

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020936

MEDICAL REVIEW(S)

**Review and Evaluation of Clinical Data
NDA #20-936**

Sponsor: SmithKline Beecham Pharmaceuticals
Drug: Paxil CR
Indication: Depression
Material Submitted: Response to 10/9/98 Approvable Letter
Correspondence Date: December 18, 1998
Date Received: December 21, 1998

I. Background

An approvable letter for this NDA was issued on 10/9/98. This letter indicated a number of clinical items to be addressed by the sponsor before final approval:

- 1) labeling.
- 2) safety update.
- 3) regulatory status update.
- 4) world literature update.

Also, we indicated that approval would require resolution of CMC deficiencies and agreement with dissolution specifications provided in the letter.

This submission contains a response to the above four clinical issues, which will be reviewed below, and a response to the dissolution specification request (Attachment 6). They indicate that CMC issues were addressed in an 11/19/98 submission.

II. Clinical Issues

A. Labeling

Attachment 1 comprises the sponsor's labeling counterproposal, using the labeling which we proposed in the approvable letter as a starting document. Clinical changes put forth by the sponsor are discussed below.

CLINICAL PHARMACOLOGY, Clinical Trials

The sponsor objects to our added statement regarding the failure of study 448 to provide evidence of efficacy for

either Paxil CR or immediate-release Paxil, arguing that mention of this trial provides no useful information to prescribers.

Given the apparent lack of assay sensitivity in this study, I tend to agree and do not object to the deletion of this paragraph.

PRECAUTIONS, Use in Patients with Concomitant Illness

A 9/18/98 labeling supplement to the Paxil (IR) NDA (NDA 20-031/S-024) included the addition of a precautionary statement regarding the use of paroxetine in patients with narrow angle glaucoma. We felt that a revision of the proposed statement was indicated and forwarded an approvable letter for that supplement on 9/29/98, which contained our revised statement.

The sponsor has not yet responded to that letter but, since the statement is likely to be applicable to Paxil CR as well as Paxil (IR), we suggested the addition of our revised statement to Paxil CR labeling.

The sponsor is requesting that this statement be omitted until this issue is resolved for Paxil (IR). At that time, an approved statement would be inserted into Paxil CR labeling.

While we do have the opportunity now to promote resolution this issue, I do not feel that this particular safety issue is of sufficient importance to merit a potential delay in the approval of this application. Thus, I do not object to postponing the addition of a relevant statement to labeling as requested by the sponsor.

ADVERSE REACTIONS, Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Paxil CR: Adverse Events Associated with Discontinuation of Treatment

The sponsor recommends that the numbers of patients dropping out due to adverse experiences be provided in addition to the percentages in the two tables in this section.

While I agree, I do prefer that this be done by indicating the number of patients in each treatment group (i.e., at the top of the Paxil CR and Placebo columns as done in

Tables 1 and 2) rather than for each event, as suggested by the sponsor.

In addition, the sponsor proposes to delete three events from the table of adverse dropouts in study 487, specifically depression, LFT's abnormal, and heavy testicles. They argue the following (see Attachment 4):

- 1) one of the two Paxil CR dropouts due to depression (487.001.01461) had been treated for less than three weeks with a submaximal dose of Paxil CR.
- 2) one of the two Paxil CR dropouts due to elevated LFT's (487.006.01236) had an elevated AST at screening, a less than two-fold elevation in ALT at termination, and took clonidine during the trial (associated with mild, transient LFT abnormalities in 1% of patients). Also, the investigator did not judge the LFT elevations to be drug related.
- 3) one patient dropped out due to a testicular disorder, described by the patient as "heavy testicles," after one dose of Paxil CR (487.011.01266); the reported adverse event term is ambiguous and not clinically meaningful.

The exclusion of one of two patients for depression and abnormal LFT's would bring the percentages below 1% and result in omission of these events from this table. Nonetheless, I do not find the sponsor's arguments for discounting the case of depression and the case of transaminase elevation persuasive. While both events did exist before treatment in these two patients, it seems that both worsened with treatment and an appreciable drug contribution to the exacerbations should not be ruled out. These events should remain in labeling.

Regarding the case of heavy testicles, I tend to agree that this term can not be reasonably interpreted by the prescribing clinician and can be omitted from this table.

ADVERSE REACTIONS, Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Paxil CR, Male and Female Dysfunction with SSRI's

The sponsor suggests adding "and Other Serotonergic Agents" to the title of this subsection. Although it is possible that the information in this section might apply to many agents with serotonergic properties, this category is too broad and reliable data regarding sexual dysfunction with

such drugs as a class is not provided. The title should remain unchanged.

The sponsor has prepared a highly critical position paper in response to our inclusion of specific information derived from a recently published observational study of sexual dysfunction associated with SSRI treatment (see Attachment 5).¹ They discuss several flaws in the Montejo-Gonzalez study which are felt to render the results unsuitable for discussion in product labeling, to include:

- 1) lack of randomization.
- 2) potential for selection bias.
- 3) unblinded treatment.
- 4) no placebo control.

The paper also conveys their consternation over our apparent concern that the incidence of sexual dysfunction is underestimated in labeling despite caveats at the beginning of the ADVERSE REACTIONS section that: 1) adverse event incidence rates in labeling cannot be used to predict incidence in usual clinical practice due to differences in multiple variables that potentially influence reporting rates and 2) incidence rates cannot be compared across investigations.

Furthermore, the sponsor is concerned that our inclusion of data from this study deviates from past Division policy, which has emphasized the importance of considering the relative (not absolute) event incidence versus placebo in interpreting clinical trial data. Also, they fear that data from this study may be used by competitors to make comparative claims against paroxetine.

The design flaws of this trial were well recognized when the labeling recommendation was made. Nonetheless, this study was chosen due to the lack of any well-designed study that systematically examined sexual dysfunction among the relevant SSRI's. It was our intention to include information from this study to illustrate the degree to which adverse event incidence may be underestimated in premarketing clinical trials and, in turn, in product labeling. In this context, this particular study was not deemed objectionable at that time.

¹ Montejo-Gonzalez AL, et al. Journal of Sex and Marital Therapy 1997;23(3):176-194.

On the other hand, the sponsor's criticisms of this study are valid and, although it was certainly not our intention that the results be used by their competitors for comparative purposes, this would remain a distinct possibility. Additionally, a discussion of specific data from the Montejo-Gonzalez investigation is not critical to our primary goal of alerting clinicians to the probability that the incidence of sexual side effects is generally underreported.

In sum, I do not object to the omission of this study data from labeling. However, I do feel that the first sentence of this paragraph should remain (i.e., "There are no adequate, controlled studies examining sexual dysfunction with paroxetine treatment.").

ADVERSE REACTIONS, Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Paxil CR, Liver Function Tests

The sponsor has objected to our presentation of data regarding LFT elevation among the elderly patients in study 487. They have suggested instead a statement that three Paxil CR patients in this study had transaminase elevations of potential clinical concern, along with the qualification that one of these had an elevated SGOT at baseline and another took concomitant medication known to elevate liver enzymes. Their suggestion deletes our small table of the incidence of enzyme elevations in the Paxil CR and placebo groups and information regarding dropouts due to abnormal LFT's.

While a revision of our display of this information is not objectionable, I do feel that the information which downplays a possible causal link between Paxil CR and LFT elevation is not warranted. Based on the information in Attachment 4, it appears that the patient with an elevated SGOT at baseline and the patient on concomitant medication "known to elevate liver transaminases" are the same patient (487.6.1236).² As discussed above, the role of clonidine in producing the abnormal LFT's in this patient is tenuous and the abnormal pre-drug SGOT appears to elevate further with treatment.

² The other two patients in this study with liver enzymes of potential clinical concern were 487.5.1308 and 487.26.1360. These patients were discussed in my original review of this NDA.

Furthermore, I do feel that the two dropouts due to elevated transaminases in this study merit some mention. In fairness to the sponsor, it should also be noted that LFT elevations in the third Paxil CR patient normalized despite continued treatment with drug.

Thus, I recommend the following description of these patients:

"In a study of elderly depressed patients, three of 104 Paxil CR patients and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern. Two of the Paxil CR patients dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. The clinical significance of these findings is unknown."

