

**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.

It 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.

151  
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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.

151

## 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

<b>1.0 Material Utilized in Review</b>	<b>3</b>
<b>2.0 Background</b>	<b>3</b>
<b>3.0 Chemistry</b>	<b>4</b>
<b>4.0 Animal Pharmacology</b>	<b>4</b>
<b>5.0 Description of Clinical Data Source</b>	<b>4</b>
<b>6.0 Human Pharmacokinetics</b>	<b>5</b>
<b>7.0 Review of Studies For Which Efficacy Claims Are Made</b>	<b>5</b>
<b>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.</b>	<b>5</b>
<b>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; Study 29060/642.</b>	<b>15</b>
<b>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.</b>	<b>20</b>
<b>8.0 Integrated Safety Information</b>	<b>26</b>
<b>9.0 Labeling Review</b>	<b>41</b>
<b>10.0 Conclusions</b>	<b>41</b>
<b>11.0 Recommendations</b>	<b>42</b>
<b>Appendix</b>	<b>43</b>

## 1.0 Material Utilized in Review

### 1.1 Materials from NDA/IND

The following items were examined during the course of this 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-IIIIR) 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-IIIIR) 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	Titratd 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:

- $\geq 20$  on the HAM-A and  $\geq 2$  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 subscale 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  $\leq 10$  on the HAM-A endpoint score or as having a score of  $\leq 2$  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. Dunnett’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 <sup>a</sup>	12 (6.7)	20 (10.6)	24 (12.2)
Lack of efficacy	8 (4.4)	5 (2.6)	8 (4.1)
Deviation from Protocol <sup>b</sup>	9 (5.0)	3 (1.6)	4 (2.0)
Lost to Follow-up	8 (4.4)	13 (6.9)	9 (4.6)
Other Reasons <sup>c</sup>	3 (1.7)	5 (2.6)	9 (4.6)
Completed	140 (77.8)	143 (75.7)	143 (72.6)

<sup>a</sup> Includes serious adverse events.

<sup>b</sup> Includes non-compliant subjects.

