases of agranulocytosis, but there were 2 reported cases of leukopenia in the paroxetine group. These two cases (subjects 637.099.03820, 641.115.00708) of leukopenia involved older patients (58 and 74 years old, respectively) with pre-existing disorders (Parkinson's disease and history of breast cancer, respectively) in which abnormally low white blood cell counts were found on the week 8 visit which met PCC criteria. These abnormal WBC values could have been associated with non drug related, pre-existing conditions/disorders given the subjects' medical histories and various abnormal values on other laboratory parameters observed at baseline, as described below.

Description of the Aforementioned Paroxetine Subjects (637.099.03820, 641.115.00708):

In the 58 y.o. subject with Parkinson's disease (subject 637.099.03820) the abnormal baseline laboratory value was a low TSH of 0.1 mU/l (normal reference range: 4.0-5.5mU/l). This subject's white blood cell count (WBC) dropped from 6.3 $x10^{9th}$ cells/l at baseline to 2.2$x10^{9th}$ cells/l after 54 treatment days (week 8 visit). At 54 days of treatment eosinophil and monocyte levels (17% and 15%, respectively) were high but reported to be within the normal range at baseline. These abnormal laboratory values met PCC criteria but were not reported to be associated with any AE's. The abnormal WBC and low neutrophils of 0.38 (normal range=1.8-8GI/L) reported on week 8 were considered "NCS" by the investigator. Given that the patient had Parkinson's disease and a low TSH level (not clear if evaluated and receiving thyroid hormone replacement therapy), the reason for the including this patient in the study remains unclear. Furthermore, it is not clear what the follow-up was for the abnormal laboratory results. A 14-day follow-up of labs was reportedly not conducted and marked on the CRF as "not required".

The 74 y.o. year old subject (subject 641.115.00708) with a history of breast cancer had low free T3 levels and thrombocytopenia (at screening platelet count was 96 $x10^{9th}$ cells/l with normal: 130-400 $x10^{9th}$ cells/l). Her low white cell blood cell count at both screening and on study visit week 8 were 3.0 $x10^{9th}$ cells/l and 2.0 $x10^{9th}$ cells/l, respectively which each met PCC criteria. According to the narratives of this subject, no AE's associated with low white cell counts were reported. A pre-existing low white count suggests that the low white cell count on

week 8 was not likely to be drug-related. In response to an inquiry made by this reviewer (a fax dated 8/7/0), the sponsor reported (in a fax dated 8/31/00) that the patients' physician considered her medical condition as "stable" and was "thought to have recovered well from her malignancy". Her blood dyscrasia was also reported as "stable" and that "no action was to be taken by the physician". The sponsor indicated that on 8/28/00 the patient was considered to be "stable and well" and was "taking Paxil® for her anxiety". A "follow-up bone marrow study" was also reported to be scheduled "in about two months". The patients abnormal laboratory values were not likely to be drug-related, given her pre-existing abnormal laboratory values and her continued treatment on Paxil® while remaining "stable and well".

There were no SAE's or adverse dropouts associated with white blood cell count or differential values meeting PCC criteria among paroxetine subjects, except for one subject. This one exception was an adverse dropout reported in subject 641.118.00851 who had a slightly elevated eosinophil at baseline (9% compared to 0-7% range for within normal limits) and on Day 56 of 13%, of which the latter met PCC criteria. This subject also had a mildly elevated alkaline phosphatase level on Day 56 (132.0IU/l). These abnormal laboratory values were "not of clinical concern" by the investigator and required no further laboratory evaluation, according to a fax from the sponsor (date 8/31/00) responding to this reviewers inquiries (a fax dated 8/7/00). The reported adverse events that led to cessation of paroxetine treatment on Day 11 were ataxia, dizziness, dyspepsia, palpitation and somnolence. This subject was a 63 y.o. Indian male with history of multiple fractures and removal of right patella . He had a current history of hyperlipidemia and hypertension for which he was receiving Lipitor and Zestril, respectively. The events resolved within at least 13 days and may have been drug-related. There was no indication of the duration of the abnormal laboratory values. These events are not unexpected and are included in the current labeling for Paxil®.

There were a total of 5 paroxetine treated subjects and 2 placebo treated subjects meeting PCC criteria on values for HgB and/or HCT. The paroxetine treated subjects had either low normal or abnormally low HgB and/or HCT levels at baseline or at screening and several subjects had pre-existing conditions that could potentially account for their anemia.

There were no reported serious adverse events or adverse dropouts among paroxetine patients due to HgB and/or HCT levels meeting PCC criteria, except for one subject. The one exception was subject 637.012.03615 who was a 57 y.o. white female with current history or menorrhagia and a low normal HCT level at baseline (35.2% with 35-46% within normal limits). The HCT decreased to 31.6% on Day 7. The study drug was stopped on Day 4 because of mild nausea, severe tinnitus and moderate tremor, which resolved with 4-8 days. These events may have been drug-related, but they are not unexpected and are described in various sections in the labeling for Paxil®. However, the anemia may be attributed to a pre-existing mild anemia associated with menorrhagia. Therefore, it is not likely that the low HCT levels were drug-related.

The reported percentage of paroxetine and placebo treated subjects having an AE "related to the hematological assessments" was 1.4% (10 subjects) and 1.1% (6 subjects) in each treatment group, respectively. These AE's included anemia, leukocytosis, leukopenia, lymphadenopathy, monocytosis, purpura, increase bleeding time, thrombocytopenia which occurred in 0 to 1 subjects in each treatment group with the exceptions of purpura (1 placebo and 2 paroxetine treated subjects) and anemia (1 placebo and 3 paroxetine subjects).

The sponsor provided laboratory transition tables. These summary tables provide results on the number of subjects showing a change (decrease or increase) or no change from baseline to

week 8 or study endpoint for each laboratory parameter. This enumeration is provided for each time-point during the study in which laboratory parameters for a given time-point are categorized as low, intermediate, or high relative to the normal reference range.

Based on visual inspection of the sponsor's transition tables, the Paroxetine and Placebo treatment groups showed similar percentages of subjects (ranging from 2 to 3%) transitioning from a higher category (high or intermediate level) to a lower category (intermediate or low) on various hematological parameters (HgB, HCT, RBC and WBC). The denominators for these percentages were the total number of subjects with transition results provided in each treatment group. Hence, these results show that treatment groups were similar in the frequency of subjects that showed a decrease (based on categorical data) in hematological parameters during treatment. Similar results were obtained for platelet counts in each treatment group in which 0.6% or less subjects decreased from baseline to week 8 or study endpoint. An increase in eosinophils (cells/l) was observed in 1.5% and 1.9% of placebo subjects at weeks 8 and study endpoint and in 2.5% and 2.0%, respectively of paroxetine subjects. One of these placebo subjects met PCC criteria, while 4 paroxetine subjects met PCC criteria. The maximum level of eosinophils among these 4 paroxetine subjects was 13% in subject 641.118.0085 who is described above.

Renal Function and Electrolyte Parameters: Potassium was the only electrolyte found to meet PCC criteria, which occurred in only 1 paroxetine subject (641.146.02209) in which the level increased from baseline to Day 59 by approximately 2-fold. Another paroxetine subject (637.062.03804) also had markedly elevated potassium, Cr and mildly elevated BUN. However, the sample from this subject was hemolyzed, according to the sponsor as indicated in a fax dated 8/31/00. A total of 6 Paroxetine treated subjects and 4 placebo treated subjects met PCC criteria for BUN and/or creatinine (these numbers include the paroxetine subject with the non-hemolyzed sample showing an elevated potassium level). The BUN levels in 2 of the 4 placebo treated subjects showed an increase from baseline to Week 8, upon visual inspection of the data, while Cr levels failed to show in any increase in any of these 4 subjects. These subjects failed to show BUN levels exceeding 12.5 umol/l, while 3 paroxetine treated subjects meeting PCC criteria showed marked elevations in either BUN or Cr (approximately a 3 to 4 fold increase from baseline). These paroxetine subjects are described in a separate subsection, below.

As determined from the transition laboratory tables (Table 7.6 in the submission), the paroxetine and placebo groups showed similar percentages of subjects (less that 1%) with an increase in Cr or potassium levels from baseline to week 8 or study endpoint. The percentages of subjects with an increase in BUN levels in the paroxetine and placebo groups were 2.4% and 1.6%, respectively, at week 8 and 2.5% and 1.7%, respectively, at study endpoint. Only 1 of these placebo subjects met high PCC criteria, while 4 of the paroxetine subjects met high PCC values, as indicated in the laboratory transition tables. **There were no SAE's or adverse dropouts associated with renal function and/or electrolyte parameters meeting PCC criteria.**

Description of Individual Paroxetine Subjects:

Subject 641.133.01610 was a 40 y.o. Hispanic male with history of enlarged prostate who also exhibited marked elevation of Cr levels from 88.4 umol/l (within normal limits) at baseline to 353.6 umol/l on Day 56 of treatment. The investigator reported the elevated Cr as an AE and the patient was described as having "completed the study as planned". The narrative did not provide any other pertinent information. It is not clear why this subject was included in the study given the abnormal baseline Cr level. Although, in response to an inquiry from this reviewer, the

sponsor reported (in a fax dated 8/31/00) that the creatinine level had normalized on a follow-up evaluation on Day 70. The investigator reported the mild elevation in ALT (noted above) "as not being clinically significant."

Subject 641.132.01559 is a 30 y.o white female which showed a marked increase in Cr and BUN from baseline levels (88.4 umol/l and 3.6 mmol/l, respectively which are within normal limits) to levels of 265.2 umol/l and 14.3 mmol/l, respectively on Day 60 of treatment. The potassium level of this patient was also increased from baseline (within normal limits: 3.5-5.3 mmol/l) to Day 60 of treatment (6.0 mmol/l). The narrative indicates that baseline WBC was elevated at $13x10^{9th}$ cells/l (3.8-10.8 within normal limits) and the subject had a history of bronchitis and was being treated with Biaxin for a "throat infection". Other concomitant medications included Percocet, Relafen, triple lesitan and Keflex (for carbuncles). The patient also has a history of gastritis, laparoscopy (exploratory), benign breast cyst and migraine. No other pertinent information was provided and the patient was reported to have completed the study as planned. However, in a fax dated 8/31/00 the sponsor indicated that all laboratory parameters that had been abnormal on Day 60, as described above, were within normal range on follow-up Day 63.

4 other paroxetine treated subjects (642.227.04466, 641.110.0045, 637.099.03861 and 126.01258) also showed an increase in their BUN levels from baseline (which were within normal limits ranging from 5.0 to 7.1 mmol/l) to a mildly elevated level (ranging from 11.1 to 11.8 mmol/l) after 42 to 59 days of treatment. These subjects are briefly described, as follows. The one subject completing only 42 days of treatment withdrew from the study because of a "lack of efficacy" and had no reported AE's. This subject was a 44 y.o. who also had mild anemia and a WBC of $3.0x10^{9th}$ cells/l on Day 42 of treatment. One of the other subjects who showed a 2-fold increase in BUN levels (5.0 mmol/l at baseline to 11.8 mmol/l on Day 67) was a 28 y.o. healthy female on Advil for headaches with an unremarkable medical history. The third subject was a 73 y.o with no concomitant medications and no reported AE's. The final subject was a 53 y.o. with history of skin cancer and sinus infection who had a slightly elevated AST level at screening that did not meet PCC criteria.

Subject 641.146.02209 was a 22 y.o. Asian female with no reported AE's. This subject showed a marked increase in potassium from baseline (4.0 mmol/l) to Day 59 of treatment (8.0 mmol/l). The narrative does not provide any other pertinent information and does not indicate if any AE's were associated with this laboratory finding or provide any follow-up status. In response to an inquiry about this subject, the sponsor reported (in a fax dated 8/31/00) that a follow-up laboratory evaluation conducted on Day 63 (14 days after treatment cessation) revealed a potassium level within normal limits (4.2 mmol/l). The sponsor also reports that the narrative indicates that "no adverse experiences were associated with these findings". There was no indication from the 8/31/00 fax from the sponsor that the Day 59 blood sample was hemolyzed.

Because of the above abnormalities regarding renal function, this reviewer examined reviews of previous supplemental NDA's and the initial NDA regarding any reports of renal impairment. However, this examination of previous clinical reviews failed to yield any remarkable findings that would merit changing the labeling of the Paxil®, regarding renal function, from that which already exists. Furthermore, a search was conducted on the AERS database on Paxil® for "renal failure", "renal impairment", and "hyperkalemia". This search revealed 27 cases since the time that the drug was approved for treatment of depression

(12/29/92). These results fail to provide any remarkable findings that would require a change in the labeling for Paxil®.

Liver function tests: 8 paroxetine treated subjects and 1 placebo treated subject met PCC criteria for at least one liver function parameter. 4 of subjects (subjects: 637.055.03668, 637.099.03849, 641.131.01517, 641.121.01002) from the paroxetine groups meeting PCC criteria for high bilirubin levels on Day 42 to 56 of treatment onset also had abnormal bilirubin levels at baseline, several of which met PCC criteria at baseline. It is not clear why these subjects were in the study, other than that the investigator(s) noted on the CRF's "that no clinically significant laboratory abnormalities were detected which would necessarily preclude the patient's entry into the study" (per fax from sponsor dated 8/31/00). In several subjects their bilirubin decreased during the treatment phase, although the levels met PCC criteria. Subject 641.131.0157 showed a bilirubin level within normal limits on a follow-up visit on Day 73 (per fax from sponsor dated 8/31/00). The bilirubin level of subject 641.121.01002 which increased to 51.3 umol/l at study endpoint was "comparable to the level at screening visit" and not considered to be clinically significant or to require further evaluations, as reported by the sponsor (fax dated 8/31/00). Two subjects (641.131.01503, 641.131.0150) receiving paroxetine showed a markedly elevated ASP on Day 21 or AST level on Day 56 of the treatment phase, respectively. However, the former subject reportedly consumed "a lot of alcohol" on the previous night according to the CRF, while the latter subject had a history of elevations in AST levels. Therefore, the observed liver function tests meeting PCC criteria among these 6 subjects are not likely to be drug-related but rather due to pre-existing conditions/disorders.

Two subjects (637.058.03692 and 637.058.03720) had elevated bilirubin levels (35 umol/l with 0-22 umol/l within normal limits) meeting PCC criteria on Days 10 and 58, respectively, after treatment onset of paroxetine. It is not certain if the bilirubinemia in these subjects were drug-related, since baseline levels were within normal limits (20 and 10 umol/l, respectively) and pre-existing conditions that could account for these abnormal laboratory parameters were not described in the narratives. These two subjects are described below. Subject 637.058.03692 had an AE leading to cessation of the study drug on Day 3 of the treatment phase in which the subject had experienced an "allergic reaction" for 2 days which was treated with Zyrtec®. The abnormal bilirubin level meeting PCC criteria was observed on Day 10 (7 days later) along with slightly elevated AST and ALT levels that did not meet PCC criteria. It is not clear if whether these abnormal laboratory values were associated with the allergic reaction experienced by the patient or some other potentially drug-related event. No pertinent details could be found in the narrative or the CRF of this subject. However, the patient is reported to have refused a follow-up evaluation (per sponsor in a fax dated 8/31/00)

The other above mentioned subject (637.058.03720) with the abnormal bilirubin level on Day 58, is a 42 y.o. WM with a current medical history that includes back pain and a past history of herniated disc who experienced "moderate back pain" on Day 54 of paroxetine treatment (4 days before his blood chemistries were drawn). The back pain was described as "acute lumbago" per a fax from the sponsor dated 8/31/00. The back pain lasted 3 days and was treated with myolastan® (a benzodiazapine) and voltarene® (an NSAID). According to a fax from the sponsor (dated 8/31/00), "follow-up laboratory studies were not required" according to the investigator.

There were two adverse dropouts and no SAE's reported in subjects with liver function tests meeting PCC criteria. One adverse drop out (subject 641.058.03692) had abnormal liver function test values and an AE "allergic reaction" that was reported to be the

reason for cessation of the study drug and is described above. The other adverse dropout (subject 641.131.01503) was reported to be due to impotence after 10 days of treatment, which continued for a period of 9 days. This subject also had elevated liver function tests revealed on Day 21 of treatment that was likely alcohol related, as described above. If the patient was consuming alcohol, impotence may also have not been drug-related. According to the submission there were 4 (0.5%) paroxetine patients and no placebo patients with AE's associated with abnormal laboratory values on liver function tests (elevations in bilirubin, SGOT, and/or SGPT among paroxetine patients.

Based on results from the transition laboratory tables 0.5% of placebo subjects and 2.1% of paroxetine subjects showed an increase in ALT levels at week 8 and 2.4% and 4.8% of placebo and paroxetine subjects, respectively, showed an increase in AST levels. Similar results were observed at study endpoint for these parameters. However, treatment groups were similar in the percentage of subjects with an increase in Alkaline phosphatase levels (approximately 0.5% of paroxetine subjects) and total bilirubin levels (approximately 1% in paroxetine subjects) at week 8 and study endpoint. Three of the paroxetine subjects and one placebo subject described in this paragraph met PCC criteria. Paxil® labeling includes "infrequent" increases in various liver enzyme levels, and "rare" increases in bilirubin levels based on results of the premarketing assessment of the drug.

8.1.7 Vital Signs

8.1.7.1 Analysis of Central Tendency

Table 8.1.7.A.(in the appendix) shows results on the mean baseline and mean change from baseline to endpoint on vital sign variables and weight for the paroxetine and placebo groups for the three studies combined. Treatment groups were similar in the mean change from baseline to endpoint on each vital sign parameter and on weight. The magnitude in the observed mean changes per treatment group was less than 2 units for each vital sign parameter. These mean changes were within the normal range and were not clinically significant. The mean changes in weight in the paroxetine and placebo groups (–0.1±2.3 kg and 0.2±1.9 kg, respectively) are not clinically significant.