ADVERSE REACTIONS, Other Events Observed During the Clinical Development of Paroxetine

The sponsor has extensively revised this section of labeling, using the corresponding section of Wellbutrin SR labeling as a model. Thus, this part of labeling now contains a single listing of miscellaneous adverse experiences reported during the premarketing development of Paxil CR for depression and Paxil (IR) for depression, OCD, and panic disorder. As we requested, events from study 487 have been incorporated. Reporting frequencies are provided for events in the Paxil CR depression studies only.

While this format does differ from that proposed in our approvable letter labeling, we did find this acceptable for Wellbutrin SR and I have no objection to its use here.

Attachment 3 contains an integrated enumeration of adverse event incidence for the pool of studies 448, 449, and 487. This enumeration, Tables 1 and 2 in this labeling, and the approved labeling for Paxil (IR) were used to verify the contents of this section of labeling. It appears to be reasonably accurate and complete.

RECENTLY REQUESTED LABELING CHANGES

Based on a recent reconsideration of the potential interaction between paroxetine and certain drugs metabolized by P450IIIA4, we have requested that the

sponsor modify Paxil labeling to contraindicate the coadministration of paroxetine and IIIA substrates with a narrow therapeutic index that possess the potential to induce serious cardiac arrhythmias (i.e., astemizole, cisapride, and pimozide). Corresponding changes to the Drug Interactions subsection of PRECAUTIONS were also requested. These requests were conveyed in a 12/21/98 letter from the Division.

Since this issue is equally applicable to Paxil CR, we should ask that similar changes be incorporated into Paxil CR labeling (see below).

CONTRAINDICATIONS

The following should be added:

"Coadministration of paroxetine and cytochrome P₄₅₀ IIIA substrates with a narrow therapeutic margin and the potential to induce malignant cardiac arrhythmias may be hazardous. Accordingly, concomitant use of astemizole, cisapride, and pimozide should be avoided (see PRECAUTIONS/Drug Interactions/Drugs Metabolized by Cytochrome P₄₅₀ IIIA₄).

PRECAUTIONS, Drug Interactions, Drugs Metabolized by Cytochrome P₄₅₀ IIIA₄

This section should be revised as follows:

"An *in vivo* interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for P₄₅₀ IIA₄, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of P₄₅₀ IIIA₄, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporin. Although these data provide some reassurance regarding inhibition of IIIA₄ by paroxetine, the prescriber should be aware that a drug may be metabolized through several different pathways and that extrapolation between substrates, or from *in vitro* data, may not be reliable. Accordingly, concomitant use of paroxetine and IIIA₄ substrates with a narrow therapeutic safety margin,

such as astemizole, cisapride, and pimozide, should be avoided (see CONTRAINDICATIONS)."

B. Safety Update

No additional clinical studies of paroxetine controlled-release tablets in depression have been conducted.

Three 10-week, double-blind, placebo-controlled studies with this formulation have been completed in 889 patients with panic disorder

Additionally, a Phase I bioequivalence study (579) of Paxil CR in normal subjects has been initiated. In Attachment 2, the sponsor provided subject narratives for individuals who experienced a serious adverse event or who withdrew from this study due to an adverse event.

One subject in study 579 had a serious adverse event four days after dosing (abdominal pain eventually diagnosed as nephroptosis or downward displacement of the kidney). Three subjects dropped out due to adverse events (erythema in one subject; vomiting, nausea, and dizziness in two other subjects). None of these events are felt to represent new hazards reasonably attributable to Paxil CR.

C. Regulatory Status Update

No marketing applications for Paxil CR have been submitted to any other country.

D. World Literature Update

The cover letter to this submission indicates that a systematic search of the worldwide literature has confirmed that there are no new findings with respect to the safety of Paxil CR. Details of this search, as requested in our approvable letter, have not been provided. Given the extensive safety experience to date with immediate-release paroxetine, their statement is considered reliable and is, by itself, acceptable to me.

III. Recommendations

This response contains no information that suggests a significant, previously unrecognized risk of Paxil CR therapy. From a clinical standpoint, this application may be approved when agreement can be reached on the labeling issues discussed above.

/S/

Gregory M. Dubitsky, M.D.
January 7, 1999

cc: NDA 20-936
HFD-120/Division File
HFD-120/GDubitsky
/TLaughren
/PDavid

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IL, PDA

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA #: 20-936
Sponsor: SmithKline Beecham
Clock Date: December 19, 1997

Drug Name

Generic Name: Paroxetine hydrochloride
controlled-release tablets
Trade Name: Paxil CR

Drug Categorization

Pharmacological Class: Selective Serotonin Reuptake
Inhibitor
Proposed Indication: Depression
NDA Classification: 3 S
Dosage Forms: 12.5, 25, 37.5, and 50mg
tablets
Route: Oral

Reviewer Information

Clinical Reviewer: Gregory M. Dubitsky, M.D.
Completion Date: July 17, 1998

**NDA 20-936: PAXIL CR FOR DEPRESSION
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ON ORIGINAL

1.0 Materials Utilized for Review

1.1 Materials from the NDA/IND

This review involved an examination of the following items:

NDA VOLUME (S)	SUBMISSION DATE	MATERIAL
1.1	12/19/97	Index
1.2	"	Draft labeling
1.3	"	Annotated draft labeling, summaries, table of studies
1.26-1.31	"	Study Report (448)
1.32-1.37	"	Study Report (449)
1.38	"	Integrated Summary of Efficacy
1.39-1.46	"	Integrated Summary of Safety
4.1	2/11/98	Adverse event dictionary
4.1	2/18/98	Demography/AE analysis
5.1-5.9	4/21/98	Study Report (487)

In addition, the sponsor's Computer Assisted New Drug Application (CANDA) was utilized extensively during the review process. The CANDA encompassed electronic case report tabulations and case report forms as well as folio views with hypertext links to supporting data for the original 12/19/97 submission.

Case report forms for the following patients (designated by study.site.patient#) were reviewed to audit the completeness and accuracy of data contained in corresponding narrative summaries and line listings:

448.008.00090 449.012.00919 487.021.01577
448.012.00228 487.005.01308

1.2 Related Reviews and Consultations for the NDA

A consultation to the Division of Pharmacovigilance and Epidemiology to evaluate the risk of myocarditis with paroxetine exposure was forwarded on 6/1/98. This response is pending at this time. The statistical review of the efficacy data by Japobrata Choudhury, Ph.D., dated 6/2/98 was also examined.

2.0 Background

2.1 Indication

Paroxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI) that was initially approved in the U.S. on December 29, 1992, as Paxil for the treatment of depression. (Subsequently, Paxil was also approved for the treatment of obsessive-compulsive disorder and panic disorder, both in 1996.) The sponsor has now developed a controlled-release (CR) formulation of paroxetine and has conducted studies to demonstrate the efficacy and safety of this product in the treatment of depression, which forms the basis of this NDA. Although the CR formulation, like the immediate release Paxil, requires only once daily administration, it possesses a delayed absorption characteristic which, in theory, could reduce the incidence of nausea which frequently accompanies the early course of treatment with SSRI's and, consequently, improve tolerance and compliance.

There are currently three other SSRI's marketed in the U.S., two of which are approved for the treatment of depression (sertraline and fluoxetine). At this time, no controlled-release formulations of an SSRI are marketed.

2.2 Important Information from Related IND's and NDA's and from Pharmacologically Related Compounds

All marketed SSRI's are presumed to have the potential of producing serious, sometimes fatal, reactions when used in combination with monoamine oxidase inhibitors (MAOI's). This risk is adequately labeled for all these products currently.

The marketed SSRI's differ in their potential to inhibit various isozymes of the cytochrome P450 system. Paroxetine is a potent inhibitor of P450 2D6 and therefore caution is warranted when paroxetine is co-administered with drugs metabolized by this isozyme.