<sup>c</sup> 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 benzodiazepine 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 ( $\pm$ SD) age of each treatment group: approximately 40 ( $\pm$  approximately 13) years.
- Mean weight and SD for each group: approximately 78 and  $\pm$ 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%
  - $\geq$  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 ( $-12.5 \pm 0.6$ , N=188 in the 20 mg group,  $-12.2 \pm 0.6$ , 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 ( $-9.6 \pm 0.7$ , N=180) for the LOCF ITT dataset. Similar results were obtained for the OC dataset and for the PPP in both LOCF and OC datasets (LOCF of the PPP: mean change of  $-9.8 \pm 0.7$ , N=151 in the placebo group,  $-12.5 \pm 0.6$ , N=167 with  $p < 0.01$ , in the 20 mg paroxetine group,  $-12.1 \pm 0.7$ , 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  $\pm$  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 ( $-1.5 \pm 0.1$ ,  $-1.4 \pm 0.1$ , respectively, N=188) and the 40 mg paroxetine group ( $-1.4 \pm 0.1$ ,  $-1.4 \pm 0.1$ , respectively, N=197) showed a significantly greater improvement ( $p < 0.001$  for each comparison) than controls ( $-0.9 \pm 0.1$ ,  $-0.9 \pm 0.1$ , 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  $\pm$  SEM) on the COVI Anxiety Scale Score:** The 20 mg paroxetine group ( $-3.3 \pm 0.2$ , N=173) and the 40 mg paroxetine group ( $-3.2 \pm 0.2$ , N=179) showed a significantly greater improvement ( $p < 0.001$  for each comparison) than controls ( $-2.3 \pm 0.2$ , 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 ( $-7.3 \pm 0.6$ ,  $N=188$  in the 20 mg group,  $-7.0 \pm 0.6$ ,  $N=197$  in the 40 mg group) than controls ( $-3.5 \pm 0.7$ ,  $N=180$ ) 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:  $12.4 \pm 0.3$ ,  $N=180$  in the placebo group,  $12.0 \pm 0.3$ ,  $N=188$  in the 20 mg paroxetine group and  $12.5 \pm 0.3$ ,  $N=197$  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  $-2.7 \pm 0.4$ ,  $N=180$  in the placebo group,  $-5.1 \pm 0.4$ ,  $N=188$  in the 20 mg paroxetine group,  $p < 0.001$  and  $-5.1 \pm 0.4$ ,  $N=197$  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 ( $6.4 \pm 0.3$ ,  $N=180$  in the placebo group,  $6.6 \pm 0.3$ ,  $N=188$  in the 20 mg paroxetine group,  $6.0 \pm 0.3$ ,  $N=197$  in the 40 mg group). The mean change (least square mean) from baseline to treatment endpoint in the Depression Subscale score was significantly greater (reflecting greater improvement) in the paroxetine groups than in controls for the LOCF dataset (mean change of  $-0.7 \pm 0.3$ ,  $N=180$  in the placebo group,  $-2.1 \pm 0.3$ ,  $N=188$  in the 20 mg group with  $p < 0.001$  compared to controls, and  $-1.9 \pm 0.3$ ,  $N=197$  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 ( $-1.8 \pm 0.6$ ,  $N=158$  in the placebo group,  $-4.8 \pm 0.5$ ,  $N=159$  in the 20 mg group,  $-4.5 \pm 0.5$ ,  $N=173$  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 ( $-1.1 \pm 0.1$ ,  $N=180$  in the controls,  $-1.6 \pm 0.1$ ,  $N=188$  in the 20 mg paroxetine group, and  $-1.6 \pm 0.1$ ,  $N=197$  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 ( $-6.1 \pm 0.6$ ,  $N=164$  in the 20 mg group,  $-6.6 \pm 0.6$ ,  $N=175$  in the 40 mg group) than that revealed in the controls ( $-3.0 \pm 0.7$ ,  $N=155$ ) 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 Table 7.1.5 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 Table 7.1.5 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 Bonferroni 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 well 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 dispensed	
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 <sup>a</sup>	6 (3.7)	17 (10.5)
Lack of efficacy	9 (5.5)	3 (1.9)
Deviation from Protocol <sup>b</sup>	5 (3.0)	3 (1.9)
Lost to Follow-up	6 (3.7)	8 (4.9)
Other Reasons <sup>c</sup>	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 ( $41.2 \pm 12.2$  and  $39.7 \pm 12.0$  years, respectively), weight ( $75.1 \pm 18.2$  and  $77.1 \pm 17.8$ , 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. Suicidality 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 (paracetamol, 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 ( $-11.8 \pm 0.7$ , N=161 in the paroxetine group,  $-9.5 \pm 0.7$ , N=163 in the placebo group,  $p < 0.01$ ) and the OC ITT dataset ( $-13.3 \pm 0.8$ , N=127 and  $-10.7 \pm 0.8$ , 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  $-9.5 \pm 0.8$ , N=140 in controls,  $-11.0 \pm 0.8$ , N=138 in the paroxetine group,  $p = 0.125$ ) and for the OC dataset ( $-11.0 \pm 0.8$ , N=114 in controls,  $-12.7 \pm 0.8$ , 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 ( $-1.3 \pm 0.1$ , N=161 in the paroxetine group,  $-0.9 \pm 0.1$ , N=163 in controls,  $p = 0.001$ ) and on the mean change on the Item 2 score ( $-1.2 \pm 0.1$ , N=161,  $-0.9 \pm 0.1$ , 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 ( $-6.6 \pm 0.5$ , N=161 in the paroxetine group,  $-4.9 \pm 0.4$ , 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 ( $-5.1 \pm 0.4$ , N=161 and  $-4.5 \pm 0.4$ , 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 ( $-3.1 \pm 0.3$ , N=152) showed a trend for greater mean improvement ( $p = 0.058$ ) than controls ( $-2.5 \pm 0.2$ , 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  $-3.5 \pm 0.3$ , N=125 in the paroxetine group and  $-2.8 \pm 0.3$ , 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 ( $-6.9 \pm 0.7$ ,  $N=161$ ) than controls ( $-4.2 \pm 0.7$ ,  $N=162$ ) 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 ( $-3.2 \pm 0.4$ ,  $N=162$  in the placebo group,  $-5.2 \pm 0.4$ ,  $N=161$  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 subscale score (mean change of  $-1.7 \pm 0.4$ ,  $N=161$  in the paroxetine group,  $-0.9 \pm 0.4$ ,  $N=162$  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 ( $-1.4 \pm 0.7$ ,  $N=148$  in the placebo group,  $-2.9 \pm 0.7$ ,  $N=144$  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  $-2.5 \pm 0.7$ ,  $N=133$  in the placebo group,  $-4.3 \pm 0.7$ ,  $N=126$  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  $-1.2 \pm 0.1$  ( $N=161$ ), compared to controls which had an improvement of  $-1.0 \pm 0.1$  ( $N=163$ ) 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  $-1.5 \pm 0.1$ ,  $N=127$  in the paroxetine group and  $-1.2 \pm 0.1$ ,  $N=133$  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 ( $-5.2 \pm 0.6$ ,  $N=152$ ) compared to controls ( $-2.8 \pm 0.6$ ,  $N=155$ ) 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  $-1.7 \pm 0.3$ ,  $N=152$  in the paroxetine group,  $-1.3 \pm 0.3$ ,  $N=155$  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 (N = 185)	Paroxetine (N = 187)
<b>Study Conclusion Reason</b>	<b>n (%)</b>	<b>n (%)</b>
<b>Completed Study**</b>	163 (88.1)	153 (81.8)
<b>Withdrawal Reason:</b>		
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)
<b>Total Withdrawn</b>	<b>22 (11.9)</b>	<b>34 (18.2)</b>

