CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-440

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	21-440
Sponsor:	Forest Laboratories, Inc.
Drug	
Established Name:	Escitalopram oxalate
Chemical Name:	(+)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran-5-carbonitrile, oxalate
Code Name:	Lu 26-054
Formulation:	10 mg and 20 mg ——— tablets
Proposed Indication:	Relapse Prevention of Major Depressive Disorder
Date of Original Submission (received):	October 29, 2001
Materials Reviewed:	Efficacy and Safety information from Study SCT-MD-03, "Placebo-Controlled Evaluation of the Safety and Efficacy of Lu 26-054 in the Prevention of Depression Relapse."
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	3/8/02

EXECUTIVE SUMMARY

Purpose of this review: This review, including this summary, is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of NDA 21-440.

Background. Lu 26-504 is escitalopram (SCT) which is the S-enantiomer of citalopram (the racemate). SCT and citalopram are selective reuptake serotonin inhibitors (SSRIs). Citalopram is currently marketed under the brand name of Celexa™ for Major Depressive disorder (MDD). The sponsor is seeking approval for efficacy claims regarding "relapse prevention" in patients with MDD (by DSM-IV criteria) based on results of Study SCT-MD-03 (referred to as MD-03). The study is entitled "Placebo-Controlled Evaluation of the Safety and Efficacy of Lu 26-054 in the Prevention of Depression Relapse." The results of this study were provided as an amendment 10/19/01 submission under NDA 21-323. Therefore, the sponsor cross-references this submission regarding the efficacy and safety results Study MD-03. NDA 21-323 was previously submitted for the approval of SCT in the treatment of MDD based on results short term trials of MDD (8-weeks). The status of NDA 21-323 is Approvable at the time of this writing.

Summary of Clinical Results. The primary objective and overall design of study MD-03 was to compare SCT treated patients to placebo on efficacy on "relapse rates" over 36-weeks of double blind treatment (Double-blind Phase) in patients with MDD who responded to 8-weeks of open label SCT treatment (Open Label Phase). A response was defined as a Montgomery Asberg Depression Rating Scale (MADRS) score of 12 or less. A relapse was defined as a MADRS≥22 or discontinuation for insufficient therapeutic response. The relapse rate is defined as the time from start of double-blind treatment to the time of relapse using survival analysis procedures. A secondary objective was to assess safety of "longterm" SCT treatment.

Study Population. 504 subjects (Ss) were enrolled within 72 hours after completing one of the short term MDD trials (Studies SCT-MD-01 or SCT-MD-02). These Ss were generally healthy, adult male and female outpatients with MDD (by DSM-IV criteria). The short term lead-in studies (SCT-MD-01 and SCT-MD-02) were double-blind, placebo controlled, parallel group trials of 8 weeks of treatment with SCT, placebo or citalopram (described in the NDA 21-323 submission). A total of 274 Ss (181 SCT Ss and 93 Placebo Ss) received at least one dose of study drug and had at least one post-baseline assessment (the Double-blind Efficacy Population).

Study Results. The risk of relapse in the SCT group was 44% lower than the placebo group (hazard ratio of SCT to placebo=0.56, p=0.013). Secondary efficacy results generally showed positive results. The safety results of the study were generally similar to that observed in the short-term (8 weeks) SCT trials (refer to Amendment 1 Clinical Review of NDA 21-323). Possible exceptions to this conclusion are results on weight gain and on treatment emergent AEs of muscoloskeletal symptoms (arthralgia, back pain), influenza-like symptoms, sinusitis and rhinitis observed in the double-blind phase or in longer term safety populations of Study MD-03.