2.3 Administrative History

A meeting was held with the sponsor on 7/3/96 to discuss the clinical development plans for a modified-release

formulation of paroxetine, then called Paxil MR,¹ with the intention of eventually replacing the marketed Paxil with the modified-release product. At that point, two European studies using this formulation had been completed, including a trial to compare the incidence of nausea between the MR formulation and the marketed Paxil. We informed the sponsor that efficacy could not be projected from the immediate release Paxil to the MR because the input functions (i.e., shape of the time/concentration curves) were different for the two formulations; however, we would likely consider one positive RCT as adequate evidence of efficacy in depression. Also, we explained that any comparative safety/tolerance claims (e.g., less nausea with the MR vs. Paxil) would have to be based on a comparison of the efficacy curves using multiple fixed doses of each formulation or, alternatively, to use an MR dose which showed clear superiority to all comparator doses for comparing adverse event incidence. SB was reminded of this requirement in three letters, dated 9/5/96, 9/16/96, and 10/23/96. However, if they elected not to pursue such comparative claims, a simple flexible dose study would be sufficient.²

An application to conduct a U.S. investigation of a controlled-release formulation of paroxetine was received on 7/23/96 and assigned IND . The SRD meeting took place on 8/15/96 and it was decided to allow the sponsor to proceed with plans to conduct a Phase 3 trial to evaluate the safety and efficacy of Paxil MR in depression (study 448). The sponsor also planned to conduct a series of pharmacokinetic studies in normal volunteers.

Protocols for two additional Phase 3 studies in depression (449 and 487) were submitted on 9/5/96 and 10/3/96, respectively. Study 487 differed from studies 448 and 449 in that it involved elderly patients. These three studies form the basis for this application.

SB also submitted protocols for three studies of Paxil MR in panic disorder under this IND.

¹ At some time, based on recommendations from our Labeling and Nomenclature Committee (see 6/26/96 consult), the sponsor changed the name of this compound from Paxil MR to Paxil CR.

² Subsequently, it became clear that the sponsor had chosen the latter option.

A pre-NDA meeting was held with the sponsor on 7/11/97 to discuss the format of an NDA for Paxil MR in depression. The firm was informed during this meeting that because one of the key studies involved an investigator currently under investigation by the Division of Scientific Investigations (Dr. Fiddes), the efficacy analyses of that data should be performed both including and excluding that site. We also responded to a series of 13 other questions from the sponsor regarding the planned NDA, including our agreement that they could submit results from two key studies (448 and 449) in the original NDA submission, with information from the third study (487) to follow as an amendment about three months thereafter. (A subsequent meeting was held with biopharmaceutics staff to discuss relevant biopharm issues on 8/12/97).

A 9/9/97 consultation response from the Labeling and Nomenclature Committee indicated that the name "Paxil CR" was acceptable.

This NDA was submitted on 12/19/97 and was considered fileable on 2/5/98. An information amendment consisting of the study report for study 487 was forwarded to us on 4/21/98.

2.4 Proposed Labeling

Paxil CR is indicated for the treatment of depression. It has not been studied in hospitalized depressed patients nor has it been systematically evaluated beyond 12 weeks. Safety and effectiveness in the pediatric population have not been established.

Paxil CR is contraindicated in patients taking MAOI's. At least 14 days should elapse between discontinuation of an MAOI and starting Paxil CR therapy; likewise, 14 days should pass after stopping Paxil CR before starting an MAOI.

Paxil CR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (Pregnancy Category C).

Co-administration of Paxil CR with drugs metabolized by cytochrome P450 2D6 should be approached with caution since paroxetine may significantly inhibit the activity of this isozyme.

Paxil CR tablets should not be chewed or crushed and should be swallowed whole. It should be taken as a single daily dose, usually in the morning. The recommended starting dose for most patients is 25 mg/day; patients not responding to this dose may benefit from dose increases in 12.5 mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at intervals of at least one week.

In elderly or debilitated patients and for patients with severe renal or hepatic impairment, the recommended starting dose is 12.5 mg/day, with increases to a maximum of 50 mg/day if indicated.

2.5 Foreign Marketing

This controlled-release formulation of paroxetine has never been marketed nor have any marketing applications been submitted to foreign regulatory agencies.

The immediate-release paroxetine is marketed in several foreign countries, mainly for the treatment of depression, and has not been withdrawn from any market.

3.0 Chemistry, Manufacturing, and Controls

The chemistry reviewer, Mona Zarifa, Ph.D., completed her review of this NDA on 4/27/98 and recommends that it be deemed approvable, with final approval pending adequate response from the sponsor to a number of CMC deficiencies, which are outlined in her review.

4.0 Animal Pharmacology and Toxicology

Only one preclinical study has been conducted with an enteric coated, modified-release formulation of paroxetine. (This study is pending a formal review by the pharmacology reviewer, Nuoyu Huang, M.D., Ph.D.). In summary, five groups of 6 female dogs/group were administered doses of 20 mg/day or 100 mg/day of paroxetine in enteric coated or non-enteric coated modified-release tablets or control for 14 days. No severe clinical signs were observed and there were no macroscopic or microscopic pathological changes in the gastrointestinal tracts of these animals. Among the 6 dogs receiving the high dose non-enteric coated tablets, 4 had a reduction in food consumption starting at day 2.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

A total of sixteen studies have been conducted with paroxetine CR: ten Phase 1 studies and six Phase 3 studies. Of the six Phase 3 studies, three were conducted in depressed patients and, together with the Phase 1 studies, comprise the safety database for this NDA.

The Phase 1 safety database had a safety cut-off date of 10/15/97. These 10 studies were conducted in 737 healthy volunteers; 371 subjects received paroxetine CR. These investigations have not been included in the integrated database for this NDA. This review will present information regarding serious adverse events and premature terminations due to adverse events in these studies.

The original cut-off date for the Phase 3 safety database was 9/22/97. As of that date, two studies in depressed patients (studies 448 and 449) had been completed and these two studies were pooled to comprise the primary integrated safety database for this NDA.

Subsequent to the 12/19/97 NDA submission, a third Phase 3 study (487), that examined antidepressant efficacy in elderly patients, was completed and the study report for this study was submitted as an information amendment to the NDA on 4/21/98. Since the patient sample for study 487 was considered demographically distinct from the sample for the integrated database (448+449), safety data from 487 has not been integrated but will be considered as a separate database.

Appendix 5.0 summarizes these studies (Table 5.1.1.1) and provides an enumeration of the participants in these trials (Table 5.1.1.2). In all, 687 subjects had received at least one dose of paroxetine CR. Of these, 316 were depressed patients in Phase 3 studies.

5.1.2 Demographics

In the Phase 1 studies, all volunteers were in the age range 18-55 years and had no history of psychiatric illness within

6 months of the start of the study. The mean age for all treatment groups was between 32-35 years. There tended to be an equal number of male and female subjects in all treatments. With respect to race, most volunteers were white (97%) in the Phase 1 combined population, with an equal distribution between black, oriental, and other (~1%) among the remaining 3%. Mean body weight was similar among treatments, with means in the range 68-73 kg.

Demographic characteristics for the pool of studies 448 and 449 and for study 487 are summarized in Appendix 5.0, Tables 5.1.2.1 and 5.1.2.2, respectively.

Among patients who participated in studies 448 and 449, more than half were in the age range 35-54 years; mean age was about 40 years old. No patients was younger than 18 and only one patient was older than 65. About two-thirds of the patients were female. The vast majority were white.

In study 487, which examined elderly depressed patients, about three-fourths of the patients were over 65, with a mean age of about 70 years. No patient was under age 60 and three patients were 85 or older. Paroxetine CR patients were almost evenly split by gender (52% male and 48% female). The vast majority were white.

In the pool of all three studies, 83 patients over the age of 65 received paroxetine CR.

5.1.3 Extent of Exposure

Among Phase 1 study volunteers who received paroxetine CR, 54% were exposed to this formulation for one day while 46% received multiple doses (mean exposure duration was 6.8 days, with a range of 1-21 days). Most subjects receiving multiple doses of active drug received 30mg of either paroxetine CR or paroxetine IR. The maximum doses of paroxetine CR and paroxetine IR were 50mg and 40mg, respectively.

For Phase 3 studies, information regarding daily dose and duration of exposure in the pool of studies 448 and 449 and in study 487 are provided in Appendix 5.0, Tables 5.1.3.1 and 5.1.3.2, respectively. Please note that these tables have been electronically copied from the sponsor's CANDA submission. The cells in each table provide the number of patients exposed to the given dose level for a total duration as indicated. Thus, patients may be counted in multiple cells (i.e., once for each dose level received) and

durations do not necessarily represent continuous periods of exposure.