8.1.7.2 Analysis of Outliers

Criteria for PCC for vital signs and weight changes are provided in Table 8.1.4.B. in the appendix. A summary table enumerating outliers based on PCC criteria is provided in Table 8.1.7.B. in the appendix. As shown in this table the percentage of outliers in each treatment group was no greater than 1% for each category except for weight in which the paroxetine group showed an incidence of 1.5% outliers in the high category and 1.7% in the low category. In the placebo group 1% of subjects were in each of the high and low categories for weight. There were no clinically significant group differences in the percentage of outliers.

There were 4 adverse dropouts and one SAE among subjects meeting PCC for vital signs and weight changes and are described in this section. One adverse dropout was on subject 637.018.03330 who met the criterion for low systolic blood pressure (89 mmHg after Day 7 from the start date of the study drug, with baseline sysBP of 100 mmHg). This 75 year old male had current history of diabetes mellitus, congestive heart disease among other illnesses, who developed "severe vomiting" on Day 1 of treatment which lasted 4 days resulting in withdrawal from the study. It is not clear if the low blood pressure was associated with dehydration, an exacerbation of the patient's underlying congestive heart disease or some other cause. The sponsor indicated (in a fax dated 8/31/00) that the heart rate obtained at the time the blood pressure was 89/65 mmHg (on Day 7 or 4 days after the vomiting ceased and while off

treatment), was unchanged from that observed at screening. The sponsor also indicated that the laboratory parameters at screening and at withdrawal were "all ok".

The adverse dropout that was also considered a SAE was a subject 641.150.02452 who was involved in a motor vehicle accident (hit by another driver) who also met PCC criterion for a decrease in weight. These events were not likely to be drug-related. The two other adverse dropouts were subjects (641.140.1959and 641.107.00314) meeting PCC criteria for decreased weight who experienced asthenia and tremor, respectively as adverse events resulting in their withdrawal from the study. The final adverse dropout occurred in subject 641.146.02207 who met PCC criteria for high systolic blood pressure, withdrew from the study because of gingivitis. These adverse events are included in the Paxil® labeling.

The percentages of post randomization AE's associated with hypertension, hypotension or syncope were no more than 0.5% in each treatment group. However, one cardiovascular event, vasodilatation was reported in paroxetine subjects at a rate of over twice that of controls (incidence of 2.7% compared to 0.8%). The percentages of AE's associated with arrhythmia, bradycardia, palpitations or tachycardia were no more than 1.1% in each treatment group. The incidences of weight gain or loss reported as AE's did not exceed 0.6% in each treatment group.

9.0 Labeling Review

The major proposed labeling changes regarding efficacy for Paxil® (tablets and oral suspension) include the following:

- An additional pharmacodynamic property of Paxil® is an "anxiolytic action" as follows (the proposed additions are indicated by underlined text):

- Under the "Clinical Trials" section of the proposed labeling the sponsor indicates "the

- Under the "Indications and Usage" se

Based on the sponsor's results described in the submission, Studies 641 and 642 support the efficacy claim of Paxil® for the treatment of GAD.

10.0 Conclusions

Two of three studies, Studies 641 and 642, revealed significant treatment group effects on the primary efficacy variable, based on the results provided in the submission. This conclusion was confirmed by a statistical analysis of the sponsor's raw data conducted by the Biometrics review Dr. Kallapa Koti.

11.0 Recommendations

Supplement SE 1-026 is approvable based on the support of Studies 641 and 642.

Karen L. Brugge, M.D.
Medical Review Officer, DNDP
FDA CDER ODE1 DNDP HFD 120

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K Brugge
A Homonnay
T Laughren

Appendix 1

Table 7.1.1.A. Investigators and Sites for Study 641, as provided by the sponsor.			
Center No.	**Investigator**	**Affiliation/ Address**	**State**
USA			
101	Mohammed Bari	MD Synergy Clinical Research	Chula Vista, CA
102	David Beck	MD University of Missouri - Columbia,	Columbia, MO
		Department of Psych/ Neuro	
103	Robert Birnbaum	MD Beth Israel Deaconess Medical Center, Boston, MA	
		Department of Psychiatry	
104	William Burke	MD University of Nebraska Medical	Omaha, NE
		Center, Psychopharmacology Research	
		Center	
105	Bruce Cohen	MD University of Virginia Health Sciences	Charlottesville,
		Center, Center for Psychiatric Clinical	VA
		Research	
106	Pedro Delgado	MD University of Arizona Health Sciences	Tucson, AZ
		Center, Department of Psychiatry,	
		70pc, Room 7402	
107	Eugene Du Boff	MD Denver Center for Medical Research	Denver, CO
108		James Mecham Ferguson MD Pharmacology Research Corporation	Salt Lake City,
			UT
109	William Gilmer	MD Northwestern University	Chicago, IL
110	Wayne Goodman	MD University of Florida College of	Gainesville, FL
		Medicine	
111	Laszlo Papp	MD Columbia University	New York, NY
112	Jon F. Heiser	MD Pharmacology Research Institute	Irvine, CA
113	Francis Haines	MD Clinical Studies Providence	East Providence,
			RI
114	Barbara Kennedy	MD University of Louisville, Department	Louisville, KY
		of Psychiatry and Behavioral Sciences,	
		Ambulatory Care Building	
115	Arifulla Khan	MD Northwest Clinical Research Center	Bellevue, WA
116	Lorrin Koran	MD Stanford University Medical Center,	Stanford, CA
		Department of Psychiatry	
117	Ronald Landbloom	MD Regions Hospital, Department of	St. Paul, MN
		Behavioral Health	
118	Sidney Lerfald	MD Suite 306, 415 Morris Street	Charleston, WV
119	Michael Liebowitz	MD The Medical Research Network, Llc	New York, NY
120	James Hartford	MD Cincinnati Medical Research Institute	Cincinnati, OH
121	Lucy Puryear	MD Baylor College of Medicine,	Houston, TX
		Department of Psychiatry	
122	Denis Mee - Lee	MD Hawaii Clinical Research Center	Honolulu, HI
123	Matthew Menza	MD Robert Wood Johnson Medical School, Piscataway, NJ	
		Department of Psychiatry	
124	Charles Merideth	MD Affiliated Research Institute	San Diego, CA
125	Kevin Miller	MD St. Louis University Health Sciences	St. Louis, MO

		Center	
126	Charles Nemeroff	MD Emory University School of Medicine	Atlanta, GA
127	Julie Oldroyd	MD The Irvine Clinical Research Center	Irvine, CA
128	Teresa Pigott	MD University of Texas Medical Branch at Galveston, TX	
129	Charles Ravaris	MD Darmouth Hitchcock Medical Center,	Lebanon, NH
		Department of Psychiatry	
130	Karl Rickels	MD Hospital of the University of	Philadelphia, PA
		Pennsylvania	
131	Robert Riesenberg	MD Biobehavioral Atlanta	Decatur, GA
132	Howard Schwartz	MD Miami Research Associates	Miami FL
133	Leslie Seiden	MD 133 East 91st Street	New York, NY
134	Hope Selamick	MD Temple University, Department of	Philadelphia, PA
		Psychology	
135	Anantha Shekhar	MD Indiana University School of Medicine Indianapolis, IN	
136	Jeffrey Simon	MD Northbrooke Research Center	Brown Deer, WI
137	Karen Weihs	MD George Washington University	Washington, DC
138	Richard Weisler	MD 900 Ridgefield Drive, Suite 320	Raleigh, NC
139	Kenneth Weiss	MD Delaware Valley Research Associates	King of Prussia,
		Inc.	PA
140	Andrew Winokur	MD Dartmouth- Hitchcock Medical Center	Labanon, NH
141	Dan Zimbroff	MD Pacific Clinical Research Medical	Upland, CA
		Group	
142	John Zwerneman	MD Health Advance Institute	South Bend, IN
143	David Brown	MD Community Clinical Research Inc.	Austin, TX
150	Rudolf Hoehn- Saric	MD 4303 North Charles Street	Baltimore, MD
Canada			
144	Jacques Bradwejn	MD Royal Ottawa Hospital	Ottawa, Ontario
145	Stanley Kutcher	MD Queen Elizabeth II Health Sciences	Halifax, Nova
		Centre	Scotia
146	Anthony Levitt	MD Sunnybrook Health Sciences Centre	Toronto, Ontario
147	Franscisco Jose Pinero-	MD Centre Universitaire en Sante de	Sherbrooke,
	Medina	l'Estrie	Quebec
148	Pierre Savard	MD Universite de Montreal	Montreal,
			Quebec
149	Richard Swinson	MD McMaster University, Dept. of	Hamilton,
		Psychiatry and Behavioral Neuro-	Ontario
		sciences	

Table 7.1.1.B. Study 642: Investigators, the SB Assigned Center Number and the Investigator Hospital or University Affiliation and Location (as provided by the sponsor)

Investigator	Center	Affiliated Institution	City	State
United States				
Apter, Jeffrey M. D.	201	Princeton Biomedical Research, P. A.	Princeton	NJ
Bakhtiar, Parvaneh M. D.	202	Lovelace Scientific Resources, Inc. (LSR) Albuquerque		NM
Carman, John M. D.	203	Carman Research	Smyrna	GA
Croft, Harry M. D.	204	The Croft Group Inc.	San Antonio	TX
Cunningham, Lynn M. D.	205	Vine Street Clinic	Springfield	IL
DePriest, Michael M. D.	206	Pharmacology Research Clinic	Las Vegas	NV
Taylor, Leslie M. D.	207	Dean Foundation for Health, Research & Education	Middleton	WI
Goddard, Andrew M. D.	208	Yale Anxiety Clinic	New Haven	CT
Holland, Peter M. D.	209	7280 W. Plametto Park Road, Ste. 203, N	Boca Raton	FL
Hollander, Eric M. D.	210	Mount Sinai School of Medicine	New York	NY
Houck, Carl M. D.	211	University of Alabama	Birmingham	AL
Kang, Jasbir M. D.	212	Western Pennsylvania Psychiatric Center	Center Township	PA
Kiev, Ari M. D.	213	Social Psychiatry Institute	New York	NY
Taylor, David M. D.	214	UCSF Langley Porter Psychiatric Institute		CA
Melchor, Pedro M. D.	215	Pharm Research, Inc.	Miami	FL
Murphy, John M. D.	216	Southwestern Research Institute	Beverly Hills	CA
Pollack, Mark M. D.	217	Massachusetts General Hospital- Psychiatry Boston		MA
Rosenthal, Murray M. D.	218	Behavioral Medicine Resources	San Diego	CA
Sheehan, David M. D.	220	University of South Florida	Tampa	FL
Stahl, Stephen M. D.	221	Clinical Neuroscience Research Center	San Diego	CA
Stein, Murray M. D.	222	University of California at San Diego	San Diego	CA
Stevens, Michael M. D.	223	Valley Mental Health	Salt Lake City	UT
Stewart, Rege M. D.	224	University of Texas Southwestern Medical Dallas School		TX
Tucker, Phebe M. D.	225	University of Oklahoma	Oklahoma City	OK
Lydiard, Bruce M. D.	230	Medical University of South Carolina	Charleston	SC
Maddock, Richard M. D.	234	University of California, Davis Medical Center	Sacramento	CA
Dietrich, Anthony M. D.	235	Five the Green	Woodstock	VT
Sambunaris, Angelo M. D.	236	Atlanta Institute of Medicine and Research Roswell		GA
Casat, Charles M. D.	237	Behavorial Health Center	Charlotte	NC
Canada				
Katzman, Martin M. D.	226	Clark Institute of Psychiatry	Toronto	Ont
Le Melledo, JM M. D.	227	University of Alberta, H Site	Edmonton	Alb
Reesal, Robin M. D.	228	Western Canada Behavioral Center	Calgary	Alb
Plamondon, Jacques M. D.	229	Centre Hospitalier U de Quebec	Laurier	Que
Saxena, Bishan M. D.	231	Hamilton Psychiatric Hospital	Hamilton	Ont
Goldner, Elliot M. D.	232	University of British Columbia	Vancouver	BC

Table 7.1.1.C. Study 637: Investigators, the SB Assigned Center Number and the Investigator Hospital or University Affiliation and Location (as provided by the sponsor)

Centre No.	Investigator	Affiliation/ Address	City
United Kingdom			
001	Dr Alun George	The Staploe Medical Centre	Ely
002	Dr Ian Parker	Comberton Surgery	Cambridge
003	Dr Katrina Young	St. Mary's Surgery	Ely
004	Dr Sally Barnard	Newnham Walk Surgery	Cambridge
006	Dr Andrew Smithers	The Surgery	Coventry
007	Dr Bhavesh Bodalia	Goodyers Lane End Surgery	Coventry
013	Dr Alun Jones	Talybont Surgery	Swansea
014	Dr Cosmo Hallstrom	Feighner Research Institute	London
016	Dr Martin Adler	Belmont Health Centre	Kenton
017	Dr Carol McKinnon	Castlemilk Health Centre	Glasgow
018	Dr William Carr	Leslie Surgery	Glenrothes
019	Dr William Aitchison	The surgery	Bridge of Weir
020	Dr Bryan Hopwood	The Burngreave Surgery	Sheffield
021	Dr Desmond Keating	Elm Lane Surgery 7	Sheffield
Ireland			
031	Dr Mary Belton	Town Hall Clinic, Town hall Centre	Co. Wicklow
032	Dr Donal O'Brien	Wilmer Road	Co. Offaly
033	Dr Paul Armstrong	Lifford Health Centre	Co. Donegal
035	Dr Christopher MacNamara	43 Harrington Street	Dublin
036	Dr Eamonn Kelly	The Surgery	Co. Wicklow
038	Dr Kevin Kelly	Emmet House Medical Centre	Co. Tipperary
040	Dr Stephen Murphy	The Park Clinic	Dublin
042	Dr Padraig McGarry	40 Ballymahon Street	Co. Longford,
043	Dr Charles Bourke	Health Centre	Co. Donegal
044	Dr Bernadette	O'Leary Medical Centre	Clonmel
045	Dr Alan Byrne	Scholarstown Family Practice	Dublin
France			
051	Dr Fabrice Buton	153 route de Vannes	Saint Herblain
052	Dr Jean- Marie Letzelter	7 quai Saint Jean	Strasbourg
054	Dr Nathan Abenhaim	35 Boulevard Tauler	Strasbourg
055	Dr Francois- Xavier Poudat	3 rue Marceau	Nantes
057	Dr Sami Atallah	6 rue Denave	Tarare
058	Dr Alain Campagne	81 rue Blaise Pascal	Tours
059	Dr Loic Boucher	25 rue V. Desormeaux	Murs Erigne
062	Dr Joel Gailledreau	Centre Medical Claude Bernard	Elancourt
Austria			
072	Dr Siegfried Kasper	Department of General Psychiatry, University Wahringer of Vienna	Gurtel
Germany			
071	Dr Frank Godemann	Psychiatrische Intensiv und Krisenintervention sstation	Berlin
074	Dr Bernhard Stahr	Felnbelliner Str. 28	Falkensee
075	Dr E. Geschke	Woltersdorfer Landstrasse 19	Eckner
076	Dr Otmar Desch	Steinstrasse 31	Berlin
077	Dr Hartmut Dorn	Grabenstrasse 41	Berlin
078	Dr Martin Schumann	Schonhauser Allee 83	Berlin

Table 7.1.1.C., continued.

Centre No.	Investigator	Affiliation/ Address	City
079	Dr Marion Gille	Fachargton Fur Innere Medigin Prenzlaver Allee 189	Berlin
080	Dr Ingrid Berndt	Muggelstrasse 28	Berlin
081	Dr Friedemann Cramer	Gross Ziethener Chaussee 16	Berlin
086	Dr Silvia Ost	Greifswalder Str 112	Berlin
088	Dr Peter Franz	Orankestrasse 84	Berlin
089	Dr Muzaffer Dilmac	Muskauer Strasse 24	Berlin
091	Dr Helmut Peter	Klinik fur Psychiatrie und Psychotherapie	Hamburg
092	Dr Katrin Bornkessel	Mandelstrasse 2	Berlin
097	Dr Ilona Weisshuhn	Bornholmerstrasse 2	**Berlin**
Italy			
099	Dr Giampietro	Casa Di Cura Villa Margherita Neurologia	Vicenza
	Nordera		

Table 7.1.2 Assessment Schedule for Studies 641, 642*, 637**

	Scrn Visit Day -1	Base-Line Visit Day 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Early W/D	Taper Interim Visit	Taper End Visit	14-Day Study F/U[c]	28-day Study F/U[g]
Screen/Baseline Evaluations													
General Patient Information	X												
MINI	X												
Psychoactive Med. History	X												
Psych Inter./Mental Status	X												
Medical/Surgical History	X												
GAD Criteria (DSM-IV)	X												
ECG Record	X	X[d]											
Inclusion/Exclusion Criteria	X	X											
Patient Randomization		X											
Informed Consent	X												
Efficacy Parameters													
HAM-A	X	X	X	X	X	X	X	X	X				
CGI (Severity of Illness)		X	X	X	X	X	X	X	X				
CGI (Global Improvement)			X	X	X	X	X	X	X				
HAD		X	X	X	X	X	X	X	X				
COVI Anxiety Scale		X				X		X	X				
Sheehan Disability Scale (SDS)		X				X		X	X				
MADRS	X	X						X	X				
Job Employment Status		X											
Job Attendance			X	X	X	X	X	X	X				
Quality of Life (EuroQol)		X						X	X				
Safety Evaluations													
Vital Signs	X	X[b]						X	X	X[b]	X[b]	X[b]	X[b]
Body Weight	X[h]							X	X				
Adverse Experience Monitoring		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Evaluation	X	X[a]						X	X	X[a]	X[a]	X[a]	X[a]
Urine Benzodiazepine Screen	X							X	X				
Physical Examination	X												
Serum Pregnancy Test	X[e]												
Miscellaneous Records													
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Medication	X	X	X	X	X	X	X	X[f]	X[f]	X[f]			
Study Medication Record		X	X	X	X	X	X	X	X	X	X		
Study Termination Record								X	X				

a Laboratory Evaluation to be performed if clinically significant values are noted at a previous visit. Laboratory evaluations were: Hematology (hemoglobin, hematocrit, WBC with differential, RBC, and platelet count); blood chemistry (creatinine, BUN, total bilirubin, alkaline phosphatase, SGPT[ALT], SGOT[AST], electrolytes, TSH, T_3, T_4 [thyroid tests at Screening Visit only]; dipstick urinalysis (if positive for blood or protein, full microscopy was performed).

b Repeat vital signs were done if results at previous visit are clinically significant.

c Follow-up Visit was completed 14 days following last dose of study medication for all patients.

d ECG to be done if results at Screening Visit were abnormal. Results of repeat evaluation were to be interpreted before patient randomization.

e For women of child-bearing potential only

f Taper medication dispensed for all eligible patients.

g F/U Visit to be scheduled within 28 days of last study medication dose for all patients with adverse experiences at 14-Day F/U Visit.

h Height was measured also.