Cardiac related safety results previously described in the Clinical review of the short term MDD trials of SCT under NDA 21-323 included bradycardia, conduction defects of a potential QT prolongation and reports of junctional nodal arrhythmias in some SCT Ss (including reports of AV block, bundle branch block and others). Study MD-03 does not appear to reveal any new findings with regards to these earlier observations. Evidence for a possible QT and QTc prolongation appeared to be revealed in the Open Label phase of Study MD-03 and in long term SCT safety populations (the > 8week and > 16 week SCT longterm safety populations) of this study. Yet, a number of methodological issues exist (such as comparing results across

independent studies or the absence of a placebo group) that impact on the interpretability of these results, as described in more depth in the review. Results of the double-blind phase of the study showed that group mean changes in QTc and QT intervals do not increase with continued (ongoing) treatment in the SCT group. This observation is based on a comparison of data collected near the end of the 8-week open label SCT phase to data collected at treatment endpoint of the double-blind phase. Using these same data, numerical comparisons between the SCT and placebo groups on mean change in QTc interval of the double-blind phase failed to show evidence for a treatment group effect on QTc prolongation with continued treatment.

Conclusions. Study MD-03 together with results of long term citalopram studies (described in Celexa® labeling) provides evidence for continued efficacy for up to approximately 36 weeks of treatment with SCT in outpatients with MDD who respond to acute (8-week) treatment (pending confirmation by Biometrics). However, efficacy claims on "prevention of relapse," as proposed by the sponsor were not supported by Study MD-03, as the study was not designed to examine the prevention of relapse with SCT treatment.

SCT appears to be adequately safe for a period of up to approximately 36 weeks of treatment at daily doses of 10 to 20 mg in generally healthy outpatients with MDD. This conclusion is based on results of Study MD-03, the short term SCT trials (under NDA 21-323), along with the known safety of citalopram (as described in Celexa® labeling for both short term and longer term treatment). Results of the short term SCT trials and Study MD-03 appear to reveal a small signal for cardiac conduction effects of SCT. It is not known if these potential effects are enhanced at higher than recommended doses in this population. However, reported cases of citalopram overdoses include cardiac observations suggesting this possibility. Patients at risk for bradycardia, QT prolongation or conduction defects may have increased risk for these conditions when receiving SCT treatment (also consider concomitant medication use and elderly). This conclusion is based on the cardiac results of the short term and longterm SCT trials (refer to Clinical reviews under NDA 21-323 and previous sections of this review), cardiac conduction changes reported in cases of CT overdose (the racemate of SCT), together with preclinical results of SCT and CT (refer to the Pharmacology and Toxicology Review under NDA 21-323). The Division Safety Team is currently reviewing these data. A preclinical study (a 13-week toxicology study in rats) revealed some evidence suggesting cardiomyopathy with SCT treatment. While Study MD-03 and the short term MDD trials failed to reveal evidence for signs of cardiomyopathy, the possibility for development of cardiac injury or cardiomyopathy with SCT treatment in humans cannot be ruled out.

Safety results of study MD-03 also revealed some evidence for weight gain associated with longterm treatment. In addition to this observation, some AEs appeared more prominent in the SCT group compared to placebo in the double-blind phase of the study that did not appear prominent in short term MDD trials (such as some musculoskelatal symptoms, influenza-like symptoms and possibly rhinitis and sinusitis).

I. Introduction and Background.

The purpose of this review is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of NDA 21-323 and NDA 21-440. Lu 26-504 is escitalopram (SCT) which is the S-enantiomer of citalopram (the racemate), a selective reuptake serotonin inhibitor (SSRI). Citalopram is currently marketed under the brand name of Celexa™ for Major Depressive disorder (MDD). The sponsor is seeking approval for efficacy claims regarding "relapse prevention" in patients with MDD (by DSM-IV criteria) based on results of Study SCT-MD-03 (referred to as MD-03), entitled "Placebo-Controlled Evaluation of the Safety and Efficacy of Lu 26-054 in the Prevention of Depression Relapse." The sponsor cross-references the amendment 10/19/01 NDA 21-323 submission regarding the efficacy and safety results of Study MD-03, since these results were submitted under NDA 21-323. NDA 21-323 is a previously submitted NDA for the approval of SCT in the treatment of MDD based on results of 8-week short term trials in patients with MDD. The status of NDA 21-323 is Approvable at the time of this writing.