Within the pool of studies 448 and 449, 30 patients received the maximum dose of paroxetine CR (62.5 mg/day) for a total duration over 8 weeks (56 days).

Among the patients in study 487, 10 patients received the maximum dose of the CR formulation (50 mg/day) for a total of longer than 8 weeks.

5.2 Secondary Source Data

5.2.1 Non-IND Studies

No studies are known to have been conducted except under IND 51-171, the sponsor's IND.

5.2.2 Post-Marketing Experience

Paroxetine CR has never been marketed.

5.2.3 Literature

No information about paroxetine CR had been published at the time of this NDA submission.

6.0 Human Pharmacokinetics and Pharmacodynamics

The sponsor conducted two investigative studies (485 and 505) to compare the bioavailability characteristics of a series of prototype controlled-release formulations, all based on the "Geomatrix" controlled-release technology. Paroxetine CR is the production-scale version of the best performing prototype evaluated in these studies.

Seven additional studies with paroxetine CR were then done in healthy volunteers to assess: 1) dose proportionality (study 472), 2) the effect of food after single doses (473 and 563) and at steady state (564), 3) steady state comparison of paroxetine CR (50mg) with standard Paxil (40mg) (study 474), and 4) bioequivalence to assess a future alternative manufacturing site (539 and 480).

Paroxetine CR is a formulation of paroxetine in which the start of tablet dissolution is delayed by the presence of an acid-resistant enteric coat and the rate of absorption is controlled by dispersing the paroxetine within a degradable polymeric matrix which gradually releases paroxetine over a period of several hours. Under standardized, fasted

conditions, there is a consistent after single doses in the range 12.5-50mg and an approximate in the absorption rate compared to standard Paxil.

Pharmacokinetic features of paroxetine, once absorbed after paroxetine CR administration, are comparable to those after Paxil administration.

After multiple dosing with paroxetine CR, steady state was reached within two weeks. The average steady state bioavailability of paroxetine CR at 50mg was shown to be similar to that of Paxil at 40mg (mean ratio 0.98, 95% CI:0.88-1.08). Compared to immediate-release Paxil, there was 31% reduction in the degree of fluctuation from peak to trough plasma concentrations. Median steady state Tmax for paroxetine CR was 10 hours, with a median delay of 5 hours compared to Paxil. The inter-subject variability of paroxetine CR at steady state was no greater than that of Paxil. CYP2D6 status (extensive vs. poor metabolizers) did not significantly influence Cmax or AUC_t nor relative bioavailability (paroxetine CR:Paxil).

Absorption lag time and Tmax were affected by dietary factors in single-dose studies, with progression of lag time with the size of the meal (up to 12 hours after a high fat breakfast). During repeat dose studies, steady state Cmax and AUC_t were unaffected by dietary state. Thus, it appears that paroxetine CR can be dosed without regard to food intake.

SB initially planned to market four strengths of Paxil CR: 12.5, 25, 37.5, and 50mg tablets. In a conversation with Chandra Sahajllawa, Ph.D., the assigned biopharmaceutics team leader, on 7/9/98, I was informed that the sponsor has dropped plans to market the 37.5 and 50mg strengths and is currently seeking approval of only the 12.5 and 25mg tablets, which were the strengths utilized in the three key clinical depression trials.

Additionally, Dr. Sahajllawa indicated that the sponsor wishes to change the manufacturing site from

The two bioequivalence studies to compare paroxetine CR from these sites (studies 539 and 480) failed to demonstrate acceptable bioequivalence. SB plans to conduct a bioequivalence study post-approval to link the products from these two sites.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

The demonstration of efficacy of paroxetine CR in the treatment of depression is based on three randomized, double-blind, placebo-controlled studies: 448, 449, and 487. The report of the latter study, which was conducted in elderly patients, was submitted as an information amendment to the NDA on 4/21/98. No other studies addressing the antidepressant efficacy of paroxetine CR have been completed.

The efficacy analyses presented in this review will focus on two widely accepted measures of antidepressant response, the Hamilton Depression Rating Scale (HAM-D) total score and the depressed mood item (item #1) of this scale, as well as the Clinical Global Impression (CGI) severity of illness item.

Each of the three studies will be discussed separately below. Please note that Appendix tables for these sections have been electronically copied from the sponsor's CANDA submission.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1 Study 448

Investigators/Locations

This study was conducted by 22 principal investigators at 20 sites. Investigators and sites are listed in Appendix 7.2.1, Table 7.2.1.1.

Objectives

The primary objective of this study was to demonstrate the efficacy of paroxetine CR in the treatment of major depression.

Population

Inclusion criteria were:

- outpatient with a primary diagnosis of DSM-IV Major Depressive Disorder.
- age 18-65 years.
- 17-item HAM-D total score ≥ 20 with a decrease of greater than 25% between screening and baseline.

Exclusionary criteria included the following:

- undergoing formal psychotherapy/psychoanalysis.
- previously unresponsive to paroxetine.
- diagnosis of another primary Axis I disorder within 6 months of screening.
- requiring concomitant MAOI, benzodiazepine, or other psychoactive drug therapy (except chloral hydrate).
- history of brief depressive episodes (≤ 8 weeks with spontaneous remission).
- DSM-IV criteria for substance abuse or dependence within 6 months of the trial.
- ECT within last 3 months.
- current, serious suicidal or homicidal risk.

Design

This was a 12-week, randomized, double-blind, placebo-controlled study. Candidates underwent a 1-week single-blind, placebo washout and those found eligible during this period were randomized evenly at the baseline visit to paroxetine CR, paroxetine IR, or placebo for a 12-week phase of treatment. This was followed by a 10-day taper phase.

Dosing was flexible and was done at 4 levels:

	<u>Paroxetine CR</u>	<u>Paroxetine IR</u>
Level 1	25 mg/day	20 mg/day
Level 2	37.5 mg/day	30 mg/day
Level 3	50 mg/day	40 mg/day
Level 4	62.5 mg/day	50 mg/day

Randomized patients started at level 1 and dosage elevations to the next level were permitted at any visit based on inadequate therapeutic response in the investigator's judgement. Dosage reductions were allowed at any time after the first week due to an adverse experience. During the first week, patients with poor tolerance could interrupt treatment for 2 days. Longer interruptions during that week or more than one dosage reduction at any time required termination from the study. During the taper phase (after completion or premature termination), a gradual reduction in dosage was undertaken over a maximum of 10 days.

Efficacy Assessments

The primary measure of efficacy was the change from baseline in the 17-item HAM-D total score at endpoint (week 12). The HAM-D was assessed at screening, baseline, and weeks 1, 2, 3, 4, 6, 8, and 12. The CGI severity of illness item was also scored at these timepoints except at screening.

Analysis

The ITT population consisted of all patients who were randomized, received at least one dose of study medication, and had at least one post-baseline assessment. HAM-D assessments with less than 90% of the scale items completed were excluded from analysis. When at least 90% were present, values for any missing items were calculated by computing the mean of the items present.

Change from baseline in HAM-D total score and depressed mood item was analyzed by analysis of variance allowing for the effect of center and prospectively defined covariates (age, sex, duration of episode, baseline severity). The effect of adding treatment-by-center and treatment-by-covariate interactions into the model was assessed.

Change from baseline in CGI-severity score was analyzed by the Wilcoxon rank sum test. No adjustment was made for center or covariates.

The primary dataset was considered to be the LOCF of the ITT population.

Baseline Demographics

Demographic characteristics at baseline are displayed in Appendix 7.2.1, Table 7.2.1.2. Age, gender, weight, and race distributions were comparable across groups, except for a slightly higher percentage of blacks in the placebo group. No patient was younger than 18 or older than 64 years of age.

Baseline Severity of Illness

Mean baseline HAM-D total scores were similar across treatment groups:

	<u>N¹</u>	<u>Mean (SE)</u>
Paroxetine CR	102	23.0 (0.26)
Placebo	101	23.4 (0.29)
Paroxetine IR	104	23.3 (0.28)

Patient Disposition

Of the 391 patients screened, 315 were randomized to double-blind treatment; 76 patients failed entrance criteria. Of the 315 patients randomized, 5 were not included in the ITT because they dropped out on the first day after randomization and were lost to follow-up. Thus, the ITT comprised 310 patients (104 paroxetine CR, 101 placebo, and 105 paroxetine IR).