Data source: Protocol, Appendix A.

* An additional visit was included in the protocol for Study 642, which occurred on Week 5 of Treatment. Assessments on this visit were the same as those conducted on Week 6 of Treatment. A Taper Interim Visit was not included in the protocol for this study.

** In Study 637, an alcohol breath test was not performed at screening. While body weight and height were obtained at screening, these parameters were not monitored over time.

Table 7.1.3 A Study 641: Summary of Baseline and Change from Baseline (Least Square Means) at Weekly Intervals HAM-A Total, by Treatment Group (ITT Efficacy Population)†

	Placebo			Paroxetine					
				20 mg			40 mg		
	N	Mean	SE	N	Mean	SE	N	Mean	SE
Baseline	180	23.9	0. 3	188	23.8	0. 3	197	23.3	0. 3
LOCF									
Wk 1	178	-4. 9	0.4	187	-4. 6	0.4	195	-4. 7	0.4
Wk 2	180	-7. 9	0.5	188	-7. 8	0.5	197	-7. 3	0.5
Wk 3	180	-9. 2	0.5	188	-9. 4	0.5	197	-9. 5	0.5
Wk 4	180	-9. 8	0.6	188	-10.7	0. 5	197	-10.8	0. 6
Wk 6	180	-9. 9	0.6	188	-12.1**	0. 6	197	-11.7*	0. 6
Wk 8	180	-9. 6	0.7	188	-12.5***	0. 6	197	-12.2**	0. 6
OC									
Wk 1	178	-4. 9	0.4	187	-4. 6	0.4	195	-4. 7	0.4
Wk 2	168	-7. 9	0.5	174	-8. 0	0.5	183	-7. 6	0.5
Wk 3	160	-9. 6	0.5	163	-9. 9	0.5	170	-10.4	0. 5
Wk 4	160	-10.1	0. 6	157	-11.3	0. 6	164	-11.4	0. 6
Wk 6	147	-10.3	0. 6	149	-13.1***	0. 6	151	-13.3***	0. 6
Wk 8	140	-10.7	0. 7	141	-13.8***	0. 6	146	-13.9***	0. 6

† Results shown in this table are those provided in Table 12, on page 54 of the Integrated Summary of Safety in the submission.
*p<0.025, **p<0.01, *** p<0.001

Table 7.1.3 B Study 642: Summary of Baseline and Change from Baseline (Least Square Means) at Weekly Intervals HAM-A Total, by Treatment Group (ITT Efficacy Population) , similar to that provided by the sponsor.

	Placebo			Paroxetine			Placebo vs. Paroxetine	
	N	Mean	SEM	N	Mean	SEM	Diff (CI)+	p- val
Baseline	163	23.6	0. 3	161	23.9	0. 3	0.3 (- 0. 5, 1.0)	0.472
LOCF								
Wk 1	160	-3. 8	0.4	159	-3. 9	0.4	-0.1 (- 1. 0, 0.9)	0.850
Wk 2	163	-6. 2	0.5	161	-6. 6	0.5	-0.4 (- 1. 5, 0.7)	0.479
Wk 3	163	-7. 1	0.5	161	-8. 2	0.5	-1.1 (- 2. 4, 0.2)	0.089
Wk 4	163	-8. 1	0.6	161	-9. 0	0.6	-0.9 (- 2. 3, 0.5)	0.190
Wk 5	163	-9. 3	0.6	161	-10.4	0. 6	-1. 1 (- 2. 6, 0.3)	0.127
Wk 6	163	-9. 6	0.6	161	-11.3	0. 7	-1. 6 (- 3. 2, -0. 1)	0. 041*
Wk 8	163	-9. 5	0.7	161	-11.8	0. 7	-2. 3 (- 4. 0, -0. 6)	0. 008*
OC								
Wk 1	160	-3. 8	0.4	159	-3. 9	0.4	-0.1 (- 1. 0, 0.9)	0.850
Wk 2	152	-6. 7	0.5	147	-7. 0	0.5	-0.3 (- 1. 5, 0.8)	0.576
Wk 3	146	-7. 8	0.6	134	-8. 8	0.6	-1.0 (- 2. 4, 0.3)	0.143
Wk 4	146	-8. 6	0.6	130	-9. 7	0.7	-1.1 (- 2. 6, 0.4)	0.155
Wk 5	141	-10.2	0. 7	135	-11.4	0. 7	-1. 2 (- 2. 7, 0.4)	0.141
Wk 6	140	-10.4	0. 7	132	-12.1	0. 7	-1. 8 (- 3. 4, -0. 2)	0. 032*
Wk 8	133	-10.7	0. 8	127	-13.3	0. 8	-2. 5 (- 4. 3, -0. 7)	0. 006*

+Differences in adjusted (Least Square) means; 95% CI used
*Significance for p< 0.05

Table 7.1.3 C Study 637: Summary of Baseline and Change from Baseline (Least Square Means) at Weekly Intervals HAM-A Total, by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor

	Placebo			Paroxetine			Placebo vs. Paroxetine	
	n	Mean	SE	n	Mean	SEM	Diff (CI)+	p- val
Baseline	183	25.9	0. 4	181	26.0	0. 4	0.1 (-0.7, 1.0)	0. 788
LOCF								
Wk 1	182	-4. 5	0.6	179	-4. 0	0.6	0. 5 (-0. 7, 1.7)	0. 396
Wk 2	183	-6. 3	0.7	181	-7. 5	0.7	-1.1 (-2.5, 0.3)	0. 114
Wk 3	183	-7. 0	0.7	181	-8. 1	0.7	-1.1 (-2.6, 0.4)	0. 141
Wk 4	183	-9. 3	0.8	181	-10.1	0. 8	-0. 8 (-2. 4, 0.8)	0. 329
Wk 6	183	-9. 8	0.8	181	-11.1	0. 8	-1. 3 (-2. 9, 0.3)	0. 111
Wk 8	183	-11.3	0. 8	181	-12.4	0. 8	-1. 1 (-2. 8, 0.5)	0. 171
OC								
Wk 1	182	-4. 5	0.6	179	-4. 0	0.6	0. 5 (-0. 7, 1.7)	0. 396
Wk 2	176	-6. 2	0.7	165	-8. 0	0.7	-1.9 (-3.3, -0. 5)	0.010*
Wk 3	168	-7. 6	0.8	149	-9. 5	0.8	-1.9 (-3.5, -0. 4)	0.016*
Wk 4	164	-10.0	0. 8	150	-11.6	0. 8	-1. 6 (-3. 3, 0.1)	0. 059
Wk 6	167	-10.3	0. 8	155	-13.1	0. 8	-2. 7 (-4. 3, -1. 1)	0.001*
Wk 8	163	-12.5	0. 8	149	-14.8	0. 8	-2. 3 (-3. 9, -0. 7)	0.005*

*Significant for p < 0.05
+Differences in adjusted (Least Square) means

Table 7.1.4 A Study 641: Summary of Baseline and Mean Change from Baseline (Least Square Means) on the COVI Anxiety Scale at Each Visit and by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor.

	Placebo			Paroxetine					
				20 mg			40 mg		
	N	Mean	SE	N	Mean	SE	N	Mean	SE
Baseline	163	9.3	0. 1	173	9.4	0. 1	179	9.2	0. 1
LOCF									
Wk 4	162	-2. 4	0.2	172	-2. 7	0.2	176	-2. 7	0.2
Wk 8	163	-2. 3	0.2	173	-3. 3 *	0.2	179	-3. 2 *	0.2
OC									
Wk 4	159	-2. 5	0.2	156	-2. 9	0.2	160	-2. 8	0.2
Wk 8	140	-2. 6	0.2	141	-3. 7 *	0.2	144	-3. 5 *	0.2

*p<0.001 when compared to the placebo group

Table 7.1.4 B Study 642: Summary of Baseline and Mean Change from Baseline (Least Square Means) on the COVI Anxiety Scale at Each Visit and by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor.

	Placebo Group			Paroxetine Group		
	N	Mean	SEM	N	Mean	SEM
Baseline	155	9.3	0. 1	152	9.3	0. 1
LOCF						
Week 4	146	-2. 1	0.2	132	-2. 4	0.2
Week 8	155	-2. 5	0.2	152	-3. 1	0.3
OC						
Week 4	140	-2. 2	0.2	115	-2. 6	0.3
Week 8	133	-2. 8	0.3	125	-3. 5*	0.3

*p<0.05 compared to placebo

Table 7.1.4 C Study 637: Summary of the Mean Change on the COVI Anxiety Scale Relative to Baseline at Each Visit and by Treatment Group : ITT Population, similar to that provided by the sponsor.

	Placebo Group			Paroxetine Group		
	n	Mean	SEM	n	Mean	SEM
Baseline	178	8.8	0. 2	175	9.1	0. 2
LOCF						
Week 4	178	-2. 0	0.2	172	-2. 5	0.2
Week 8	178	-2. 6	0.3	175	-3. 1	0.3
OC						
Week 4	163	-2. 1	0.3	147	-2. 6	0.3
Week 8	163	-2. 9	0.3	149	-3. 5*	0.3

P<0.05 compared to placebo

Table 7.1.5 A Study 641: Summary of Responders of the Hamilton Anxiety Rating Scale (HAM- A) Total </= 10 at Each Visit by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor.

	Placebo			Paroxetine					
				20 mg			40 mg		
	n	N	%	N	N	%	N	N	%
LOCF									
Wk 1	6	178	3.4%	9	187	4.8%	6	195	3.1%
Wk 2	26	180	14.4%	28	188	14.9%	30	197	15.2%
Wk 3	45	180	25.0%	44	188	23.4%	60	197	30.5%
Wk 4	51	180	28.3%	63	188	33.5%	81	197	41.1%
Wk 6	58	180	32.2%	86	188	45.7%*	94	197	47.7%*
Wk 8	59	180	32.8%	92	188	48.9%*	102	197	51.8%**
OC									
Wk 1	6	178	3.4%	9	187	4.8%	6	195	3.1%
Wk 2	25	168	14.9%	27	174	15.5%	30	183	16.4%
Wk 3	43	160	26.9%	40	163	24.5%	58	170	34.1%
Wk 4	49	160	30.6%	56	157	35.7%	71	164	43.3%
Wk 6	53	147	36.1%	77	149	51.7%*	81	151	53.6%*
Wk 8	56	140	40.0%	79	141	56.0%*	88	146	60.3%**

*p<0.01, **p<0.001 when compared to controls
n= number of responders, N= total number of patients assessed

Table 7.1.5 B Study 641: Proportion of Responders Based on CGI Global Improvement Score of 1 or 2 at Each Visit by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor.

	Placebo			Paroxetine					
				20 mg			40 mg		
	n	N	%	n	N	%	n	N	%
LOCF									
Wk 1	14	178	7.9%	14	187	7.5%	19	195	9.7%
Wk 2	35	180	19.4%	41	188	21.8%	47	197	23.9%
Wk 3	62	180	34.4%	77	188	41.0%	91	197	46.2%*
Wk 4	70	180	38.9%	93	188	49.5%	111	197	56.3%***
Wk 6	79	180	43.9%	111	188	59.0%**	130	197	66.0%***
Wk 8	82	180	45.6%	116	188	61.7%**	134	197	68.0%***
OC									
Wk 1	14	178	7.9%	14	187	7.5%	19	195	9.7%
Wk 2	34	168	20.2%	39	174	22.4%	44	182	24.2%
Wk 3	58	160	36.3%	71	164	43.3%	87	170	51.2%**
Wk 4	68	160	42.5%	84	157	53.5%	100	164	61.0%***
Wk 6	69	147	46.9%	97	149	65.1%**	114	151	75.5%***
Wk 8	73	140	52.1%	95	140	67.9%**	117	146	80.1%***

*p<0.025 **p<0.01, ***p<0.001 when compared to controls.
n= number of responders, N= total number of patients assessed

Table 7.2.1.A. Study 642: Summary of Responders of the Hamilton Anxiety Rating Scale (HAM-A) Total </= 10 at Each Visit by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor.†

	Placebo			Paroxetine		
	n	N	(%)	n	N	(%)
LOCF						
Wk 1	6	160	(3. 8)	2	159	(1. 3)
Wk 2	20	163	(12.3)	17	161	(10.6)
Wk 3	31	163	(19.0)	35	161	(21.7)
Wk 4	45	163	(27.6)	44	161	(27.3)
Wk 5	59	163	(36.2)	56	161	(34.8)
Wk 6	57	163	(35.0)	76	161	(47.2)*
Wk 8	61	163	(37.4)	88	161	(54.7)***
OC						
Wk 1	6	160	(3. 8)	2	159	(1. 3)
Wk 2	20	152	(13.2)	17	147	(11.6)
Wk 3	31	146	(21.2)	34	134	(25.4)
Wk 4	44	146	(30.1)	40	130	(30.8)
Wk 5	57	141	(40.4)	55	135	(40.7)
Wk 6	55	140	(39.3)	72	132	(54.5)**
Wk 8	58	133	(43.6)	81	127	(63.8)****

n= number of responders, N= total number of patients assessed

†Note that the following is different than that of previous tables: *p<0.05, **p<0.025, ***p.01, ****p<0.001 compared to controls using Student t-test. Significance for alpha=0.05, per sponsor.

Table 7.2.1.B. Study 642. Proportion of Responders Based on CGI Global Improvement Score of 1 or 2 at Each Visit by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor.†

	Placebo			Paroxetine		
	n	N	(%)	n	N	(%)
LOCF						
Wk 1	9	160	(5. 6)	10	159	(6. 3)
Wk 2	29	163	(17.8)	34	161	(21.1)
Wk 3	43	163	(26.4)	49	161	(30.4)
Wk 4	68	163	(41.7)	67	161	(41.6)
Wk 5	75	163	(46.0)	79	161	(49.1)
Wk 6	75	163	(46.0)	92	161	(57.1)*
Wk 8	77	163	(47.2)	100	161	(62.1) ***
OC						
Wk 1	9	160	(5. 6)	10	159	(6. 3)
Wk 2	29	151	(19.2)	34	147	(23.1)
Wk 3	43	146	(29.5)	45	134	(33.6)
Wk 4	66	146	(45.2)	60	130	(46.2)
Wk 5	72	140	(51.4)	76	135	(56.3)
Wk 6	73	140	(52.1)	87	132	(65.9)**
Wk 8	74	133	(55.6)	92	127	(72.4)***

n= number of responders, N= total number of patients assessed

†Note that the following is different than for tables on previous pages: *p<0.05, **p<0.025, ***p.01, ****p<0.001 compared to controls using Student t-test. Significance for alpha=0.05, per sponsor.

Table 7.3.1 A. Study 637: Summary of Responders Based on the HAM-A Total of </= 10 : ITT Population, similar to that provided by the sponsor.

	Placebo Group			Paroxetine Group		
	n	N	%	n	N	%
LOCF						
Wk 1	6	182	3.3	10	179	5.6
Wk 2	22	183	12.0	37	181	20.4*
Wk 3	44	183	24.0	50	181	27.6
Wk 4	56	183	30.6	65	181	35.9
Wk 6	75	183	41.0	83	181	45.9
Wk 8	85	183	46.4	90	181	49.7
OC						
Wk 1	6	182	3.3	10	179	5.6
Wk 2	21	176	11.9	37	165	22.4**
Wk 3	42	168	25.0	46	150	30.7
Wk 4	52	164	31.7	62	151	41.1
Wk 6	72	167	43.1	82	155	52.9
Wk 8	81	163	49.7	85	149	57.0

n= number of responders, N= total number of patients assessed
*p<0.05, **p<0.025, ***p.01, ****p<0.001 when compared to controls (Student t-test).
Significance for alpha=0.05 per sponsor.

Table 7.3.1.B. Study 637: Summary of Responders for CGI Items 1 or 2 at Each Visit : ITT Population, similar to that provided by the sponsor.