\*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  $6.8 \pm 7.7$  and  $7.8 \pm 8.5$  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 than 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 $\pm$ 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 ( $-12.4 \pm 0.8$ , N=181 in the paroxetine group,  $-11.3 \pm 0.8$ , N=183 in the placebo group,  $p=0.171$ ). Analysis of the OC ITT dataset showed greater improvement in the paroxetine group ( $-14.8 \pm 0.8$ , N=149) than controls ( $-12.5 \pm 0.8$ , 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  $-13.9 \pm 0.9$ , N=124 in the paroxetine group and of  $-11.7 \pm 0.8$  in the placebo group ( $p=0.017$ ) for the LOCF dataset. The mean scores (least square means) at baseline were  $26.0 \pm 0.5$  and  $25.8 \pm 0.5$  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 ( $-1.3\pm 0.1$ , N=181 in the paroxetine group,  $-1.1\pm 0.1$ , N=183 in controls,  $p=0.011$ ) and a trend for an improvement on the mean change of the Item 2 score ( $-1.3\pm 0.1$ , N=181,  $-1.1\pm 0.1$ , 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 Subscales score of  $-8.0\pm 0.5$  (N=149) and the controls showed a mean change of  $-6.5\pm 0.4$  (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 ( $-3.1\pm 0.3$ , N=175) showed a trend for greater mean improvement ( $p=0.059$ ) than controls ( $-2.6\pm 0.3$ , 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  $-3.5\pm 0.3$ , N=149 in the paroxetine group and  $-2.9\pm 0.3$ , 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 ( $-7.7\pm 0.8$ , N=180) than controls ( $-5.5\pm 0.8$ , 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 ( $-5.1\pm 0.4$ , N=180 in the paroxetine group,  $-3.7\pm 0.4$ , 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 ( $-2.7\pm 0.4$ , N=179) than in controls ( $-1.8\pm 0.4$ , 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  $-4.2\pm 0.5$  (N=169), while the placebo group showed an improvement of  $-3.0\pm 0.5$  (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 ( $-5.2 \pm 0.5$ ,  $N=149$ ,  $-3.5 \pm 0.5$ ,  $N=163$ , respectively).

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

- **Mean change from baseline to treatment endpoint (least square means $\pm$ SEM) on the CGI Severity Illness Score:** The paroxetine group showed a trend ( $p=0.027$ ) for a greater mean improvement ( $-1.5 \pm 0.1$ ,  $N=181$ ), than controls ( $-1.2 \pm 0.1$ ,  $N=183$ ). This group difference was considered significant by the sponsor. Analysis of the OC dataset revealed a significant treatment group difference (mean change of  $-1.7 \pm 0.1$ ,  $N=149$  in the paroxetine group,  $-1.3 \pm 0.1$ ,  $N=163$  in the placebo group,  $p < 0.01$ ).
- **Mean change from baseline to treatment endpoint (least square means $\pm$ SEM) on the SDS Total, Work, Family and Social Items:** The paroxetine group showed an improvement on the mean SDS Total Score of  $-5.0 \pm 0.8$  ( $N=139$ ) and the controls showed an improvement of  $-3.2 \pm 0.8$  ( $N=139$ ) 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 gastritis 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 subject 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	Placebo N=529 (%)				Paroxetine N=735 (%)			
	n		n		n		n	
	Revised Summary+				Data Source Summary++			
<b>Body as a Whole</b>								
Asthenia	1	(0.2)	13	(1.8)	1	(0.2)	11	(1.5)
<b>Digestive System</b>								
Nausea	1	(0.2)	15	(2.0)	1	(0.2)	13	(1.8)
<b>Nervous System</b>								
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)
<b>Skin and Appendages</b>								
Sweating	1	(0.2)	8	(1.1)	1	(0.2)	7	(1.0)
<b>Urogenital System</b>								
*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  $\geq 5\%$ . 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<sup>†</sup>**

	<b>Paroxetine N=444</b>	<b>Placebo N=327</b>
<b>Adverse Event (AE):</b>	<b>%</b>	<b>%</b>
Gender Non-Specific	27.9	14.7
<b>AE's occurring in Paroxetine subjects with at least twice the rate of Placebo subjects:</b>		
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
<b>AE's occurring in at least 1% of subjects in a treatment group:</b>		
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
<b>Gender Specific* in Females</b>	<b>1.1</b>	<b>1.0</b>
<b>Gender Specific in Males</b>	<b>0.6</b>	<b>0.8</b>

<sup>†</sup> 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  $\geq 2$  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.