The numbers of ITT patients in-study by visit are displayed in Appendix 7.2.1, Table Table 7.2.1.3. In the paroxetine CR group, 69% (72/104) of patients completed the study. Overall dropout rates were roughly comparable (31% paroxetine CR, 27% placebo, and 33% paroxetine IR).

Dosing Information

Mean daily dose (mg/day) during the study for the active drug groups is as follows:

	<u>Wk 4</u>	<u>Wk 8</u>	<u>Wk 12</u>
Paroxetine CR	46.2	49.5	50.0
Paroxetine IR	36.6	38.6	39.5

Concomitant Medications

The most frequently reported concomitant medications were ibuprofen (29% of all patients), acetaminophen (28%), and aspirin (20%). No concomitant psychotropic medication, except chloral hydrate, was allowed during the study.

Seven patients (2 paroxetine CR, 1 paroxetine IR, and 4 placebo patients)² were identified by the sponsor as protocol violators because they used prohibited concomitant medications during the trial, including five who used an antidepressant. Concomitant medication usage for each of these patients was examined and, in my judgement, none was

¹ Among the ITT patients, two paroxetine CR and one paroxetine IR patient did not complete the HAM-D at baseline.

² Paroxetine CR: 448.20.00046, 448.20.00052; Paroxetine IR: 448.01.00303; Placebo: 448.06.00141, 448.16.00110, 448.18.00233, and 448.20.00050.

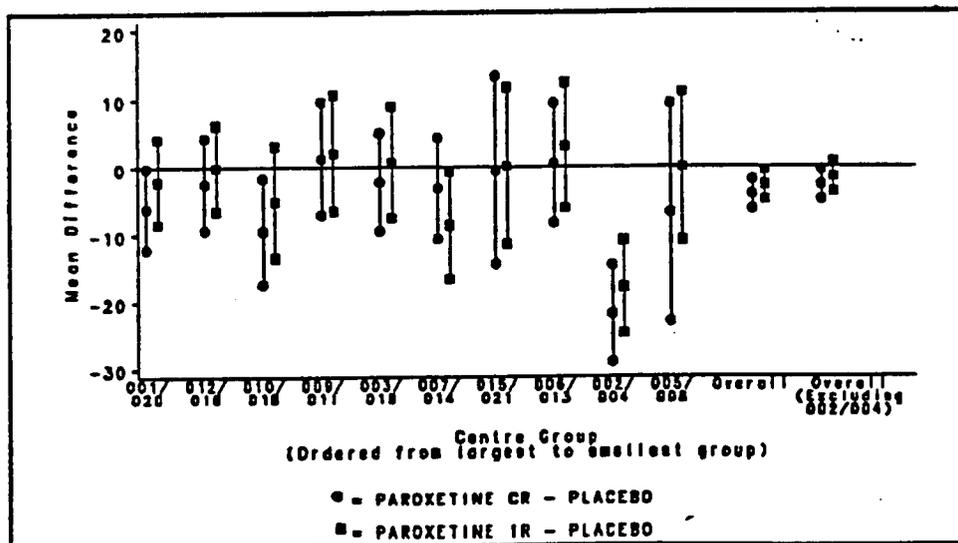
felt to constitute a source of significant bias in the efficacy results of this study.

Efficacy Results

Appendix 7.2.1 (Tables 7.2.1.4-7.2.1.9) provides the mean changes from baseline, with adjustment for covariates as mentioned above, for the HAM-D total score, HAM-D depressed mood item, and CGI-severity score for all three treatment groups, as well as statistical testing of inter-group comparisons, for both the LOCF (last observation carried forward) and OC (observed cases) datasets of the ITT population.

To evaluate treatment-by-center interaction, the sponsor grouped sites that recruited a small number of patients with those recruiting larger numbers. This analysis revealed a significant treatment-by-center interaction for one center group, Center 2/4 ($p < 0.01$) (see Figure 345 below). Center 2, which had 18 patients (6 per group), demonstrated a lower placebo response and greater drug response than the general study population. Based on raw HAM-D total score changes from baseline to last visit for center #2 patients, the mean unadjusted change for paroxetine CR was -22.8 (N=6) and for placebo -1.8 (N=6). The contribution of center #4 is difficult to discern because it involved a small number of patients (2 per group) and the individual changes from baseline for the paroxetine CR and placebo patients in this center were quite variable.

Figure 345 Change from Baseline in HAMD Total Score at Endpoint - Inter-Center Consistency Difference and 95% Confidence Interval for PAR-448



There was only one dropout from center #2: patient 448.2.00081, who received placebo, dropped out after 55 days because of relocation to Virginia.

The sponsor examined the placebo patients from center #2 and discovered that they had a greater number of previous depressive episodes, were more severely depressed at baseline, and had more frequent courses of antidepressant therapy than the overall patient population. Thus, it was speculated that they would be less likely to experience a placebo response.

It is remarkable that each of the six paroxetine CR patients in center #2 had a decrease in HAM-D total score of at least 20 and each of the six placebo patients had a decrease less than 6.³ The corresponding mean changes for all other center groups were -11.9 for paroxetine CR and -10.6 for placebo. Thus, both the magnitude of this deviation and its consistency are unexpected and raise the question of unblinding in this center. While this question probably cannot be definitively answered, it does cast some doubt on the results of analyses which include this center.

SmithKline Beecham Regulatory Compliance conducted an audit of this site and found no protocol violations. It was discovered, however, that the administration of the HAM-D scale deviated from the instructions provided at the Investigator's Meeting: rather than rating this scale on the basis of an unstructured interview, this center provided patients with a copy of the scale during the rating. This could conceivably bias the rating of the depressed mood item, which relies on spontaneous reporting of the mood state by the patient. The sponsor opined that this deviation would be unlikely to bias HAM-D total score data.

To be conservative, the sponsor reanalyzed these data excluding center group 2/4. These results are provided in Appendix 7.2.1 (Tables 7.2.1.10-7.2.1.15) as well.

On the primary measure of efficacy (the LOCF mean change from baseline in HAM-D total score), paroxetine CR was significantly better than placebo at weeks 6, 8, and 12 (p-values < 0.021). At week 12, paroxetine CR patients experienced an adjusted mean decrease in HAM-D total score of 12.7 points compared to a decrease of 9.9 for placebo patients (difference of 2.8). (Curiously, paroxetine IR did

³ Paroxetine CR patients in 448.02: #74, 78, 79, 164, 171, and 242; placebo patients in 448.02: #73, 80, 81, 165, 170, and 243.

not beat placebo to a statistically significant degree on this measure.)

In the OC dataset for this variable, results were even more robust favoring paroxetine CR over placebo (p-values ≤ 0.002).

However, when one excludes center group 2/4, results were less promising. For the HAM-D total score (LOCF), paroxetine CR was numerically better than placebo, but not to a statistically significant degree. This cannot be attributed solely to a decrease in sample size, since the effect size suffered (CR/placebo difference of 1.3 at week 12). The results in the OC dataset were better but not consistently so: paroxetine CR beat placebo at weeks 6 and 8 but not at week 12. In pairwise comparisons with placebo, Paroxetine IR performed no better than the CR formulation.

With respect to the HAM-D depressed mood item, the superiority of paroxetine CR over placebo was strong and consistent during the last several weeks of the trial for both LOCF and OC datasets, with and without center group 2/4.

On the CGI-severity score, paroxetine CR was significantly better than placebo in both LOCF and OC datasets at weeks 6, 8, and 12 when all centers were included. But, when center group 2/4 was excluded, results were weaker, with failure to demonstrate statistically significant superiority in the LOCF dataset. CR/placebo differences were significant in the OC dataset, though. Paroxetine IR did not beat placebo at any visit in either dataset on this variable.

It might be argued that a more valid timepoint at which to evaluate efficacy in this study would be week 8, since in analyses both with and without center group 2/4, less than 70% (62-66%) of the patients in the CR and placebo groups were still in-study at week 12; week 8 completion rates were well over 70% in these groups in both analyses. However, in the analysis including all centers, the results would be essentially the same; if center group 2/4 is excluded, the only important difference would be statistical significance at week 8 in the OC analysis of the HAM-D total score, which disappears at week 12. This difference would not change the overall conclusion drawn from this study, in my opinion.