	Placebo Group			Paroxetine Group		
	n	N	%	n	N	%
LOCF						
Wk 1	15	182	8.2	17	179	9.5
Wk 2	29	183	15.8	53	181	29.3***
Wk 3	56	183	30.6	73	181	40.3
Wk 4	73	183	39.9	86	181	47.5
Wk 6	92	183	50.3	114	181	63.0**
Wk 8	91	183	49.7	114	181	63.0**
OC						
Wk 1	15	182	8.2	17	179	9.5
Wk 2	28	176	15.9	52	166	31.3****
Wk 3	54	168	32.1	66	150	44.0*
Wk 4	68	164	41.5	81	151	53.6*
Wk 6	90	167	53.9	112	155	72.3****
Wk 8	89	163	54.6	108	149	72.5***

n= number of responders, N= total number of patients assessed
*p<0.05, **p<0.025, ***p.01, ****p<0.001 when compared to controls, Student t-test.
Significance for alpha=0.05 per sponsor.

Table 8.1.1.A. Non- Fatal Serious Adverse Experiences - Studies 637, 641 and 642 (ITT Population), as provided by the sponsor.

Patient Number	Age (years)	Sex	Days on Study at Event Onset	Total Days on Dbl- Blind Study Drug	Serious Adverse Experience	Severity	Relationship	Action
Paroxetine								
637.017.03612	41	F	34	31	Anxiety	Severe	Probably Unrelated	None
637.031.03396	27	M	68	62	Chest Pain	Severe	Unrelated	None
637.052.03711	20	F	39	57	Anxiety	Severe	Unrelated	Dose Increased
637.092.03458	51	F	6	7	Abdominal Pain/ Gastritis	Severe	Unrelated	Drug Stopped
641.120.00972	63	F	61	60	Chest Pain	Severe	Unrelated	None
641.126.01253	48	M	12	18	Skin Carcinoma	Moderate	Unrelated	None
641.150.02452	54	M	69	56	Trauma (Car Accident)	Mild	Unrelated	None
642.216.03776	45	F	83	56	Pneumonia	Severe	Unrelated	None
642.225.04217	37	F	3	3	Hallucinations	Mild	Possibly Related	Drug Stopped
Placebo								
637.001.03297	58	M	43	55	Chest Pain	Moderate	Probably Unrelated	None
637.018.03607	65	M	33	62	Accidental Overdose	Mild	Unrelated	None
637.020.03575	56	M	26	56	Accidental Overdose	Moderate	Unrelated	None
637.057.03750	48	M	56	56	Depression	Severe	Possibly Related	Drug Stopped
637.057.03758	38	M	89	57	Nephritis	Severe	Unrelated	None
637.058.03662	32	F	41	58	Unintended Pregnancy	--	Unrelated	None
637.074.03433	52	F	5	3	Vascular Disorder	Moderate	Unrelated	None

Table 8.1.1.B. Serious Adverse Experiences - Study 646, as provided by the sponsor.

Patient Number	Age (years)	Sex	Treatment	Duration of Treatment at Onset of Event	Serious Adverse Experience	Relationship	Action/ Outcome
Paroxetine							
646.153.04604	32	F	Single- Blind Paroxetine	2 days	Overdose with benzodiazepines	Related	Drug Stopped
646.151.04531	39	F	Single- Blind Paroxetine	30 days	Grand mal convulsion	Related	Drug Stopped
646.154.04919	48	M	Single- Blind Paroxetine	11 days	Trauma (car accident)	Unrelated	Not Stated
646.307.05113	51	F	Single- Blind Paroxetine	29 days 37 days	Gastritis Bronchitis	Possibly Related Unrelated	Dose Reduced
646.150.06652	66	F	Blinded	60 days	Head Injury (fall)	Unrelated	None
646.200.04886	52	F	Single- Blind Paroxetine	1 day	Overdose (mistake in dosing instructions)	Unrelated	None
646.107.05083	52	F	Blinded	74 days	Pulmonary carcinoma	Unrelated	Death
646.302.05107	32	M	Blinded	61 days	Anxiety Insomnia Alcohol Abuse	Possibly Related	Drug Stopped

Table 8.1.2 Summary of Treatment Phase Emergent Adverse Experiences Leading to Withdrawal of 2 or More Patients by Body Systems and Preferred Terms - Studies 637, 641 and 642 (ITT Population), as provided by the sponsor.

Adverse Experiences Body Systems Preferred Terms	Placebo N =529 n	(%)	Paroxetine N = 735 n	(%)	Placebo N =529 n	(%)	Paroxetine N = 735 n	(%)
	Data Source Summary+				Revised Summary++			
Body as a Whole								
Asthenia	1	(0.2)	11	(1.5)	1	(0.2)	13	(1.8)
Chest Pain	0	(0.0)	2	(0.3)	0	(0.0)	2	(0.3)
Headache	3	(0.6)	4	(0.5)	3	(0.6)	5	(0.7)
Cardiovascular System								
Palpitation	1	(0.2)	2	(0.3)	1	(0.2)	2	(0.3)
Digestive System								
Bruxism	0	(0.0)	1	(0.1)	0	(0.0)	2	(0.3)
Constipation	0	(0.0)	1	(0.1)	0	(0.0)	2	(0.3)
Diarrhea	1	(0.2)	2	(0.3)	1	(0.2)	2	(0.3)
Dry Mouth	1	(0.2)	0	(0.0)	1	(0.2)	3	(0.4)
Gingivitis	0	(0.0)	2**	(0.3)	1	(0.2)	1	(0.2)
Nausea	1	(0.2)	13	(1.8)	1	(0.2)	15	(2.0)
Vomiting	1	(0.2)	3	(0.4)	1	(0.2)	3	(0.4)
Nervous System								
Agitation	1	(0.2)	2	(0.3)	1	(0.2)	2	(0.3)
Amnesia	0	(0.0)	2	(0.3)	0	(0.0)	2	(0.3)
Anxiety	1	(0.2)	1	(0.1)	2	(0.4)	2	(0.3)
Concentration Impaired	0	(0.0)	2	(0.3)	0	(0.0)	2	(0.3)
Confusion	0	(0.0)	2	(0.3)	1	(0.2)	2	(0.3)
Depression	1	(0.2)	3	(0.4)	2	(0.4)	3	(0.4)
Dizziness	1	(0.2)	7	(1.0)	1	(0.2)	7	(1.0)
Insomnia	1	(0.2)	5	(0.7)	2	(0.4)	5	(0.7)
Libido Decreased	2	(0.4)	3	(0.4)	2	(0.4)	5	(0.7)
Nervousness	2	(0.4)	3	(0.4)	2	(0.4)	3	(0.4)
Paresthesia	0	(0.0)	3	(0.4)	0	(0.0)	3	(0.4)
Somnolence	1	(0.2)	14	(1.9)	1	(0.2)	15	(2.0)
Thinking Abnormal	0	(0.0)	2	(0.3)	0	(0.0)	2	(0.3)
Tremor	0	(0.0)	4	(0.5)	0	(0.0)	4	(0.5)
Respiratory System								
Respiratory Disorder	0	(0.0)	1	(0.1)	0	(0.0)	2	(0.3)
Skin and Appendages								
Sweating	1	(0.2)	7	(1.0)	1	(0.2)	8	(1.1)
Special Senses								
Tinnitus	0	(0.0)	2	(0.3)	0	(0.0)	2	(0.3)
Urogenital System								
*Abnormal Ejaculation	1	(0.5)	6	(2.1)	1	(0.5)	7	(2.5)
*Female Genital Disorders	0	(0.0)	1	(0.2)	0	(0.0)	3	(0.7)
*Impotence	1	(0.5)	2	(0.7)	1	(0.5)	2	(0.7)

* Percentage corrected for gender
+ For one placebo patient and 7 paroxetine patients, AE leading to withdrawal not identified; for 3 placebo and 3 paroxetine patients AE leading to withdrawal was reported to occur after stopping study medication.
** One patient, gingivitis lead to temporary stoppage

++ Includes AEs from patients identified as having a data issue (see text of review for details)

Table 8.1.3. Comparison of Treatment Phase Emergent Adverse Experiences Occurring in 5% or More of the North American or European Populations in Any Treatment Regimen, as provided by the sponsor.

	Study 637 (Europe)				Studies 641 and 642 (N. A.)			
	Placebo		Paroxetine		Placebo		Paroxetine	
Body Systems	N= 185		N= 187		N= 344		N= 548	
Preferred Terms	n	(%)	n	(%)	n	(%)	n	(%)
Body as a Whole								
Asthenia	10	(5.4)	13	(7.0)	24	(7.0)	92	(16.8)
Headache	14	(7.6)	13	(7.0)	60	(17.4)	111	(20.3)
Infection	2	(1.1)	4	(2.1)	16	(4.7)	37	(6.8)
Digestive System								
Constipation	0	(0. 0)	8	(4. 3)	9	(2. 6)	69	(12. 6)
Decreased Appetite	0	(0. 0)	4	(2. 1)	6	(1. 7)	34	(6. 2)
Diarrhea	10	(5.4)	8	(4.3)	25	(7.3)	59	(10.8)
Dry Mouth	3	(1.6)	5	(2.7)	22	(6.4)	75	(13.7)
Dyspepsia	4	(2.2)	4	(2.1)	22	(6.4)	29	(5.3)
Nausea	5	(2.7)	38	(20.3)	23	(6.7)	110	(20.1)
Nervous System								
Dizziness	2	(1.1)	5	(2.7)	22	(6.4)	40	(7.3)
Insomnia	6	(3.2)	10	(5.3)	36	(10.5)	69	(12.6)
Libido Decreased	0	(0.0)	5	(2.7)	8	(2.3)	64	(11.7)
Nervousness	1	(0.5)	1	(0.5)	14	(4.1)	28	(5.1)
Somnolence	0	(0.0)	13	(7.0)	24	(7.0)	100	(18.2)
Tremor	1	(0.5)	11	(5.9)	3	(0.9)	23	(4.2)
Respiratory System								
Respiratory Disorder	6	(3.2)	5	(2.7)	21	(6.1)	45	(8.2)
Yawn	0	(0.0)	1	(0.5)	1	(0.3)	30	(5.5)
Skin and Appendages								
Sweating	0	(0.0)	5	(2.7)	8	(2.3)	41	(7.5)
Urogenital System								
*Abnormal Ejaculation	0	(0.0)	2	(4.2)	4	(3.0)	68	(28.9)
*Female Genital Disorders	0	(0.0)	0	(0.0)	2	(1.0)	20**	(6.4)

*Percentage corrected for gender
** Excludes patient 642.214.04609 (coding error)

Table 8.1.4.A. Predefined Clinical Laboratory Values of Potential Clinical Concern*

Parameter Hematology	Value	Units	Parameter Blood Chemistry	Value	Units
White Blood Cells	<=3, ≥ 16.0	10^ 9/ L	ALT/ SGPT	≥165	IU/ L
Basophils	≥10	%	Alkaline Phosphatase	≥390	IU/ L
Eosinophils	≥10	%	AST/ SGOT	≥150	IU/ L
Lymphocytes	≥75	%	Blood Urea Nitrogen	≥11	mmol/ L
Monocytes	≥15	%	Serum Creatinine	≥177	mcmol/ L
Segmented Neutrophils	<=15	%	Total Bilirubin	≥34	mcmol/ L
Neutrophils Bands	>10	%	Potassium	<=3.0, ≥ 6.0	Mmol/ L
Platelets	≥ 75, ≥700	10^ 9/ L	Sodium	<=126, ≥156	Mmol L
Red Blood Cells Male	<=8	10^ 12/ L	Free T3	<=3.5, ≥ 6.5	Pmol/ L
Female	<=10	10^ 12/ L	Free T4	<=10.3, ≥ 23. 2	Pmol/ L
Hematocrit Male	<=37	%TSH		≥10	mU/ L
Female	<=32	%			
Hemoglobin Male	<=115	g/ L			
Female	<=95	g/ L			

* as provided by the sponsor. Note: PCC criteria were not employed for Urine dipstick results.

Table 8.1.4.B. Predefined Changes in Vital Sign Values and Body Weight of Potential Clinical Concern as provided by the sponsor.

Systolic Blood Pressure	normal range = 90 - 180 mmHg increase of ≥40 mmHg, decrease of ≥30 mmHg
Diastolic Blood Pressure	normal range = 50 – 105 mmHg increase of ≥30 mmHg, decrease of ≥20 mmHg
Pulse Rate	normal range = 50 - 120 bpm increase or decrease of ≥30 bpm
Weight	no normal range defined increase or decrease of ≥7%

Table 8.1.5. Mean Clinical Lab Value at Baseline and Change from Baseline at Endpoint in Hematology Values - Studies 637, 641 and 642 (ITT Population), as provided by the sponsor.

	Placebo N= 529			Paroxetine N=735		
Parameter	**n**	**mean**	**SD**	**n**	**mean**	**SD**
White Blood Cells (10^ 9/ L)						
Baseline	472	6.7	1. 69	613	6.7	1. 78
Change at endpoint	472	-0. 0	1.45	613	-0. 1	1.56
Basophils (10^ 9/ L)						
Baseline	472	0.0	0. 03	613	0.0	0. 03
Change at endpoint	472	-0. 0	0.04	613	-0. 0	0.04
Eosinophils (10^ 9/ L)						
Baseline	472	0.2	0. 14	613	0.2	0. 16
Change at endpoint	472	-0. 0	0.12	613	0.0	0. 14
Lymphocytes (10^ 9/ L)						
Baseline	472	2.0	0. 63	613	2.0	0. 60
Change at endpoint	472	-0. 0	0.46	613	0.0	0. 47
Monocytes (10^ 9/ L)						
Baseline	472	0.4	0. 15	613	0.4	0. 15
Change at endpoint	472	-0. 0	0.15	613	-0. 0	0.16
Segmented Neutrophils (10^ 9/ L)						
Baseline	472	4.1	1. 40	613	4.1	1. 45
Change at endpoint	472	0.0	1. 38	613	-0. 1	1.36
Platelets (10^ 9/ L)						
Baseline	472	239.6	50.27	616	240.2	53.71
Change at endpoint	472	0.5	30.09	616	2.4	29.48
Red Blood Cells (10^ 12/ L)						
Baseline	472	4.5	0. 51	614	4.5	0. 52
Change at endpoint	472	-0. 0	0.37	614	-0. 1	0.37
Hematocrit (%)						
Baseline	472	41.4	3. 80	615	41.8	3. 78
Change at endpoint	472	-0. 2	2.25	615	-0. 4	2.30
Hemoglobin (g/ L)						
Baseline	472	140.0	13.09	614	141.3	13.60
Change at endpoint	472	-1. 1	7.14	614	-1. 9	7.97

*Mean Baseline values and values for mean changes from Baseline to Endpoint were calculated based on Screening values.

Table 8.1.6 Mean Clinical Lab Value at Baseline and Change from Baseline at Endpoint in Blood Chemistry Values - Studies 637, 641 and 642 (ITT Population), as provided by the sponsor.

	Placebo N= 529			Paroxetine N= 735		
Parameter	**n**	**mean**	**SD**	**n**	**mean**	**SD**
Alanine Aminotransferase (IU/ L)						
Baseline	477	19.8	13.53	631	20.4	13.22
Change at Endpoint	477	-0. 3	11.00	631	1.7	13.54
Alkaline Phosphatase (IU/ L)						
Baseline	477	67.3	20.62	631	68.3	19.99
Change at Endpoint	477	0.3	9. 68	631	3.5	11.03
Aspartate Aminotransferase (IU/ L)						
Baseline	477	18.3	6. 57	631	18.8	7. 54
Change at Endpoint	477	0.3	6. 40	631	1.8	10.40
Blood Urea Nitrogen (mmol/ L)						
Baseline	477	5.0	1. 59	631	5.0	1. 37
Change at Endpoint	477	0.1	1. 17	631	0.2	1. 22
Serum Creatinine (mcmol/ L)						
Baseline	477	78.6	19.45	631	77.7	22.28
Change at Endpoint	477	0.8	19.13	631	2.8	34.43
Total Bilirubin (mcmol/ L)						
Baseline	476	9.8	7. 68	631	9.7	8. 52
Change at Endpoint	476	-1. 4	7.25	631	-1. 6	8.17
Potassium (mmol/ L)						
Baseline	474	4.3	0. 51	629	4.3	0. 43
Change at Endpoint	474	-0. 0	0.53	629	-0. 0	0.54
Sodium (mmol/ L)						
Baseline	478	140.7	2. 26	631	140.9	2. 29
Change at Endpoint	478	0.1	2. 75	631	-0. 4	2.77

* Only assessed at Screening Visit

Table 8.1.7.A. Summary of Treatment Phase Mean Values for Vital Signs and Body Weight at Baseline and Mean Change from Baseline - Studies 637, 641 and 642 (ITT Population), as provided by the sponsor.

Parameter	Placebo N= 529			Paroxetine N = 735		
Timepoint	n	Mean	S. D.	n	Mean	S. D.
Systolic BP (sitting)						
Baseline	487	124.5	14.4	654	124.9	15.1
Change at Endpoint	487	-2. 0	11.7	654	-2. 0	12.4
Diastolic BP (sitting)						
Baseline	487	77.9	9. 0	654	78.1	9. 5
Change at Endpoint	487	-1. 7	8.4	654	-0. 4	8.4
Pulse						
Baseline	486	71.9	9. 4	653	72.6	9. 5
Change at Endpoint	486	0.4	9. 5	653	1.1	9. 6
Weight						
Baseline	314	76.7	17.8	475	77.1	18.2
Change at Endpoint	314	0.2	1. 9	475	-0. 1	2.3

Table 8.1.7.B. Incidence of Vital Sign and Body Weight Changes Meeting Potential Clinical Concern Criteria - Studies 637, 641 and 642 (ITT Population), as provided by the sponsor.

Parameter		Placebo		Paroxetine	
		n/ N*	(%)	n/ N*	(%)
Systolic BP (mmHg)					
	High	0/ 487	(0.0)	2/ 654	(0.3)
	Low	5/ 487	(1.0)	6/ 654	(0.9)
Diastolic BP (mmHg)					
	High	2/ 487	(0.4)	3/ 654	(0.5)
	Low	1/ 487	(0.2)	0/ 654	(0.0)
Pulse (bpm)					
	High	0/ 486	(0.0)	0/ 653	(0.0)
	Low	2/ 486	(0.4)	1/ 653	(0.2)
Weight (kg)					
	High	3/ 314	(1.0)	7/ 475	(1.5)
	Low	3/ 314	(1.0)	8/ 475	(1.7)

/s/

Karen Brugge
12/20/00 01:13:53 PM
MEDICAL OFFICER

Thomas Laughren
1/28/01 09:55:27 AM
MEDICAL OFFICER
I agree that this supplement is approvable. See memo to file for more detailed comments.--TPL

 Printed by Russell Katz

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 26-Feb-2001 10:47am
From: Karen Brugge
BRUGGEK
Dept: HFD-120 WOC2 4027
Tel No: 301-594-2850 FAX t-

TO: Russell Katz (KATZR)

CC: Thomas Laughren (LAUGHREN)
CC: Paul Andreason (ANDREASONP)
Subject: Re: sNDA 20-031 S026, Paxil/GAD Subject with elevated Cr

Russ,

Re: page 37 of my review on sNDA 20-031 S026 regarding Subject 341.133.01610, 40 y.o. Hispanic male with Cr of 88.4 umol/l at baseline and Cr of 353 umol/l on Day 56 of the treatment phase. My comment in my review regarding the patient having an "abnormal baseline Cr level" appears to be incorrect. I went back and double checked the results provided in the submission and information that the sponsor sent (dated June 16,2000) in response to my request for additional info. The normal range for Cr in the units of umol/l is approximately 44-124, such that the value of 88 at baseline for the above subject is within normal limits. In a fax from the sponsor dated 8/31/2000 (in response to my inquiry about the above subject) they indicated that the baseline level was indeed within normal limits and that a follow-up level on Day 70 revealed that the Cr level "returned to within the normal range and the investigator indicated that no further laboratory evaluations were required". The sponsor also indicated that this subject also had a mildly elevated ALT of 49 IU/l on Day 56 (normal is 0-48). The sponsor did not provide any other additional information in their 8/31/200 fax in response to my request for info regarding the diagnostic work-up, diagnosis and follow-up on this patient.

Please let me know if you need anything else.

Karen

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-031/S-026

STATISTICAL REVIEW

Statistical Review and Evaluation

NDA #:	20031/S-026
Sponsor:	SmithKline Beecham Pharmaceuticals
Drug:	Paxil Tablets
Indication:	Generalized Anxiety Disorder
Date received:	4-28-2000
Statistical reviewer:	Kallappa M. Koti, Ph.D.
Medical officer:	Karen Brugge, M.D.

Table of contents- on the next page, please.

Table of Contents

1. INTRODUCTION

2. DESIGN AND EFFICACY

2.1 Methodology
2.2 Efficacy variables
2.3 Statistical consideration

3. SPONSOR'S ANALYSES AND CONCLUSIONS

3.1 Sponsor's data analyses results
3.2 Sponsor's efficacy summary and conclusions

4. REVIEWER'S ANALYSES AND COMMENTS

4.1 Study 641- Fixed dose study
4.2 Study 642- Flexible dose study
4.3 Study 637- Flexible dose study
4.4 Efficacy results- in tabulated form

5. OVERALL CONCLUSIONS

6. APPENDIX

1. INTRODUCTION

Generalized Anxiety Disorder (GAD) has been recognized as a distinct Axis I anxiety disorder since its introduction in the third edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association in 1980. GAD is characterized by excessive anxiety and worry, occurring in more days than not for at least six months, about a number of events or activities such as school or work performance. Epidemiology studies have shown that the lifetime prevalence of DSM-defined GAD is 5.1% in the U.S. and between 1.9 and 5.4% in various regions of Europe. GAD primarily affects females, and exhibits a high degree of chronically.

Effective pharmacological treatment for GAD has been demonstrated in controlled clinical trials with benzodiazepines, buspirone, and venlafaxine, but the clinical utility of these agents has been limited. Interest has therefore developed to explore the potential utility of other pharmacotherapies to treat GAD, specifically the selective serotonin uptake inhibitors. Paroxetine (Paxil®) is a selective serotonin reuptake inhibitor approved for the treatment of depression, Panic Disorder, Obsessive Compulsive Disorder (OCD) and Social Anxiety Disorder. This submission deals with the the sponsor's completed clinical program that is supposed to demonstrate that paroxetine is safe and effective in the treatment of Generalized Anxiety Disorder.

2. DESIGN AND EFFICACY

The use of paroxetine in the treatment of GAD is supported by the findings from three randomized, parallel-group, double-blind, placebo-controlled multi-center studies, identified as Studies 637, 641 and 642. These three trials included an 8-week treatment phase, and were initiated in the autumn of 1998; all were completed in 1999. In addition, there is an ongoing study assessing relapse in GAD patients. This study, identified as protocol 646, is being conducted in Europe.

2.1 Methodology

Each of the three completed studies 637, 641 and 642 were multi-center, randomized, double-blind, placebo controlled parallel group studies of outpatients with a predominant psychiatric diagnosis of Generalized Anxiety Disorder.

At entry all patients were given a physical examination to include a medical history, clinical laboratory assessments and an ECG. Each patient's psychiatric status and history was evaluated in a formal interview that included the completion the Mini International Neuropsychiatric Interview (MINI). Eligible patients underwent a one-week, single blind, run-in phase to further evaluate their suitability for study, and to identify placebo responders. Following the run-in phase, patients who continued to meet the inclusion and exclusion criteria were randomized to receive paroxetine or placebo. Individuals diagnosed with comorbid Axis I disorders and those with significant depressive symptomatology were denied entry. However, patients with comorbid Dysthymia were permitted to enter the trials as long as it was not the predominant diagnosis.

In study 641, a fixed dose design was employed in which patients were randomized in a 1:1:1 ratio to receive either 20 mg/day of paroxetine, 40 mg/day of paroxetine or placebo. Paroxetine patients initiated treatment at 10 mg/day and increased their dose in weekly increments of 10 mg until they reached their assigned dose.

A schedule of study assessments and procedures is presented in Table 2.1.1 below.

Table 2.1.1: Outline of Study Procedures for 29060/641

	Scrn Visit Day	Base Line Visit Day 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8
Screen/Baseline Evaluation								
Informed Consent	X							
MINI	X							
GAD Criteria (DSM-IV)	X							
Inclusion/Exclusion Criteria	X	X						
Patient Randomization		X						
Efficacy Parameters								
HAM-A	X	X	X	X	X	X	X	X
CGI (Severity of Illness)		X	X	X	X	X	X	X
CGI (Global Improvement)			X	X	X	X	X	X
HAD		X	X	X	X	X	X	X
COVI Anxiety Scale		X				X	X	X
Sheehan Disability Scale (SDS)		X				X	X	X
MADRS	X	X						X
Quality of Life (EuroQol)		X						X
Dispense Study Medication								X

Study 642 has an extra visit at Week 5.

In studies 637 and 642, a flexible dose design was employed in which patients were randomized in a 1:1 ratio to receive either paroxetine in a range of 20-50 mg once daily, or placebo. In study 637, patients initiated paroxetine treatment at 20 mg/day, while in study 642, the starting dose of paroxetine was 10 mg/day. Both trials permitted doses up to 50 mg/day in weekly increments of 10 mg.

All three protocols required a taper phase at the completion of the 8-week treatment period. During this phase, the paroxetine patients who were receiving doses of 30 mg or higher were titrated down at decrements of 10 mg/week to the 20 mg regimen. The taper phase was followed by a follow-up phase of 2-6 weeks duration. In study 641, patients assigned to the 20 mg regimen remained on the 20 mg daily regimen during the taper phase, in studies 637 and 642 patients receiving 20 mg per day did not participate in the taper phase.

2.2 Efficacy Variables

The outcome measures employed were identical in all three studies. Each protocol defined a single primary efficacy measure, the mean change from baseline in the Hamilton Rating Scale for Anxiety (HAM-A) Total score. The HAM-A is a reliable and validated measure of anxiety that is commonly employed in anxiety studies. Details are provided in Appendix 1.

The protocol described several secondary and global assessments of improvements as well as various symptom rating scales, the COVI, HAD and MADRS. Also defined by the protocols were assessment of the target symptoms, (HAM-A psychic anxiety and tension items), a functional disability scale (Sheehan Disability Scale), and health and economic and quality of life instruments (Job status and EURoQol).

COVI anxiety scale measures severity of anxiety. In particular, this secondary efficacy variable is an assessment of to what extent does the subject evidence anxiety in verbal report, behavior and somatic complaints. Each of these three components are evaluated in to five categories: 1=Not at all; 2=Some what; 3=Moderately; 4=Considerably; 5= Very much. The variable COVI ranges from 3 to 15.

Another secondary efficacy variable is the Clinical Global Impression (CGI) – Global Improvement score. This score was an answer to: Compared with his/her condition on admission to the study, how much has he/she changed? There were eight possible answers/scores: 0=Not assessed; 1=Very much improved; 2=Much improved; 3=Minimally improved; 4=No change; 5=Minimally worse; 6=Much worse; 7=Very much worse.

2.3 Statistical Consideration

The primary comparison of interest for efficacy was paroxetine versus placebo in the intent to treat population at the endpoint. The change from baseline of efficacy variables was analyzed by the general linear models (SAS/GLM) procedure. Type III sums of squares were used. Non-parametric methods were used for treatment comparisons when the data suggested that the underlying assumptions of the proposed parametric analysis were violated.

Categorical efficacy variables were analyzed, via categorical modeling procedure (CATMOD) of the SAS System or Cochran-Mantel-Haenszel (CMH) using the FREQ procedure of the SAS System.

All hypotheses were tested at an overall two-tailed alpha level of 0.05. In the fixed dose study, 641, Dunnett's test was used to maintain the overall experiment-wise error rate. Testing of hypothesis of significance of interactions (e.g., treatment-by-site, treatment-by-covariate) was performed at an alpha level of 0.1.

The intent to treat (ITT) population for analyses included all patients who received any double-blind medication and for who at least one valid post-baseline efficacy evaluation was conducted. This population constituted the primary population of interest for efficacy. Patients were included in the population regardless of whether the entry criteria were fulfilled or the protocol was otherwise violated.

Two data sets were used to analyze the efficacy results: last observation carried forward data set (LOCF) and observed case data set (OC). In the LOCF data set, the last available on-therapy (treatment phase) observation for each patient was used to estimate missing data points. In the OC data set, efficacy data were evaluated only for the time point when they were collected; i.e., no data were carried forward to estimate missing data points. The LOCF data set was thus generated from the OC data set.

3. SPONSOR'S ANALYSES AND CONCLUSIONS

3.1 Sponsor's data analyses results

The change from baseline of efficacy variables was analyzed by the general linear models procedure, in SAS version 6.12. Type III sums of squares were used. About the model choics, the sponsor writes (for example, in BRL-029060/RSD-101336/1/CPMS-641): The statistical model adopted for all change from baseline efficacy variables was determined by analyzing HAM-A Total at endpoint. A full model was tested using effects for treatment, investigational site, and treatment-by-site interaction. The interaction term was not significant and therefore dropped from the final analysis model. The model determined from the assessment at endpoint was used for all other time-points. All other change from baseline secondary efficacy variables were analyzed via the model determined by HAM-A Total at endpoint. The sponsor's results are reproduced in Tables 3.1.1 through 3.1.3. The sponsor claims that the *mean change* shown in these tables is the adjusted mean. These results are based on the analysis of variance with factors site and treatment without the interaction term.

Table 3.1.1*: **HAM-A Total Score Mean Baseline and Mean Change from Baseline (All Studies) (ITT Population)**

Study 641 (Fixed Dose)

	Placebo			20 mg			40 mg		
	N	Mean Change	SE	N	Mean Change	SE	N	Mean Change	SE
Baseline	180	23.9	0.3	188	23.8	0.3	197	23.3	0.3
LOCF Wk 8	180	-9.6	0.7	188	-12.5	0.6	197	-12.2	0.6
OC Wk 8	140	-10.7	0.7	141	-13.8	0.6	146	-13.9	0.6

* Source: NDA Supplement for Efficacy, Volume 001 (p. 000085)

Table 3.1.1 continued..

Study 641: Treatment Difference

	20 mg vs. Placebo		40 mg vs. Paroxetine	
	Difference (CI)+	**p-value**	**Difference (CI)+**	**p-value**
Baseline	-0.0 (-0.8, 0.7)	0.901	-0.5 (-1.3, 0.2)	0.103
LOCF Wk 8	-2.9 (-4.6, -1.2)	< 0.001*	-2.6 (-4.0, -0.6)	0.008*
OC Wk 8	-3.0 (-4.8, -1.2)	< 0.001*	-2.5 (-4.3, -0.7)	0.006*

Table 3.1.1 continued...

Study 642 (Flexible Dose)

	Placebo			Paroxetine			Placebo vs. Paroxetine	
	N	**Mean**	**SE**	**N**	**Mean**	**SE**	**Diff (CI)++**	**p-value**
Baseline	163	23.6	0.3	161	23.9	0.3	0.3 (-0.5, 1.0)	0.472
LOCF Wk 8	163	-9.5	0.7	161	-11.8	0.7	-2.3 (-4.0, -0.6)	0.008*
OC Wk 8	133	-10.7	0.8	127	-13.3	0.8	-2.5 (-4.3, -0.7)	0.006*

Study 637 (Flexible Dose)

	Placebo			Paroxetine			Placebo vs. Paroxetine	
	N	**Mean**	**SE**	**N**	**Mean**	**SE**	**Diff (CI)++**	**p-value**
Baseline	183	25.9	0.4	181	26.0	0.4	0.1 (-0.7, 1.0)	0.7888
LOCF Wk 8	183	-11.3	0.8	181	-12.4	0.8	-1.1 (-2.8, 0.5)	0.171
OC Wk 8	163	-12.5	0.8	149	-14.8	0.8	-2.3 (-3.9, -0.7)	0.005*

Table 3.1.2*: **Overview of Secondary Efficacy Variables at Week 8 LOCF (ITT Population)**

Fixed Dose Study 641

Secondary variable	**20 mg**			**40 mg**		
	Diff	(C.I)	p-value	Diff	(C.I)	p-value
Mean Change in HAM-A Item 1[+]	-0.5	(-0.8, -0.3)	< 0.001	-0.5	(-0.7, -0.2)	< 0.001
Mean Change in HAM-A Item 2[++]	-0.5	(-0.8, -0.3)	< 0.001	-0.5	(-0.8, -0.3)	< 0.001
Mean CGI Severity Score	-0.5	(-0.8, -0.3)	< 0.001	-0.5	(-0.8, -0.2)	< 0.001
Responder CGI Score 1 & 2	16.1	(4.5, 27.8)	0.002	22.5	(11.0, 33.9)	<0.001
Mean Change in COVI	-1.0	(-1.6, -0.4)	<0.001	-0.9	(-1.5, -0.3)	<0.001
[+]Item 1: Anxiety Item; [++]Item 2: Tension Item						

* Source: NDA Supplement for Efficacy, Volume 001 (p. 000085)

Table 3.1.3: **Overview of Secondary Efficacy Variables at Week 8 LOCF (ITT Population)**

Flexible Dose Studies

Secondary variable	Study 642			Study 637		
	Diff	(C.I)	p-value	Diff	(C.I)	p-value
Mean Change in HAM-A Item 1*	-0.4	(-0.6, -0.2)	0.001	-0.3	(-0.5, -0.1)	0.041
Mean Change in HAM-A Item 2**	-0.3	(-0.5, -0.1)	0.005	-0.2	(-0.4, 0.0)	0.071
Mean CGI Severity Score	-0.3	(-0.5, 0.0)	0.042	-0.3	(-0.5, 0.0)	0.027
Responder CGI Score 1 & 2	14.9	(4.0, 25.7)	0.007	13.3	(3.1, 23.4)	0.011
Mean Change in COVI	-0.6	(-1.2, 0.0)	0.058	-0.5	(-1.0, 0.0)	0.059
*Item 1: Anxiety Item; **Item 2: Tension Item						

3.2 Sponsor's Efficacy Summary and Conclusions

In summary, the results from these well-controlled clinical trials provide convincing evidence that paroxetine is effective in the treatment of Generalized Anxiety Disorder. Collectively the results derived from the primary and secondary measures clearly demonstrate that the effects of paroxetine are robust and clinically meaningful. In addition, the results allow clear recommendation for the dosing of paroxetine in the treatment of Generalized Anxiety Disorder.

4. REVIEWER'S ANALYSES AND COMMENTS

The protocol defined the primary efficacy variable as the change from baseline in the total HAM-A score at the week 8 endpoint for all three studies. Technically, HAM-A Total score ranges from 0 to 56. Lower HAM-A Total score means that the subject is close to *normal*. The protocol defined primary efficacy variable- change from baseline in the Week 8 HAM-A Total score which is abbreviated as HMA_DTOT, as used in this review, is

HMA_DTOT = Week 8 HAM-A Total - Baseline HMA-A Total .

Analysis of covariance (ANCOVA) that includes the terms treatment and site is the protocol specified method of analysis for all three studies.