Conclusions

Interpretation of this study is complicated by the treatment-by-center interaction observed at center group 2/4. Especially troublesome is the fact that the repeat analysis, which excluded this center group, did not yield consistent evidence of efficacy for paroxetine CR over placebo and clearly failed with respect to the primary outcome, i.e. change from baseline in HAM-D total score in the LOCF dataset at week 12. Also of concern is the fact that the drug/placebo treatment difference in this analysis is small (1.3) and much smaller than in the analysis including all centers (2.8).

Examination of data from center 2 reveals that the experience at this center is an aberration relative to other center groups in this study, to the other studies in this NDA, and probably to most other key efficacy trials in other NDA's. The magnitude of the effects reported in this center are, therefore, not ones which could be reasonably expected in the vast majority of patients who will take paroxetine CR and it is on this basis that I feel that this center group should be excluded from the analyses used to ascertain efficacy in this study and to infer effectiveness in the general patient population.

In fairness, it should also be noted that paroxetine IR, an approved treatment for depression, did not beat placebo with respect to the primary analysis measure and failed no better than paroxetine CR in the reanalysis.

Thus, given the failure of the active comparator, this study is considered failed.

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7.2.2 Study 449

Investigators/Locations

This study was conducted by 21 principal investigators at 20 sites. Investigators and sites are listed in Appendix 7.2.2, Table 7.2.2.1.

Center #17, led by Robert Fiddes, M.D. at the Southern California Research Institute, Whittier, CA, was terminated by the sponsor following reports from the FDA of unspecified irregularities. According to a telephone call on June 11, 1998, from Alfreda Burnett of the Division of Scientific Investigations, Dr. Fiddes is in the process of being disqualified and his data was not to be accepted in support of an NDA.

Seventeen patients (5 paroxetine CR, 6 placebo, and 6 paroxetine IR) had been enrolled at this site; this comprises 5.1% of the 333 patients in this study. Only 8 patients from this center (4 paroxetine CR, 1 placebo, and 3 paroxetine IR) completed the study.

The sponsor analyzed primary efficacy variables with and without patients from Dr. Fiddes' site.

Objectives

The primary objective of this study was to demonstrate the efficacy of controlled-release paroxetine in the treatment of major depression.

Population

Inclusion criteria were:

- outpatient with a primary diagnosis of DSM-IV Major Depressive Disorder.
- age 18-65 years.
- 17-item HAM-D total score ≥ 20 with a decrease of greater than 25% between screening and baseline.

Exclusionary criteria included the following:

- undergoing formal psychotherapy/psychoanalysis.
- previously unresponsive to paroxetine.
- diagnosis of another primary Axis I disorder within 6 months of screening.

- requiring concomitant MAOI, benzodiazepine, or other psychoactive drug therapy (except chloral hydrate).
- history of brief depressive episodes (≤ 8 weeks with spontaneous remission).
- DSM-IV criteria for substance abuse or dependence within 6 months of the trial.
- ECT within last 3 months.
- current, serious suicidal or homicidal risk.

Design

This was a 12-week, randomized, double-blind, placebo-controlled study. Potential candidates were screened during a 1-week, single-blind placebo washout period. Those found to be eligible were evenly randomized at the baseline visit to one of three treatments: paroxetine CR, placebo, or paroxetine IR. The 12-week treatment phase was followed by a 10-day taper phase.

A flexible dosing scheme was utilized, with 4 dose levels:

	<u>Paroxetine CR</u>	<u>Paroxetine IR</u>
Level 1	25 mg/day	20 mg/day
Level 2	37.5 mg/day	30 mg/day
Level 3	50 mg/day	40 mg/day
Level 4	62.5 mg/day	50 mg/day

Randomized patients started at level 1 and dosage elevations to the next level were permitted at any visit based on inadequate therapeutic response in the investigator's judgement. Dosage reductions were allowed at any time after the first week due to an adverse experience. During the first week, patients with poor tolerance could interrupt treatment for 2 days. Longer interruptions during that week or more than one dosage reduction at any time required termination from the study. During the taper phase (after completion or premature termination), a gradual reduction in dosage was undertaken over a maximum of 10 days.

Efficacy Assessments

The primary measure of efficacy was the change from baseline in the 17-item HAM-D total score at endpoint (week 12). HAM-D assessments were made at screening, baseline, and at weeks 1, 2, 3, 4, 6, 8, and 12. The CGI severity item was also measured at these timepoints except at screening.

Analysis

The ITT population consisted of all patients who were randomized, received at least one dose of study medication, and had at least one post-baseline assessment. HAM-D assessments with less than 90% of the scale items completed were excluded from analysis. When at least 90% were present, values for any missing items were calculated by computing the mean of the items present.

Change from baseline in HAM-D total score and depressed mood item was analyzed by analysis of variance allowing for the effect of center and prospectively defined covariates (age, sex, duration of episode, baseline severity). The effect of adding treatment-by-center and treatment-by-covariate interactions into the model was assessed.

Change from baseline in CGI-severity score was analyzed by the Wilcoxon rank sum test. No adjustment was made for center or covariates.

The primary dataset was considered to be the LOCF of the ITT population.

Baseline Demographics

Demographic characteristics at baseline are provided in Appendix 7.2.2, Table 7.2.2.2. Age, gender, weight, and racial composition were roughly comparable across the three treatment groups. No patient under age 18 or over age 64 was enrolled with the exception of one 71 year old patient.

Baseline Severity of Illness

Mean baseline HAM-D total scores were similar across treatment groups:

	<u>N¹</u>	<u>Mean (SE)</u>
Paroxetine CR	108	23.8 (0.33)
Placebo	110	23.5 (0.30)
Paroxetine IR	110	23.7 (0.29)

¹ Among the ITT patients, two paroxetine IR patients did not complete the HAM-D at baseline.

Patient Disposition

Of the 429 patients screened, 333 were randomized to double-blind treatment; 96 patients failed entrance criteria. Of the 333 patients randomized, 3 were not included in the ITT because they dropped out on the first day after randomization and were lost to follow-up. Thus, the ITT comprised 330 patients (108 paroxetine CR, 110 placebo, and 112 paroxetine IR).

The numbers of ITT patients in-study by visit are displayed in Appendix 7.2.2, Table 7.2.2.3. In the paroxetine CR group, 75% (81/108) of patients completed the study. Overall dropout rates were roughly comparable (25% paroxetine CR, 30% placebo, and 33% paroxetine IR).

Dosing Information

Mean daily dose (mg/day) during the study for the active drug groups is as follows:

	<u>Wk 4</u>	<u>Wk 8</u>	<u>Wk 12</u>
Paroxetine CR	41.8	47.0	46.6
Paroxetine IR	33.7	36.5	37.0

Concomitant Medications

The most frequently reported concomitant medications were acetaminophen (35% of all patients), ibuprofen (23%), and aspirin (23%). No concomitant psychotropic medication, except chloral hydrate, was allowed during the study.

Two patients (1 paroxetine CR and 1 paroxetine IR patient)² were identified by the sponsor as protocol violators because they used prohibited medication during the trial. These usages were reviewed and, in my judgement, in neither patient was the concomitant medication usage likely to significantly bias the efficacy findings of this study.

Efficacy Results

Appendix 7.2.2 (Tables 7.2.2.4-7.2.2.6) provides the mean changes from baseline, with adjustment for covariates as mentioned above, for the HAM-D total score, HAM-D depressed mood item, and CGI-severity score for all three treatment groups, as well as statistical testing of inter-group comparisons, for both the LOCF (last observation carried

² CR: 449.020.00735 and IR: 449.018.01048.

forward) and OC (observed cases) datasets of the ITT population. Please note that, for this study, LOCF results were available only at week 12 and not for each visit.

As discussed previously in this section, analyses were also conducted without efficacy data from Dr. Fiddes' site (see Appendix 7.2.2, Tables 7.2.2.7-7.2.2.9).

To evaluate treatment-by-center interaction, the sponsor grouped sites that recruited a small number of patients with those recruiting larger numbers. Results were consistent across center groups: treatment-by-center group interactions were not statistically significant for the HAM-D total score at week 12 LOCF ($p=0.882$) or OC ($p=0.847$).