4.1 Study 641- Fixed dose study

Demographics

The LOCF population of this study consisted of 314 (55.6%) females and 251 (44.4%) males. There were 476 (84.2%) Caucasians, 26 (4.6%) Blacks, 10 (1.8%) Orientals. The remaining 53 (9.4%) belonged to other races. The youngest of these patients was 18 years old and the oldest was 74. The average age was 40.5 years.

Baseline comparison

- The data from Baseline Visit contained 162, 172 and 179 observations on the HAM-A Total score under placebo, Paxil 20 mg and Paxil 40 mg groups, respectively. The

mean baseline HAM-A Totals for placebo, 20 mg and 40 mg of paroxetine were 24.42, 24.06 and 23.92, respectively. One way analysis of variance indicated that there is no significant differences among these three treatment groups (p-value = 0.4197).

- One-way analysis of variance on the baseline HAM-A Total indicated that the three treatment groups- placebo, paroxetine 20mg and paroxetine 40mg are not significantly different (p-value = 0.404). The data from Baseline Visit contained 185 and 187 observations on severity of illness (CGI_RSEV) under placebo and Paxil groups, respectively. The median observation was 4 in both treatment groups. The Wilcoxon rank-sum test indicates that there was no significant difference among the two treatment groups (p-value = 0.914) with respect to severity of illness.

Protocol defined Primary efficacy endpoint HMA_DTOT

LOCF analysis

The LOCF data contain a total of 565 observations. Of these 565, the treatment groups placebo, Paxil 20 mg, and Paxil 40 mg had 180, 188 and 197 observations, respectively. The SAS output for the analysis of variance model on the primary efficacy variable that includes the terms for treatment and site is presented below. The data provide sufficient evidence to claim that each of the two paroxetine groups is statistically significantly different from placebo and that the two paroxetine- groups 20 mg/day and 40 mg/day are not significantly different with respect to the change from baseline in the Week 8 HAM-A Total scores. The LOCF observed means of the protocol defined primary efficacy variable for placebo, paroxetine 20 mg and paroxetine 40 mg are –9.74, -12.56 and –12.23, respectively.

SAS OUTPUT: STUDY 641- LOCF DATA

General Linear Models Procedure

Dependent Variable: HMA_DTOT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	44	4170.8230165	94.7914322	1.80	0.0017
Error	520	27441.0884879	52.7713240		
Corrected Total	564	31611.9115044			

R-Square	C.V.	Root MSE	HMA_DTOT Mean
0.131938	-62.90236	7.2643874	-11.548673

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	42	3326.6346188	79.2055862	1.50	0.0251
TRT	2	861.1286804	430.5643402	8.16	0.0003

General Linear Models Procedure
Least Squares Means

TRT	HMA_DTOT LSMEAN	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3
0	-9.7362504	1	.	0.0002	0.0010
20	-12.5621739	2	0.0002	.	0.6592
40	-12.2317917	3	0.0010	0.6592	.

OC analysis

The OC data contain a total of 427 observations on the protocol defined primary efficacy variable.. Of these 427, the treatment groups placebo, Paxil 20 mg, and Paxil 40 mg had 180, 188 and 197 observations, respectively. The SAS output for the analysis of variance model that includes the terms for treatment and site is presented below. The data provide sufficient evidence to claim that each of the two paroxetine groups is statistically significantly different from placebo and that the two paroxetine- groups 20 mg/day and 40 mg/day are not significantly different with respect to the change from baseline in the Week 8 HAM-A Total scores. The adjusted means of the primary efficacy variable for placebo, paroxetine 20 mg and 40 mg are –11.0, -13.94 and –14.06, respectively.

SAS OUTPUT: STUDY 641- OC DATA
General Linear Models Procedure

Dependent Variable: HMA_DTOT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	44	4632.4176899	105.2822202	2.44	0.0001
Error	382	16475.3434342	43.1291713		
Corrected Total	426	21107.7611241			

R-Square	C.V.	Root MSE	DIFF Mean
0.219465	-50.72773	6.5672804	-12.946136

Source	DF	Type III SS	Mean Square	F Value	Pr > F
BLOCK	42	3792.9175351	90.3075604	2.09	0.0002
TRT	2	811.1196013	405.5598006	9.40	0.0001

General Linear Models Procedure
Least Squares Means

TRT	LSMEAN	DIFF i/j	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) 1	2	3
0	-10.9969062	1	.	0.0003	0.0001
20	-13.9394710	2	0.0003	.	0.8828
40	-14.0561945	3	0.0001	0.8828	.

Secondary efficacy variable HMA_DIT1
LOCF analysis

HMA_DIT1 is the change from baseline in the Week 8 Hamilton Rating Scale Item 1 (Anxiety Item). The LOCF data contain 180, 188 and 197 observations under placebo, Paxil 20 mg and Paxil 40 mg, respectively. The analysis of variance model that includes terms treatment and site yields adjusted means of –0.93, -1.46 and –1.40, respectively for placebo and Paxil 20 mg and Paxil 40 mg, respectively. Furthermore, these data provide sufficient evidence to claim that each of the paroxetine groups is significantly different from placebo (p-value < 0.001). There is no significant difference between the two paroxetine groups- 20 mg and 40 mg (p-value = 0.547).

Secondary efficacy variable HMA_DIT1
OC analysis

The OC data contain 140, 141 and 146 observations under placebo, Paxil 20 mg and Paxil 40 mg, respectively. The analysis of variance model that includes terms treatment and site yields adjusted means of –1.13, -1.63 and –1.63, respectively for placebo and Paxil 20 mg and Paxil 40 mg, respectively. Furthermore, these data provide sufficient evidence to claim that each of the paroxetine groups is significantly different from placebo (p-value = 0.0001). There is no significant difference between the two paroxetine groups- 20 mg and 40 mg (p-value = 0.9906).

Secondary efficacy variable HMA_DIT2

LOCF analysis

HMA_DIT2 is the change from baseline in the Week 8 Hamilton Rating Scale Item 2 (Tension Item). The LOCF data contain 180, 188 and 197 observations under placebo, Paxil 20 mg and Paxil 40 mg, respectively. The analysis of variance model that includes terms for treatment and site yields adjusted means of –0.89, -1.42 and –1.42, respectively for placebo and Paxil 20 mg and Paxil 40 mg, respectively. Furthermore, these data provide sufficient evidence to claim that each of the paroxetine groups is significantly different from placebo (p-value < 0.001). There is no significant difference between the two paroxetine groups (p-value = 0.976).

Secondary efficacy variable HMA_DIT2

OC analysis

The OC data contain 140, 141 and 146 observations under placebo, Paxil 20 mg and Paxil 40 mg, respectively. The analysis of variance model that includes terms for treatment and site yields adjusted means of –1.06, -1.57 and –1.71, respectively for placebo and Paxil 20 mg and Paxil 40 mg, respectively. Furthermore, these data provide sufficient evidence to claim that each of the paroxetine groups is significantly different from placebo (p-value = 0.0001). There is no significant difference between the two paroxetine groups (p-value = 0.2353).

Secondary efficacy variable COV_DTOT

LOCF analysis

The secondary efficacy variable COV_DTOT represents the change from baseline in the Week 8 COVI Anxiety scale. That is,

COV_DTOT = Week 8 COVI Total score – Baseline COVI Total score.

The LOCF data on COV_DTOT has 163, 173 and 179 observations under placebo, Paxil 20 mg and Paxil40 mg, respectively, with observed means of –2.4, -3.31 and –3.29. The normality assumption for any (one-way or two-way) analysis of variance model for the change from baseline in the Week 8 COVI anxiety scale COV_DTOT (for treatment comparison) does not hold good (p-value < 0.05). However, the Wilcoxon rank-sum test for these data indicates the three treatment groups are significantly different (p-value = 0.0002). Results of pair-wise analyses of COV_DTOT are as follows. (a) Paroxetine 20 mg is significantly different from placebo (p-value = 0.0003). (b) Paroxetine 40 mg is significantly different from placebo (p-value = 0.0005). (c) The two paroxetine groups are not significantly different (p-value = 0.7862).

Secondary efficacy variable COV_DTOT

OC analysis

The OC data on COV_DTOT has 140, 141 and 144 observations under placebo, Paxil 20 mg and Paxil40 mg, respectively, with observed means of –2.55, -3.69 and –3.54. The Wilcoxon rank-sum test for these data indicates the three treatment groups are significantly different (p-value = 0.0001). Results of pair-wise analyses of COV_DTOT

are as follows. (a) Paroxetine 20 mg is significantly different from placebo (p-value = 0.0001). (b) Paroxetine 40 mg is significantly different from placebo (p-value = 0.0003). (c) The two paroxetine groups are not significantly different (p-value = 0.645).

Secondary efficacy variable CGI_DSEV

LOCF analysis

The secondary efficacy variable CGI_DSEV represents the change from baseline in the Week 8 Illness Severity. That is,

CGI_DSEV = Week 8 Illness Severity – Baseline Illness Severity.

The LOCF data on CGI_DSEV has 180, 188 and 197 observations under placebo, Paxil 20 mg and Paxil40 mg, respectively. One-way analysis of variance yields a mean of –1.06, -1.56 and –1.55 for placebo, Paxil 20 mg and Paxil 40 mg, respectivley. Results of pair-wise analyses of CGI_DSEV are as follows. (a) Paroxetine 20 mg is significantly different from placebo (p-value = 0.0001). (b) Paroxetine 40 mg is significantly different from placebo (p-value = 0.0001). (c) The two paroxetine groups are not significantly different (p-value = 0.9314).

Secondary efficacy variable CGI_DSEV

OC analysis

The LOCF data on CGI_DSEV has 140, 140 and 146 observations under placebo, Paxil 20 mg and Paxil40 mg, respectively. One-way analysis of variance yields a mean of –1.2, -1.77 and –1.87 for placebo, Paxil 20 mg and Paxil 40 mg, respectivley. Results of pair-wise analyses of CGI_DSEV are as follows. (a) Paroxetine 20 mg is significantly different from placebo (p-value = 0.0001). (b) Paroxetine 40 mg is significantly different from placebo (p-value = 0.0001). (c) The two paroxetine groups are not significantly different (p-value = 0.4798).

Subgroup analysis – by sex (LOCF)

Analysis of variance shows that the two gender groups were not significantly different with respect to the change from baseline in the Week 8 HAM-A Total score. The data for the subgroup of females (only) indicated that both paroxetine groups are significantly different from placebo. However, the data for the subgroup of males (only) indicated that only the paroxetine 40 mg is significantly different from placebo.

4.2 Study 642- Flexible dose study

Demographics

The LOCF population of this study consisted of 206 (63.6%) females and 118 (36.4%) males. There were 271 (83.6%) Caucasians, 12 (3.7%) Blacks, 2 (0.6%) Orientals. The remaining 39 (12%) belonged to other races. The youngest of these patients was 19 years old and the oldest was 80. The average age was 40.5 years.

Baseline comparison

- The data from Baseline Visit contained 164 and 162 observations on the HAM-A Total (HMA_RTOT) under placebo and Paxil groups, respectively. The means for placebo and Paxil groups were 24.13 and 24.26, respectively. One-way analysis of variance indicates that there was no significant difference among the two treatment groups (p-value = 0.7434) with respect to the HAM-A Total score.

- The data from Baseline Visit contained 164 and 162 observations on severity of illness (CGI_RSEV) under placebo and Paxil groups, respectively. The median observation was 4 in both treatment groups. The Wilcoxon rank-sum test indicates that there was no significant difference among the two treatment groups (p-value = 0.4965) with respect to severity of illness.

Protocol defined Primary efficacy endpoint HMA_DTOT
LOCF analysis

As mentioned earlier, the sponsor analyzes the primary efficacy variable by the general linear models (SAS/GLM). This reviewer pooled all the small sites with less than 5 patients. The data contain 163 and 161 observations under placebo and Paxil, respectively. The analysis of variance model that includes terms for treatment and site indicates that Paxil and placebo are significantly different (p-value = 0.0077). The adjusted mean changes for placebo and Paxil are –9.53 and –11.81, respectively. That is, the reduction in the Week 8 HAM-A under paroxetine is significantly larger compared to placebo.

Protocol defined Primary efficacy endpoint HMA_DTOT
OC analysis

The OC data contains 133 and 127 observations under placebo and Paxil, respectively. Once again, This reviewer pooled all the small sites with less than 5 patients. The analysis of variance model that includes terms for treatment and site yields adjusted means of –10.66 and –13.23 for placebo and Paxil, respectively. The OC data do provide sufficient evidence to conclude that the test drug is significantly different from placebo (p-value = 0.0044). That is, the reduction in the Week 8 HAM-A under paroxetine is significantly larger compared to placebo.

Secondary efficacy variable HMA_DIT1
LOCF analysis

The LOCF data contain 163 and 161 observations under placebo, and Paxil, respectively. The analysis of variance model that includes terms for treatment yields adjusted means of –0.91, and –1.31, respectively for placebo and Paxil, respectively. Furthermore, these data provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.0007). That is, the reduction in the Week 8 Hamilton Item 1 score under paroxetine is significantly larger compared to placebo.

Secondary efficacy variable HMA_DIT1

OC analysis

The OC data contain 140 and 132 observations under placebo, and Paxil, respectively. The analysis of variance model to compare treatments yields adjusted means of –1.11, and –1.54, respectively for placebo and Paxil, respectively. Furthermore, these data provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.0008). In other words, the reduction in the Week 8 Hamilton Item 1 score under paroxetine is significantly larger compared to placebo.

Secondary efficacy variable HMA_DIT2

LOCF analysis

The LOCF data contain 163 and 161 observations under placebo, and Paxil, respectively. The analysis of variance model that includes terms for treatment and site yields adjusted means of –0.88, and –1.20, respectively for placebo and Paxil, respectively. These data provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.0043). That is, the reduction in the Week 8 Hamilton Item 2 score under paroxetine is significantly larger compared to placebo.

Secondary efficacy variable HMA_DIT2

OC analysis

The LOCF data contain 140 and 132 observations under placebo, and Paxil, respectively. The analysis of variance model to compare treatments yields adjusted means of –1.02, and –1.43, respectively for placebo and Paxil, respectively. These data do provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.0016). In other words, the reduction in the Week 8 Hamilton Item 2 score under paroxetine is significantly larger compared to placebo.

Secondary efficacy variable COV_DTOT

LOCF analysis

The LOCF analysis of data on COV_DTOT contains 154 and 152 observations under placebo and Paxil, respectively. The analysis of variance model with terms for treatment and site gives adjusted means of –2.53 and –3.1 for placebo and Paxil, respectively. The LOCF data do not provide sufficient evidence to indicate that the two treatment groups are significantly different (p-value = 0.0576).

Secondary efficacy variable COV_DTOT

OC analysis

The OC analysis of data on COV_DTOT contains 133 and 125 observations under placebo and Paxil, respectively. The analysis of variance model with terms for comparing treatments gives adjusted means of –2.8 and –3.41 for placebo and Paxil, respectively. The OC data do not provide sufficient evidence to indicate that the two treatment groups are significantly different (p-value = 0.059).

Secondary efficacy variable CGI_DSEV
LOCF analysis

The LOCF analysis of data on CGI_DSEV contains 163 and 161 observations under placebo and Paxil, respectively. The one-way analysis of variance gives estimated means of –1.07 and –1.27 for placebo and Paxil, respectively. The LOCF data do not provide sufficient evidence to conclude that the two treatment groups are significantly different (p-value = 0.1499).

Secondary efficacy variable CGI_DSEV
OC analysis

The OC analysis of data on CGI_DSEV contains 140 and 132 observations under placebo and Paxil, respectively. The analysis of variance (with factors- sites and treatment) gives adjusted means of –1.26 and –1.51 for placebo and Paxil, respectively. The OC data do not provide sufficient evidence to conclude that the two treatment groups are significantly different (p-value = 0.0838).

Subgroup analysis – by sex (LOCF)

Analysis of variance shows that the two gender groups were not significantly different with respect to the change from baseline in the Week 8 HAM-A Total score. The data for the subgroup of females (only) indicated that Paxil is not significantly different from placebo. This was also the case for males.

4.3 Study 637- Flexible dose study

Demographics

The LOCF population of this study consisted of 256 (70.3%) females and 108 (29.7%) males. Almost all, 262 (99.5%) patients were Caucasians and only 2 belonged to other racial groups. The youngest of these patients was 18 years old and the oldest was 78. The average age was 46.1 years.

Baseline comparison

- The data from Baseline Visit contained 185 and 187 observations on the HAM-A Total (HMA_RTOT) under placebo and Paxil groups, respectively. The means for placebo and Paxil groups were 25.64 and 25.64, respectively. One-way analysis of variance indicates that there was no significant difference among the two treatment groups (p-value = 0.9975) with respect to the HAM-A Total score.

- The data from Baseline Visit contained 185 and 187 observations on severity of illness (CGI_RSEV) under placebo and Paxil groups, respectively. The median observation was 4 in both treatment groups. The Wilcoxon rank-sum test indicates that there was no significant difference among the two treatment groups (p-value = 0.914) with respect to severity of illness.

Protocol defined Primary efficacy endpoint HMA_DTOT
LOCF analysis

The LOCF data contain 183 and 181 observations in placebo and paroxetine, respectively. There were 23 sites (out of 45) with less than 4 subjects. Seven sites had just 1 subject each. Therefore, this reviewer kept the site factor out of analysis. The one-way analysis of variance model to compare the treatments shows that paroxetine and placebo are not significantly different (p-value = 0.2808). The mean change from baseline in Week 8 HAM-A total score under paroxetine and placebo are -13.52 and –12.52, respectively. That is, the reduction in the Week 8 HAM-A total score under paroxetine is not significantly different from placebo.