On the HAM-D total score and HAM-D depressed mood item, paroxetine CR performed significantly better than placebo at week 8 and 12 (OC) and at week 12 (LOCF). The drug/placebo difference in adjusted HAM-D total score means at week 12 (LOCF) was 3.1.

Regarding the CGI-severity score, paroxetine CR was clearly better than placebo at week 8 in the OC dataset, but this significance disappeared at week 12, when the median scores were about the same. At week 12 in the LOCF dataset, paroxetine CR was superior to placebo ($p=0.042$).

When one excludes Dr. Fiddes' site (center #17), the results were similarly significant with the exception of the difference in median CGI-severity scores, which was not statistically significant at week 12 (LOCF) ($p=0.074$). However, this difference did trend toward significance.

Conclusions

The results of this study provide evidence of the efficacy of paroxetine CR, compared to placebo, in the treatment of major depression.

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7.2.3 Study 487

Investigators/Locations

This study was conducted at 31 sites in the United States and Canada. Principal investigators and site locations are listed in Appendix 7.2.3, Table 7.2.3.1. Note that centers #10 and #16 only screened patients; none were randomized to treatment at these two sites.

The sponsor, in a 7/16/97 letter to the Division which was copied to DSI and the relevant IRB, described compliance issues which had come to light at center #3, led by
at

According to this correspondence, 8 patients had signed an outdated version of the informed consent document upon entering the study. When the error was discovered, informed consent was obtained again using the correct version of the form. However, the original forms were destroyed and, when patients gave consent the second time, they were instructed to back-date the forms to the dates on which they originally gave consent. While both of these latter actions are prohibited, alleged that the sponsor's CRA instructed the site to take these actions; this was denied by the sponsor. Additionally, one subinvestigator claimed academic credentials which she did not possess.

The sponsor did not believe that patient safety or the assessment of efficacy had been compromised by these improprieties. No further action has been taken regarding this site, which enrolled 7% (23/323) of the patients in this study.

Objectives

The primary objective of this study was to demonstrate the efficacy of paroxetine CR in the treatment of major depression.

Population

To be included in this trial, patients had to meet the following criteria:

- outpatient with a primary diagnosis of DSM-IV Major Depressive Disorder using the SCID.
- at least 60 years old and deemed appropriate for paroxetine treatment in the dosage range 10-40 mg/day.

- 17-item HAM-D total score ≥ 18 with a decrease of not more than 25% between screening and baseline.
- capable of complying with instructions and participating in a 12 week trial.

The following criteria were exclusionary:

- previously unresponsive to paroxetine therapy.
- requiring concomitant therapy with an MAOI, benzodiazepine, or other psychoactive drug except for chloral hydrate.
- ECT within 3 months of study entry.
- diagnosis of another Axis I disorder as a primary or dominant diagnosis within 6 months prior to screening.
- met DSM-IV criteria for substance abuse or dependence within 6 months of the study.
- current, serious suicidal or homicidal risk.
- history of brief depressive episodes (≤ 8 weeks with spontaneous remission).
- diagnosis of any neurological condition that may contribute to secondary depression (e.g., Parkinson's disorder).
- diagnosis of dementia.
- score ≤ 24 on the Mini Mental Status Exam.
- undergoing formal psychotherapy or psychoanalysis.

Design

This was a 12-week, randomized, double-blind, placebo-controlled study in depressed, elderly outpatients. All study candidates underwent a one week, single-blind placebo run-in during which no psychotropic medication other than chloral hydrate was permitted. Subsequently, those eligible were evenly randomized at the baseline visit to one of three treatments: paroxetine CR, placebo, or paroxetine IR. After 12 weeks of treatment, patients were tapered during a 10 day period.

Dosing was flexible and was done at 4 levels:

	<u>Paroxetine CR</u>	<u>Paroxetine IR</u>
Level 1	12.5 mg/day	10 mg/day
Level 2	25 mg/day	20 mg/day
Level 3	37.5 mg/day	30 mg/day
Level 4	50 mg/day	40 mg/day

Randomized patients started at level 1 and dosage elevations to the next level were permitted at any visit based on inadequate therapeutic response in the investigator's judgement. Dosage reductions were allowed at any time after the first week due to an adverse experience. During the first week, patients with poor tolerance could interrupt treatment for 2 days. Longer interruptions during that week or more than one dosage reduction at any time required termination from the study. During the taper phase (after completion or premature termination), a gradual reduction in dosage was undertaken over a maximum of 10 days.

Efficacy Assessments

The primary measure of efficacy was the change from baseline in the 17-item HAM-D total score at study endpoint (week 12). The HAM-D was administered at screening, baseline, and at weeks 1, 2, 3, 4, 6, 8, 10, and 12. The CGI severity of illness was also rated at these visits, except at screening.

Analysis

The ITT population consisted of all patients who were randomized, received at least one dose of study medication, and had at least one post-baseline assessment. HAM-D assessments with less than 90% of the scale items completed were excluded from analysis. When at least 90% were present, values for any missing items were calculated by computing the mean of the items present.

Change from baseline in HAM-D total score and depressed mood item was analyzed by analysis of variance allowing for the effect of center and prospectively defined covariates (age, sex, duration of episode, baseline severity). The effect of adding treatment-by-center and treatment-by-covariate interactions into the model was assessed.

Change from baseline in CGI-severity score was analyzed by the Wilcoxon rank sum test. No adjustment was made for center or covariates.

The primary dataset was considered to be the LOCF of the ITT population.

Baseline Demographics

Demographic information at baseline is displayed in Appendix 7.2.3, Table 7.2.3.2. Age, gender, weight, and racial distribution were roughly comparable across treatment

groups. No patient was under age 60 and about half of the patients in each group were in the age range 66-74 years.

Baseline Severity of Illness

Mean baseline HAM-D scores were comparable among the three treatment groups:

	<u>N¹</u>	<u>Mean (SE)</u>
Paroxetine CR	103	22.1(0.34)
Placebo	107	22.1(0.29)
Paroxetine IR	103	22.3(0.31)

Patient Disposition

Of the 396 patients screened, 323 were randomized to double-blind treatment; 73 patients failed entrance criteria. Of the 323 patients randomized, 4 were not included in the ITT because they dropped out within the first 3 days after randomization and yielded no on-drug assessment. Thus, the ITT comprised 319 patients (104 paroxetine CR, 109 placebo, and 106 paroxetine IR patients).

The numbers of ITT patients in-study by visit are displayed in Appendix 7.2.3, Table 7.2.3.3. In the paroxetine CR group, 78% (81/104) of patients completed the study. Overall dropout rates were roughly comparable (22% paroxetine CR, 23% placebo, and 28% paroxetine IR).

Dosing Information

Mean daily doses (mg/day) of active drug for patients in-study at weeks 4, 8, and 12 are as follows:

	<u>Wk 4</u>	<u>Wk 8</u>	<u>Wk 12</u>
Paroxetine CR	31.1	31.9	31.1
Paroxetine IR	27.6	28.1	26.6

Concomitant Medications

The most frequently reported concomitant medications were aspirin (34% of all patients), acetaminophen (25%), and vitamins (23%). No concomitant psychotropic agents, other than chloral hydrate, were allowed during the study. No

¹ Among the ITT patients, one paroxetine CR, two placebo, and three paroxetine IR patients did not complete the HAM-D at baseline.

patients were reported by the sponsor as protocol violators because of taking prohibited medication.

Efficacy Results

Appendix 7.2.3 (Table 7.2.3.4-7.2.3.9) displays the mean changes from baseline, with the previously mentioned covariate adjustments, for the HAM-D total score, HAM-D depressed mood item, and CGI severity score for the three treatment groups, as well as statistical testing of the inter-group comparisons for both the LOCF (last observation carried forward) and OC (observed cases) datasets of the ITT population.

Evaluation of treatment-by-center effects involved the grouping of small centers with large centers. The results were consistent across centers: treatment-by-center group interaction was not statistically significant for HAM-D total score at week 12 LOCF ($p=0.609$) or OC ($p=0.896$).

With respect to the HAM-D total score, there was a strong trend toward statistical superiority of paroxetine CR over placebo at weeks 6 and 8 ($p=0.057$) in the LOCF dataset, with clear superiority at weeks 10 and 12. The drug/placebo difference in the change from baseline at week 12 was 2.6 points in the HAM-D total score. In the OC dataset, paroxetine CR beat placebo to a degree that was highly statistically significant at weeks 6, 8, 10, and 12 (p -values <0.01).