Protocol defined Primary efficacy endpoint HMA_DTOT
OC analysis

The OC data at Week 8 contained 163 and 149 observations under placebo and paroxetine groups, respectively. The one-way analysis of variance model to compare the treatments shows that paroxetine and placebo are significantly different (p-value = 0.0262). The mean change from baseline in Week 8 HAM-A score under paroxetine and placebo are –15.4 and –13.37, respectively. In other words, the reduction in the Week 8 HAM-A total score under paroxetine is significantly higher compared to placebo.

Secondary efficacy variable HMA_DIT1
LOCF analysis

The LOCF data contain 183 and 181 observations under placebo, and Paxil, respectively. The analysis of variance model to compare the treatments yields adjusted means of –1.10, and –1.38, respectively for placebo and Paxil, respectively. Furthermore, these data provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.0114). That is, the LOCF data on Hamilton Item 1 score support the efficacy of Paxil Tablets.

Secondary efficacy variable HMA_DIT1
OC analysis

The OC data contain 163 and 149 observations under placebo, and Paxil, respectively. The analysis of variance model to compare treatments yields adjusted means of –1.21, and –1.54, respectively for placebo and Paxil, respectively. Furthermore, these data provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.0031). In other words, the OC data on Hamilton Item 1 score support the efficacy of Paxil Tablets.

Secondary efficacy variable HMA_DIT2
LOCF analysis

The LOCF data contain 183 and 181 observations under placebo, and Paxil, respectively. The analysis of variance mode to compare treatments yields adjusted means of –1.08, and –1.27, respectively for placebo and Paxil, respectively. Furthermore, these data do not

provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.071). That is, the LOCF data on Hamilton Item 1 score do not support the efficacy of Paxil Tablets.

Secondary efficacy variable HMA_DIT2

OC analysis

The OC data contain 163 and 149 observations under placebo, and Paxil, respectively. The analysis of variance model to compare treatments yields adjusted means of –1.24, and –1.56, respectively for placebo and Paxil, respectively. Furthermore, these data provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.004). In other words, the OC data on Hamilton Item 1 score support the efficacy of Paxil Tablets.

Secondary efficacy variable COV_DTOT

LOCF analysis

The LOCF analysis of data on COV_DTOT contains 178 and 175 observations under placebo and Paxil, respectively. The one-way analysis of variance gives adjusted means of –2.74 and –3.16 for placebo and Paxil, respectively. The LOCF data do not provide sufficient evidence to indicate that the two treatment groups are significantly different (p-value = 0.1461).

Secondary efficacy variable COV_DTOT

OC analysis

The OC analysis of data on COV_DTOT contains 163 and 149 observations under placebo and Paxil, respectively. The one-way analysis of variance gives adjusted means of –2.94 and –3.46 for placebo and Paxil, respectively. The OC data do not provide sufficient evidence to indicate that the two treatment groups are significantly different (p-value = 0.081).

Secondary efficacy variable CGI_DSEV

LOCF analysis

The LOCF analysis of data on CGI_DSEV contains 183 and 181 observations under placebo and Paxil, respectively. The one-way analysis of variance gives adjusted means of –1.17 and –1.45 for placebo and Paxil, respectively. The LOCF data provide sufficient evidence to conclude that the two treatment groups are significantly different (p-value = 0.0271).

Secondary efficacy variable CGI_DSEV

OC analysis

The OC analysis of data on CGI_DSEV contains 163 and 149 observations under placebo and Paxil, respectively. The one-way analysis of variance gives adjusted means of –1.3 and –1.7 for placebo and Paxil, respectively. The LOCF data provide sufficient evidence to conclude that the two treatment groups are significantly different (p-value = 0.0047).

Subgroup analysis – by sex (LOCF)

Analysis of variance shows that the two gender groups were not significantly different with respect to the change from baseline in the Week 8 HAM-A Total score. The data for the subgroup of females (only) indicated that Paxil is not significantly different from placebo. This was also the case for males.

4.4 Efficacy results- in tabular form

Table 4.4.1: Reviewer's Summary of efficacy results

Study	Efficacy Endpoint	LOCF analysis	OC analysis
637	**Primary**	Not significant (p-value 0.281)	Significant (p-value 0.0262)
	Secondary HMA_Item 1 HMA_Item2	Significant (p-value = 0.0114) **Not** significant (p-value = 0.127)	Significant (p-value = 0.0031) Significant (p-value = 0.0083)
641	**Primary**	Both Paxil groups 20 mg and 40 mg are significantly different from placebo (p-value < 0.01)	Both Paxil groups 20 mg and 40 mg are significantly different from placebo (p-value < 0.01)
	Secondary HMA_Item1 HMA_Item2	Both Paxil groups 20 mg and 40 mg are significantly different from placebo (p-value < 0.01) *	Both Paxil groups 20 mg and 40 mg are significantly different from placebo (p-value < 0.01) *
642	**Primary**	Significant (p-value 0.0077)	Significant (p-value = 0.0044)
	Secondary HMA_Item1 HMA_Item2	Significant (p-value = 0.0007) Significant (p-value = 0.0043)	Significant (p-value = 0.0008) Significant (p-value = 0.0016)

* for both secondary efficacy variables..

Table 4.4.2: **Endpoint (WK-8) HMA_DTOT adjusted means**
ITT Population-LOCF analyses

Study 637		**Study 641**		**Study 642**	
Treatment	Mean	Treatment	Mean	Treatment	Mean
Placebo	-12.52	Placebo	-9.74	Placebo	-9.53
Paroxetine	-13.52	Paxil 20 mg	-12.56	Paroxetine	-11.81
		Paxil 40 mg	-12.23		

Table 4.4.3: Adjusted Mean Differences and Standard Errors
Study 641- LOCF data

	Paxil 20mg-Placebo	Paxil 40 mg-Placebo	Paxil 20mg-Paxil 40m
Difference	-2.826	-2.496	-0.33
Standard Error	0.759	0.751	0.742

Table 4.4.4: Adjusted Mean Difference: Paxil-Placebo
LOCF data

Study 642		Study 637	
Difference	Standard Error	Difference	Standard Error
-2.28	0.706	-1.0	0.921

5. OVERALL CONCLUSIONS

- The data from **Study 641** provide sufficient evidence to claim that the change from baseline in the Week 8 Hamilton Anxiety scale under paroxetine is significantly larger than that of under placebo. That is, Study 641 data on the protocol defined primary efficacy indicate that paroxetine is effective in the treatment of Generalized Anxiety Disorder. The Study 641 data on several secondary efficacy variables are supportive of this conclusion.

- The efficacy data from **Study 642** also provide sufficient evidence to claim that paroxetine is effective in the treatment of Generalized Anxiety Disorder. That is, the change from baseline in the Week 8 Hamilton Anxiety scale under paroxetine is significantly larger than that of under placebo. The Study 642 data on several secondary efficacy variables support the efficacy of the study drug.

- However, the efficacy data from **Study 637** do not provide sufficient evidence to claim that paroxetine is effective in the treatment of Generalized Anxiety Disorder.

/S/

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HFD-710 / Dr. Chi
HFD-710 / Dr. Jin
HFD-710 / Dr. Koti
HFD-710 / Chron

6. APPENDIX

HAMILTON ANXIETY RATING SCALE (HAM-A): They are based on the following fourteen items.

1. **Anxious Mood** (worries, anticipation of the worst, fearful anticipation, irritability).
2. **Tension** (feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax).
3. **Fears** (of dark, of strangers, of being left alone, of animals of traffic, of crowds).
4. **Insomnia** (difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors).
5. **Intellectual** (difficulty in concentration, poor memory).
6. **Depressed mood** (loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing).
7. **Somatic-Muscular** (pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone).
8. **Somatic-Sensory** (tinnitus, blurring of vision, hot and cold flashes, feelings of weakness, prickling sensation).
9. **Cardiovascular symptoms** (tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat).
10. **Respiratory symptoms** (pressure or constriction in chest, choking feelings, sighing, dyspnea).
11. **Gastrointestinal symptoms** (difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation).
12. **Genitourinary Symptoms** (frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence).
13. **Autonomic symptoms** (dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, rising of hair).
14. **Behavior at Interview** (fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos).

Each had five possible response levels:

0 = Not present; 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very Severe.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-031/S-026

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

ITEM 13/14 - PATENT INFORMATION

The following patent information is being submitted pursuant to 21 C.F.R. 314.53.

Patent No.	Expiry Date	Type of Patent	Patent owner
4 721 723	December 29, 2006	Drug	Beecham Group p.l.c. Brentford, England
5 872 132	May 19, 2015	Drug	SmithKline Beecham Corp.
5 900 423	May 19, 2015	Drug	SmithKline Beecham Corp.

EXCLUSIVITY SUMMARY for NDA # 20-031 SUPPL # S-026
Trade Name Paxil Generic Name paroxetine HCl

Applicant Name GlaxoSmithKline HFD- 120

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE-1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /__/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-031 _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # Study 641

Investigation #2, Study # Study 642

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # Study 641

Investigation #__, Study # Study 642

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # 23,280 YES /_X_/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # 23,280 YES /_X_/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title:_____

/S/ 4/13/01

Signature of Office of Division Director Date

cc:
Archival NDA
HFD-120/Division File
HFD-120/Homonnay
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

M E M O R A N D U M

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

DATE: January 28, 2001

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

SUBJECT: Recommendation for Approvable Action for
Paxil tablets (paroxetine) for the treatment of generalized anxiety disorder

TO: File NDA 20-031/S-026
[**Note:** This overview should be filed with the 4-28-00
original submission.]

1.0 BACKGROUND

Paroxetine is a selective serotonin reuptake inhibitor currently approved and marketed for depression, OCD, panic disorder, and social anxiety disorder in an immediate release tablet, i.e., Paxil (NDA 20-031, originally approved for depression in December, 1992). S-026 provides data in support of a new claim for this same Paxil tablet in the treatment of generalized anxiety disorder (GAD) in a dose range of 20-50 mg/day.

It should be noted that, at the current time, there are a number of older drugs, mostly benzodiazepines, approved for the treatment of what is now known as GAD. At the time of these approvals, the approach to labeling was to grant a claim for the "management of anxiety disorders or for the short-term relief of the symptoms of anxiety." Buspirone (Buspar), a nonbenzodiazepine compound with a primary serotonergic effect, i.e., it's a prominent 5HTA1 agonist, is a more recent drug that was approved for a similar claim in 1985. More recently, venlafaxine (Effexor XR), a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a weak inhibitor of neuronal dopamine reuptake, was the first drug approved explicitly for GAD (3-11-99).

Given the symptom overlap in patients with depression and GAD, one of the concerns identified early in the development of this new indication for venlafaxine was how this overlap would be sorted out in making a judgement regarding the specific benefit of this product in GAD. During the review of the Effexor XR

application for GAD, we were persuaded that there was an effect of this drug specific to GAD that would justify this specific claim.

We held an end-of-phase 2 meeting with SKB on 9-3-98 to discuss the sponsor's development program for Paxil in GAD. We generally endorsed the planned program, but did indicate that we would need to address the question of specificity of response to GAD, e.g., by showing an effect on HAM-A items 1 (anxiety) and 2 (tension).

Since the proposal is to use the currently approved Paxil immediate release tablets for this expanded population, there was no need for chemistry, pharmacology, or biopharmaceutical reviews of this supplement. The focus was on clinical data. The primary review of the efficacy and safety data was done by Karen Brugge, M.D., from the clinical group. Kallappa Koti, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The studies supporting this supplement were conducted under IND 23,280. The original supplement for this expanded indication (S-026) was submitted 4-28-00.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

As Paxil tablets are already marketed, there were no CMC issues requiring review for this supplement.

3.0 PHARMACOLOGY

As Paxil tablets are already marketed, there were no pharm/tox issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

As Paxil tablets are already marketed, there were no biopharmaceutics issues requiring review for this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of 3 double-blind, randomized, 8-week, placebo-controlled trials (641, 642, and 637) in adult outpatients meeting DSM-IV criteria for generalized anxiety disorder (GAD). The identified primary outcome measure for these studies was change from baseline for the Hamilton Anxiety Rating Scale (HAM-A) total score. The HAM-A is a widely used instrument in evaluating treatments for GAD, and has been shown to be sensitive to drug effects. Its total score ranges from 0 to 56 (14 items with ratings from 0-4). There were several secondary outcome measures in these trials, including, among others, HAM-A items 1 (anxiety) and 2 (tension), and the CGI.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study 641

This was a randomized, double-blind, parallel group, 8-week, fixed-dose study (50 US and Canadian sites) comparing paroxetine immediate release tablets (20 or 40 mg/day, taken as a single am dose) and placebo in adult outpatients meeting DSM-IV criteria for GAD. Patients were started at 10 mg, and doses were increased at 10 mg weekly increments until the assigned dose was reached. Patients could not have other Axis I disorders, in particular, major depression. However, patients with co-morbid dysthymic disorder could be included. There were 180-197 patients per group in the sample analyzed, with the % completing to 12 weeks ranging from 73-78%.

Overall, the HAM-A total score results from this study consistently favored paroxetine over placebo for both dose groups at weeks 6 and 8 for both LOCF and OC analyses. The p-values were < 0.001 at week 8 for both doses in the OC analyses, and < 0.001 and < 0.01, respectively, for the 20 and 40 mg/day doses in the LOCF analyses. Dunnett's test was used to adjust for the two doses. For the CGI Improvement, 80% of paroxetine 40 mg completers and 68% of paroxetine 20 mg completers met the response criterion (score of 1 or 2) compared to 52% for placebo. For the HAM-A total score, the difference between paroxetine and placebo in mean change from baseline for both the LOCF and OC analyses at 8 weeks, for both 20 and 40 mg, was roughly 3 units. Paroxetine was also superior to placebo for both dose groups, both LOCF and OC analyses, for HAM-A items 1 and 2.

5.1.2.2 Study 642

This was a randomized, double-blind, parallel group, 8-week, flexible-dose study (35 US and Canadian sites) comparing paroxetine immediate release tablets (20 to 50 mg/day, taken as a single am dose) and placebo in adult outpatients meeting DSM-IV criteria for GAD. Patients were started at 10 mg and were titrated in weekly increments of 10 mg. Patients could not have other Axis I disorders, in particular, major depression. However, patients with co-morbid dysthymic disorder could be included. There were roughly 150 patients per group in the sample analyzed, with the % completing to 12 weeks ranging from 77-81%. The mean week 8 paroxetine dose for completers was 37 mg.

Overall, the HAM-A total score results from this study consistently favored paroxetine over placebo at weeks 6 and 8 for both LOCF and OC analyses. The p-values were 0.006 at week 8 in the OC analysis, and 0.008 at week 8 in the LOCF analysis. For the CGI Improvement, 72% of paroxetine completers met the response criterion (score of 1 or 2) compared to 56% for placebo. For the HAM-A total score, the difference between paroxetine and placebo in mean change from baseline for both the LOCF and OC analyses at 8 weeks was roughly 2.5 units. Paroxetine was also superior to placebo, on both LOCF and OC analyses, for HAM-A items 1 and 2.

5.1.2.2 Study 637

This was a randomized, double-blind, parallel group, 8-week, flexible-dose study (50 European sites) comparing paroxetine immediate release tablets (20 to 50 mg/day, taken as a single am dose) and placebo in adult outpatients meeting DSM-IV criteria for GAD. Patients were started at 20 mg and were titrated in weekly increments of 10 mg. Patients could not have other Axis I disorders, in particular, major depression. However, patients with co-morbid dysthymic disorder could be included. There were roughly 185 patients per group in the sample analyzed, with the % completing to 12 weeks ranging from 82-88%. The mean week 8 paroxetine dose for completers was 27 mg.
Overall, the HAM-A total score results from this study did not favor paroxetine over placebo at weeks 6 or 8 for the LOCF analysis. The p-values were 0.111 at week 6 and 0.171 at week 8, in the LOCF analyses. Paroxetine was superior to placebo in the OC analysis, for both week 6 (p=0.001) and week 8 (p=0.005). For the CGI Improvement, 73% of paroxetine completers met the response criterion (score of 1 or 2) compared to 55% for placebo. For the HAM-A total score, the difference between paroxetine and placebo in mean change from baseline at 8 weeks was 1.1 units for the LOCF and 2.3 for the OC analyses. Paroxetine was superior to placebo, on both LOCF and OC analyses, for HAM-A item 1, and on the OC analysis for item 2.

5.1.3 Comment on Other Important Clinical Issues Regarding Paxil for Social Phobia

Evidence Bearing on the Question of Dose/Response for Efficacy

Of the 3 studies in the development program, two involved flexible dosing in a range of 20-50 mg/day (642 & 637), and thus, provided no evidence pertinent to the issue of dose response. The mean doses for completers to 8 weeks in these two studies were 37 and 27 mg/day, respectively, but these findings are not interpretable regarding dose response since patients in such trials are often pushed to the higher end of the permitted dose range, regardless of need. Study 641 was most informative regarding dose response, and this study suggested no advantage at a dose of 40 mg compared to 20 mg/day. Thus labeling must be clear in noting that the only pertinent evidence suggests no benefit in doses above 20 mg/day.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender. There was no indication of differences in response based on gender.

Size of Treatment Effect

It is difficult to clinically interpret the effect sizes on the measures observed for these 3 studies in terms of differences between drug and placebo in change from baseline. HAM-A total scores were roughly 24 for the 2 positive studies at baseline, and in the LOCF analyses, there were decreases of roughly 12 units at the week 8 endpoint for patients assigned to paroxetine. As is the case for other psychiatric indications, the mean score after treatment was still within a range that would be considered clinically ill. On the other hand, these changes are consistent with those seen for other drugs believed to be effective for GAD, so I am inclined to consider this a clinically relevant treatment effect.