Regarding improvement in the HAM-D depressed mood item, paroxetine CR was superior to placebo ($\alpha \leq 0.050$) from week 4 onward in both LOCF and OC datasets, with robust differences at weeks 10 and 12 ($p \leq 0.001$).

Changes in the CGI severity score were not as marked but do support the HAM-D results. In the LOCF, the difference in median scores trended toward significance at week 10 with drug superiority at week 12. Paroxetine CR beat placebo at weeks 6, 8, and 12 in the OC dataset.

Conclusions

This study provides solid evidence of the antidepressant efficacy of paroxetine CR compared to placebo in depressed, elderly outpatients.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

The sponsor's analysis plan did prospectively define covariates (namely age, gender, baseline HAM-D total score, and duration of current depressive episode) which might influence treatment response. Since there was a significant treatment-by-center interaction in the efficacy results for study 448, plans for pooling studies 448 and 449 in a meta-analysis were not undertaken and data for each study (448, 449, and 487) was presented separately.

For all three studies, the primary statistical analysis in each study adjusted for center and the above covariates. If a particular covariate was found to have a significant effect in the model ($p \leq 0.05$), then the statistical significance of the interaction of this covariate with treatment in the model was tested. If a significant treatment-by-covariate interaction was found ($p \leq 0.10$), then the interaction was further explored using appropriate subgroups. This discussion will generally focus on results from analysis of HAM-D total score change from baseline data at week 12 in the LOCF dataset.

Race was not specified a priori as a covariate since race was not considered by the sponsor as likely to affect response to therapy. While I do not necessarily agree, comparisons of the drug/placebo difference in HAM-D total score between white and non-white subgroups cannot be meaningfully interpreted because the relatively small numbers of non-white patients in studies 448 and 449.

A significant covariate interaction was demonstrated for the baseline severity of illness in studies 448 and 449. A subgroup analysis was performed by comparing patients with a baseline HAM-D total score < 25 versus those with a baseline score ≥ 25 . However, interpretation of this interaction is complicated by the apparently opposite effects seen in these two studies.

In study 448, for both the paroxetine CR and paroxetine IR treatment groups, more severely depressed patients responded better in terms of change in HAM-D total score than the less ill patients when all centers were included in the analysis, with the more severely ill placebo patients doing worse than the less ill placebo patients ($p = 0.013$ for-week 12 LOCF). However, after excluding center group 2/4, which

demonstrated a pronounced drug/placebo difference as described above, the interaction became non-significant ($p=0.257$ at week 12 LOCF). Thus, the sponsor attributes the interaction to the poor placebo response in center group 2/4.

In study 449, patients with less severe illness appeared to have a slightly better response to paroxetine CR, whereas the opposite was true for paroxetine IR in this study. But the assessment of baseline severity-by-treatment interaction was not statistically significant ($p=0.114$ at week 12 LOCF).

An assessment of the baseline severity-by-treatment interaction in study 487 was also found to be non-significant ($p=0.694$ at week 12 LOCF).

Overall, given these opposing findings and the relatively small numbers of patients in the more severely ill subgroups, which produced wide confidence intervals, it is concluded that there is no clear effect of baseline severity on therapeutic response.

Additionally, in study 487, there was a statistically significant interaction between duration of current depressive episode and treatment at week 12 in the OC dataset ($p=0.003$), but not at week 12 in the LOCF ($p=0.167$). In the OC subgroup analysis (duration groups: <6 months, 7-12 mos., 13-18 mos., 19-24 mos., and >24 mos.), it appeared that paroxetine CR patients with episodes of less than 6 months or longer than 2 years seem to respond less well than the other subgroups. Also, placebo patients with longer episode duration show an inferior response than placebo patients with episodes of recent onset. Response to paroxetine IR seemed fairly even across subgroups. The conflicting results between the two formulations, lack of significant interaction in the LOCF dataset, and large confidence intervals in most subgroups render interpretation difficult but do not, overall, suggest any clear relationship between episode duration and response.

Blood samples for pharmacokinetic examination were obtained from representative samples of patients in studies 448, 449, and 487 at week 4 or week 6 after patients had been on a constant dose of study drug for at least one week. A pooling of this data from studies 448 and 449 revealed no obvious relationship between steady state plasma concentrations of paroxetine (C_{av}) and change from baseline in HAM-D total score. Data from these studies will be pooled with information from study 487 in the future to assemble a larger dataset for PK/PD analysis.

7.3.2 Size of Treatment Effect

Treatment effect size was examined in terms of the difference between paroxetine CR and placebo in the adjusted mean change from baseline to week 12 in HAM-D total score using the LOCF dataset. Results are shown below for the three key studies (448, 449, and 487). Results for paroxetine IR, which is approved for depression, are also displayed for reference.

**Table 7.3.2:
Treatment Effect Size as Expressed by the Adjusted Mean Change from Baseline to Week 12 in the HAM-D Total Score (LOCF)**

Study #	Paroxetine CR			Paroxetine IR		
	Drug	Placebo	Δ^*	Drug	Placebo	Δ^*
448**	-12.0	-10.7	-1.4	-10.7	-10.7	0.0
449	-13.3	-10.2	-3.1	-12.1	-10.2	-1.9
487	-12.1	-9.5	-2.6	-12.3	-9.5	-2.8

* Δ = (Drug Adj. Mean Change) minus (Placebo Adj. Mean Change); statistically significant differences ($\alpha=0.05$) are bolded.

** Excludes center group 2/4.

The observed drug/placebo difference in the two studies that provided reasonable evidence of efficacy (449 and 487) was approximately 3 HAM-D units, which was statistically significant in both cases. The one study in which the approved paroxetine IR beat placebo (487) showed an IR/placebo difference of similar magnitude. It is difficult to judge the clinical significance of this difference but comparable findings for other recently reviewed antidepressants have been considered sufficient to support the approval of those agents.

7.3.3 Choice of Dose

No fixed dose efficacy trials have been conducted with paroxetine CR and, thus, no definitive conclusions can be made regarding dose-response for this formulation.

A fixed dose study conducted in the original paroxetine (IR) depression program (PAR 09) was somewhat flawed in design and, thus, did not provide data on which to make any definitive statement about the benefits of doses higher than the starting dose for that formulation (20 mg/day), which might have been extrapolated to the CR formulation.

For most patients, the sponsor has proposed 25 mg/day as the initial dose, with increases in 12.5 mg/day/week increments to a maximum of 62.5 mg/day in patients not demonstrating an adequate therapeutic response. Elderly or debilitated patients and patients with severe renal or hepatic impairment should be started at 12.5 mg/day with increases to a maximum of 50 mg/day if indicated.

Based on the dose ranges employed in the two flexible dose supportive studies (25 to 62.5 mg/day in 449 (non-elderly adults) and 12.5 to 50 mg/day in 487 (elderly adults), these recommendations appear to be reasonable.

7.3.4 Duration of Treatment

No study addressing the long-term efficacy of paroxetine CR has been conducted. However, study PAR 083, which was completed during the depression development program for paroxetine immediate-release, did provide evidence for the maintenance of efficacy for up to 1 year following acute response at an average daily dose of about 30 mg. Thus, it may be reasonable to continue treatment with paroxetine CR for periods exceeding 12 weeks.

7.4 Conclusions Regarding Efficacy

The sponsor has provided evidence from two adequate, well-controlled studies that support the antidepressant effectiveness of paroxetine in the short-term treatment of depression (studies 449 and 487).

It is my opinion that study 448 does not provide convincing evidence of efficacy. There was a clear center group-by-treatment interaction involving center group 2/4, due primarily to an unusually pronounced treatment effect at center 2. Although the analyses which include all centers provide solid evidence of efficacy, the analyses that exclude center group 2/4 fail to demonstrate the superiority of paroxetine CR over placebo except on the HAM-D depressed mood item. Strong results on the depressed mood item, while important to a demonstration of antidepressant efficacy, cannot, in my opinion, serve alone as sufficient evidence of efficacy. Also, it does not seem that the poor results from the exclusion of center group 2/4 are attributable to smaller sample sizes and a consequent loss of statistical power, since the HAM-D total score effect size is considerably diminished.