Duration of Treatment

There were no data presented in this supplement pertinent to the question of the long-term efficacy of Paxil for GAD.

Specificity of Response for GAD

Although there was a finding of greater improvement on the MADRS in patients on paroxetine compared to placbeo, this is not surprising, given the overlap in symptoms of various depressive disorders and GAD. Patients with significant depression were not enrolled in these trials. In addition, these studies showed superiority of paroxetine over placebo on items 1 (anxiety) and 2 (tension) of the HAM-A, both considered reasonably specific for GAD. Thus, I consider this a reasonable demonstration of a specific response to paroxetine in patients with GAD.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of a beneficial effect of Paxil tablets in the treatment of GAD. Studies 641 and 642 are both positive, both on the primary outcome and most secondary outcomes, and study 637 shows effect sizes of the same magnitude and is at least supportive. The sponsor is currently conducting a relapse prevention trial. Since GAD is also a disorder found in the pediatric population and, once approved for this indication, Paxil will likely be used in pediatric patients, we will require adequate and well-controlled trials of Paxil for GAD in this population as well.

5.2 Safety Data

Dr. Brugge's safety review of S-026 was based on an integrated database consisting of a pooling of safety data for the three 8-week studies. There was no safety update.

Overall, 735 patients were exposed to Paxil in the sponsor's development program for generalized anxiety disorder. This represented an exposure time on paroxetine of approximately 100 years. Patients in this integrated database were roughly 2/3 female and predominantly white. The mean ages for the 3 studies ranged from 40 to 45 years of age. Seventy-five percent of exposure was in the 11-30 mg/day range, with about 20% having mean doses over 30 mg/day.

Given our prior knowledge of the risks associated with the immediate release Paxil tablet in the same dose range utilized in this program, the focus in the safety review was on any differences between the recognized safety profile for this drug in its approved indications from that observed in the GAD population.

5.2.1 Overview of Adverse Event Profile for Paxil Tablets in GAD

Overall, the adverse events profile for Paxil tablets in GAD was comparable to that observed in patients with depression, OCD, panic disorder, and social anxiety disorder receiving this drug.

5.2.2 Conclusions Regarding Safety of Paxil in GAD

There were no new safety findings to suggest a substantially different safety profile for Paxil tablets in GAD compared to that observed for the other 4 approved indications, and no basis for substantial changes in the labeling for Paxil from the standpoint of safety.

5.3 Clinical Sections of Labeling

We have modified the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

Dr. Brugge reviewed the published literature for Paxil in GAD included in the NDA; SKB found only a single reference pertaining to the safety of paroxetine in GAD. This reference did not discover any previously unrecognized important safety concerns for this drug. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Paxil is not approved for the treatment of GAD anywhere at this time. We will ask for an update on the regulatory status of Paxil for GAD in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this supplement to the PDAC.

9.0 DSI INSPECTIONS

DSI inspected 1 site from study 641 and 2 sites from study 642. No significant deviations were found. Thus, they recommended that we accept data from these 2 studies.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes to the sponsor's draft dated 4-28-00.

10.2 Foreign Labeling

Paxil is not approved for GAD anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a literature update and a regulatory status update. We will request pediatric studies in the approval letter.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that SKB has submitted sufficient data to support the conclusion that Paxil tablets are effective and acceptably safe in the treatment of GAD. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:

Orig NDA 20-031/S-026
HFD-120
HFD-120/TLaughren/RKatz/KBrugge/PAndreason/AMHomonnay

DOC: MEMPXGAD.AE1

/s/

Thomas Laughren
1/28/01 09:51:40 AM
MEDICAL OFFICER

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: December 5, 2000

TO: Anna Marie Homonnay, R. Ph., Regulatory Project Manager
Karen Brugge, M.D., Clinical Reviewer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Constance Lewin, M.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-031/SE1-026

APPLICANT: SmithKline Beecham Pharmaceuticals

DRUG: Paxil (paroxetine)

CHEMICAL CLASSIFICATION: 6

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Generalized Anxiety Disorder

ACTION GOAL DATE: February 28, 2001

I. BACKGROUND:

Routine clinical inspections were conducted in support of the above-noted application and focused on protocols #641 and #642 by the clinical investigators noted below. Goals of inspections included validation of the primary efficacy endpoint data and subject safety parameters at the sites, along with an analysis of the adequacy of informed consent.

II. RESULTS (by protocol/site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Hartford	Cincinnati	Ohio	August 22, 2000	October 30, 2000	NAI
Khan	Bellevue	Washington	August 22, 2000	September 26, 2000	VAI
Melchor	Miamik	Florida	August 22, 2000	October 11, 2000	NAI

Protocol #641

1. Site #1 (James T. Hartford, M.D. – Cincinnati, Ohio):

Thirty-one (31) subjects were screened, twenty-five (25) of whom enrolled in the study at this site. Eighteen (18) subjects completed the study. Seven (7) subjects discontinued (4 due to adverse events and 3 due to non-compliance).

Records for eight (8) subjects were reviewed, along with informed consent for all subjects. No violations of federal regulations were noted.

Data acceptable

2. Site #2 (Arifulla Khan, M.D. – Bellevue, Washington):

Thirty-two (32) subjects were randomized at this site, twenty-two (22) of whom completed the study. Nine of the ten discontinuations were due to consent withdrawal or loss to follow-up; one was due to a protocol violation. Inspection found adequate documentation of attempts to contact those lost to follow-up. No under-reporting of adverse events was noted.

Records for seventeen (17) subjects were reviewed, along with informed consent for all subjects. A Form FDA 483 was issued for three protocol deviations and several recordkeeping deficiencies, none of which adversely impact data acceptability.

In addition to the above findings, the following sponsor/site discrepancies have been noted in review of the establishment inspection report: Data provided by the sponsor indicate that 28 subjects were randomized, whereas the site's enrollment log indicates that 32 subjects were randomized. In addition, sponsor-provided data indicate that 6 subjects were discontinued after randomization, while the site's enrollment log shows that 10 subjects were actually discontinued post-randomization.

Data acceptable

Protocol #642

Site of Pedro Melchor, M.D. – Miami, Florida:

Twenty-four (24) subjects were enrolled at this site, four (4) of whom discontinued (3 due to non-serious adverse events, 1 lost to follow-up). Records were reviewed for twelve (12) subjects, along with informed consent for all subjects. No violations of federal regulations were noted.

Data acceptable

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Clinical inspections in support of pending NDA 20-031/SE1-026 focused on the conduct of protocol #641 by Drs. James T. Hartford and Arifulla Khan and on the conduct of protocol #642 by Dr. Pedro Melchor. None of the inspectional observations noted during inspection of Dr. Arifulla Khan appear to affect the reliability of the data from that site. Inspection of Drs. Hartford and Melchor found that they conducted protocols #641 and #642, respectively, in accordance with pertinent federal regulations. Accordingly, it is recommended that the data submitted by these clinical investigators may be used in support of pending NDA 20-031/SE1-026.

Key to Classification:

NAI = No deviation from regulations. Data acceptable
VAI = Minor deviation(s) from regulations. Data acceptable
VAI-r = Deviation(s) from regulations, response requested. Data acceptable
OAI = Significant deviations from regulations. Data unreliable

/S/

Constance Lewin, M.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

/S/

Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

DISTRIBUTION:
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Date: 8/7/00
Re: NDA 20-031/S-026
Indication: Generalized Anxiety Disorder
From: Karen Brugge, M.D. and Paul Andreason, M.D.

The subjects described below with abnormal laboratory values met the criteria for "Potential Clinical Concern" (PCC). Please provide any additional information that may be helpful in clarifying some areas of uncertainty, as described below:

1. **Subject 637.099.03820**: This 58 y.o. subject, with Parkinson's disease, had an abnormal baseline laboratory value for TSH of 0.1 mU/l (normal reference range: 4.0-5.5mU/l). This subject's white blood cell count dropped from 6.3 $x10^{9th}$ cells/l at baseline to 2.2$x10^{9th}$ cells/l after 54 treatment days (week 8 visit). At 54 days of treatment, eosinophil and monocyte levels (17% and 15%, respectively) were high but reported to be within the normal range at baseline. These abnormal laboratory values met PCC criteria, but were not reported to be associated with any AE's. Given the Parkinson's disease and low TSH level, it is not clear why this patient was included in the study and what the follow-up was for the abnormal laboratory results.

2. **Subject 641.115.00708A**: This 74 y.o. year old subject, with a history of breast cancer, had low free T3 levels and thrombocytopenia at screening with a platelet count of 96 $x10^{9th}$ cells/l (normal: 130-400 $x10^{9th}$ cells/l). Her white cell blood cell count at both screening and on study visit week 8 were also low with 3.0 $x10^{9th}$ cells/l and 2.0 $x10^{9th}$ cells/l, respectively, which met PCC criteria. According to the narratives for this subject, no AE's were associated with low white cell counts. A pre-existing low white count suggests that this abnormal laboratory parameter was not likely to be drug-related. It is not clear why this subject was included or what her condition and laboratory status was at follow up.

3. **Subject 641.118.00851**: This subject was a 63 y.o. Indian male with a history of multiple fractures, removal of his right patella, and current history of hyperlipidemia and hypertension for which he was receiving Lipitor and Zestril, respectively. An adverse dropout was reported with a slightly elevated eosinophil count at baseline (9% compared to 0-7% range for within normal limits) and of 13% on Day 56, the latter which met PCC criteria. This subject also had a mildly elevated alkaline phosphatase level on Day 56 (132.0 IU/l). The reported adverse events that led to cessation of paroxetine treatment on Day 11 were ataxia, dizziness, dyspepsia, palpitation and somnolence. The events resolved within at least 13 days. There was no indication of the duration of the abnormal laboratory values.

4. **Subject 637.062.03804**: This subject was a 29 y.o. healthy WF on no concomitant medications and whose laboratory values were within normal limits at screening. On Day 54 of treatment (in the 50 mg paroxetine group) she had a markedly elevated creatinine of 645umol/l (normal range: 44-124 umol/l) and a potassium of 7.5umol/l, (normal range: 3.5-5.3 umol/l). BUN was mildly elevated from 10.3 at baseline to 11.4 umol/l on Day 54 (normal range 2.5-9.0 umol/l). The narrative for this subject indicated that the "patient completed the study as planned" and that "no further data are available". Therefore, results of a diagnostic work-up, follow-up, resolution, and treatment of these abnormal findings remain unclear.

5. **Subject 641.133.01610**: This subject was a 40 y.o. Hispanic male with a history of enlarged prostate who also exhibited marked elevation of creatinine levels from 88.4 umol/l (within normal limits) at baseline to 353.6 umol/l on Day 56 of treatment. This subject also had a mildly elevated ALT level of 93 IU/l (normal 0-48)which did not meet PCC criteria. The investigator reported the elevated creatinine as a negative adverse event and the patient was described as having "completed the study as planned". It is not clear why this subject was included in the study, given the abnormal baseline creatinine level and what the work-up, diagnosis and follow-up was for this patient.

6. **Subject 641.132.01559:** This subject was a 30 y.o. WF who showed a marked increase in creatinine and BUN from baseline levels of 88.4 umol/l and 3.6 mmol/l, respectively, to levels of 265.2 umol/l and 14.3 mmol/l, respectively, on Day 60 of treatment. The potassium level of this patient was also increased from baseline (within normal limits) to Day 60 of treatment to 6.0 mmol/l (normal: 3.5-5.3 mmol/l). The narrative indicates that the baseline WBC was elevated at $13x10^{9th}$ cells/l (normal limits: 3.8-10.8) and the subject had a history of bronchitis and was being treated with Biaxin for a "throat infection". Other concomitant medications included Percocet, Relafen, Triple Lesitan and Keflex (for carbuncles). The patient also had a history of gastritis, laparoscopy (exploratory), benign breast cyst and migraine. The patient was reported to have completed the study as planned. The work-up diagnosis, follow-up, resolution and treatment of these abnormal findings are unclear.

7. **Subject 641.146.0229**: This subject was a 22 y.o. Asian female with no reported AE's. This subject showed a marked increase in potassium from baseline at 4.0 mmol/l (within normal limits) to Day 59 of treatment (8.0 mmol/l). The narrative does not indicate if any AE's were associated with this laboratory finding or follow-up status. The diagnostic work-up and diagnosis of this abnormal laboratory value is unclear.

8. **Subjects 637.055.03668, 637.099.03849, 641.131.01517, 641.121.01002:** These four subjects were from the paroxetine groups and met PCC criteria for high bilirubin levels on Day 42 to 56 of treatment onset. They also had abnormal bililrubin levels at baseline, some of which met PCC criteria at baseline. It is not clear why these subjects were included in the study.

9. **Subjects 637.058.03692 and 637.058.03720**: These two subjects had elevated bilurubin levels of 35 umol/l (0-22 umol/l within normal limits) meeting PCC criteria on Days 10 and 58, respectively. After treatment onset of paroxetine, baseline levels were within normal limits (20 and 10 umol/l, respectively. The former subject dropped out of the study on day 3 after he experienced an "allergic reaction" for 2 days which was treated with Zyrtec®. The abnormal bilirubin level meeting PCC criteria was observed on Day 10 (7 days later) along with slightly elevated AST and ALT levels that did not meet PCC criteria. No follow-up or pertinent details could be found in the narrative or in the CRF on this subject.

10. **Subject (637.058.03720)**: This subject was a 42 y.o. WM with an abnormal bilirubin level on Day 58 with a medical history that included back pain and a past history of herniated disc. He experienced "moderate back pain" on Day 54 of paroxetine treatment (4 days before his blood chemistries were drawn). It is not clear where the back pain was located (i.e. whether it was right sided in an area suggestive of referred pain from the liver or gall bladder versus located near the area of previously experienced pain associated with a past herniated disc). The back pain lasted 3 days and was treated with Myolastan® (a benzodiazapine) and Voltaran® (an NSAID). Amylase and/or SGGT levels were not reported to have been drawn and no other symptoms/signs were described in the narrative.

11. **Subject 637.018.03330:** met the criterion for low systolic blood pressure (89 mmHg after Day 7 from the start date of the study drug, with baseline systolic BP of 100 mmHg). This 75 year old male had current history of diabetes mellitus, congestive heart disease among other illnesses. He developed "severe vomiting" on Day 1 of treatment which lasted 4 days, resulting in withdrawal from the study. It is not clear if the low blood pressure was associated with dehydration, an exacerbation of the patient's underlying congestive heart disease or some other cause. Information regarding a diagnostic work-up, follow-up and treatment cannot be found in the submission. Given the patient's congestive heart disease at baseline, it is also not clear why this patient was included in the study.

6/29/00
To: Assistant Director Thomas Kline
US Regulatory Affairs, SmithKline Beecham
Fax: 610/917-7665
From: Karen Brugge, M.D. and Paul Andreason, M.D
Medical Officers, CDER, FDA
Re: sNDA 20-031

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19

Thank you for speaking with us on the telephone today. Per our discussion:

- According to the submission approximately 7 to 9% of subjects in each treatment group of Study 637 had Parkinson's disease with a similar percentage of subjects receiving dopamine agonists. Therefore, the screening of subjects in the European study (Study 637) does not seem to reflect the methods described in the protocol of the sponsor's submission. The submission indicates that patients with the following clinically findings were to be excluded from the study: "clinically significant abnormalities on ... or physical examination at screening which had not resolved prior to the baseline visit", or with "clinically significant condition which in the opinion of the investigator would have rendered the patient unsuitable for the study...". Hence, our questions regarding the above are the following:
  - **a.** Why were Parkinson's patients included in Study 637 ?
  - **b.** Are the screening methods accurately described in the submission?
- Would you please provide a copy of the HAD scale with the items numbered so that we may confirm which items were used for the Anxiety and Depression subscale.

Thank you for considering the above and we look forward to your response.

Cc: Annemarie Homonnay, CSO

********** -COMM. JOURNAL- ********** DATE JUN-12-2000 ***** TIME 15:07 *** P.01

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********** - - ***** - 3015942859- **********

Attn: Thomas Kline, Assistant Director of Regulatory Affairs
Smith Kline Beechum
Fax: 610/917-7665
From: Karen Brugge, M.D. and Paul Andreason, M.D., CDER Medical Reviewers, FDA
Date: 6/12/00

Thank you for our telephone conversation today. As we discussed, please provide the following for each of the 3 completed studies (#637, 641, 642) by June 16, 2000:

- Line Listing of each of the following:
  - Serious Adverse Events (SAE)
  - Adverse Dropouts
  - All patients meeting criteria for "Potential Clinical Concern" (PCC) for Clinical Laboratory Tests, Vital Sign parameters and Weight. Also provide PCC criteria for urinalysis measures and provide line listing for those meeting PCC criteria.
  - Adverse dropouts due to PCC as a separate listing
  - Adverse dropouts due to an abnormal safety assessment (e.g. abnormal laboratory values) as a separate listing

Please include patient identification number, preferred term, verbatim term and location of the narrative (case summary). Please include baseline measures and follow-up measures regarding patients in the above line listings with safety assessments (e.g. laboratory measures, vital sign parameters, etc.) that were the reason for the SAE, Adverse dropout or the reason for meeting PCC criteria.

- Although the submission describes adverse dropouts and SAE's due to meeting PCC for various safety assessments (including urinalysis results) the actual numbers were not provided in all sections. Please provide these numbers for each of the safety assessments in each of the three completed studies. Also provide outcome of patients with abnormal urinalysis such as hematuria.
- Please provide an adverse event thesaurus

Please do not hesitate to contact me regarding questions or problems regarding the above at 301/594-5540.

Cc. CSO Annemarie Homonnay - FYI re: sNDA 20-031