Efficacy and safety results from Study MD-03 were submitted as a 31 hard copy volume, dated 10/19/01 as an amendment submission under NDA 21-323 (which also included SAS Transport data sets and of Case Report Forms of serious adverse events and adverse dropouts as described in their cover letter). However, proposed efficacy claims and safety changes in labeling that are based on this longer term study are made under the separate NDA21-440. This separate NDA was submitted because Study MD-03 was not completed with results analyzed until late in the review cycle of NDA 21-323. The submission of a separate NDA was previously discussed between the Division and the sponsor (refer to the sponsor references a 12/19/00 letter under [redacted]. As previously agreed upon, the sponsor cross-references the amendment 10/19/01 NDA 21-323 submission for both efficacy and safety results of Study MD-03 supporting their efficacy and safety claims proposed in NDA 21-440.

A. Indication of Proposed Direction of Use

The sponsor recommends (under the Dosage and Administration section of proposed labeling) a starting dose of 10 mg of SCT, administered daily, in the morning or evening (with or without food). Patients failing to respond to one week of the 10 mg daily dose, are recommended by the sponsor, to benefit from an increase in the daily dose to 20 mg. The present submission includes claims pertaining to efficacy in "preventing relapse" with 36 weeks of dosing at 10 to 20 mg a day following 8 weeks of initial treatment. The sponsor makes their claim for continued treatment for the "prevention of relapse" under a new subsection of the Dosage and Administration section of labeling, "Continuation Treatment," in addition to having a subsection of "Maintenance Treatment."

B. State of Armamentarium for Indication

Classes of pharmacological drug products or specific drug products (generic names) currently approved for treatment of MDD include the following:

- A number of SSRIs
- Tricyclics, historically referred to as Tricyclic antidepressant agents (such as imipramine and others)
- Monoamine Oxidase Inhibitors
- Serotonin and Norepinephrine reuptake inhibitors
- Serotonin 2 antagonists and serotonin reuptake inhibitors (Trazodone and Nefazadone)

- Bupropion, which appears to be a weak blocker of the neuronal uptake of serotonin and norepinephrine, as well as having some inhibitory effect on reuptake of dopamine.

C. Administrative History
Refer to the second paragraph under the major section heading, above (Section I, Introduction and Background).

D. Related Reviews
Related NDAs are described in previous sections. NDA 20-822s and 21-046 are related NDAs on the racemic compound, Celexa™ (citalopram hydrobromide) tablet and oral solution formulations. These Celexa™ drug products were approved for treatment of MDD. The date of approval for Celexa™ for this indication was 7/17/98.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Biopharmaceutics, Statistics, and/or other Consultant Reviews.
There is no new chemistry, animal pharmacology or biopharmaceutical information to review in this submission. At the time of this writing, there are no statistical issues regarding the results of Study MD-03.

III. Human Pharmacokinetics and Pharmacodynamics
There are no pharmacokinetic or pharmacodynamic issues to review in this submission.

IV. Description of Clinical Data and Sources

A. Overall Data: Materials from NDA

The following items were utilized during the course of this clinical review.

Documents Utilized in Clinical Review	
DATE	DESCRIPTION
October 29, 2001	• NDA 21-440 N000; a one volume paper submission containing proposed labeling information and various required certifications and completed forms. NDA 21-323 10/19/01 amendment submission (BM) cross-referenced in NDA 21-440: 31 Hard copy clinical volumes for Study MD-03 which included Electronic Case Report Forms and SAS Transport data sets. Other sections of NDA 21-323 were also cross-referenced to support NDA 21-440. • Additional NDA 21-440 submissions:12/10/01 N-BM, 1/10/02 N-BM, 2/15/02 NC.

B. Tables Listing the Clinical Trials

Table IV.B.1. Clinical Studies Reviewed from this Submission					
Protocol No	**Study Design**	**Treatment Groups (36 weeks of Double-blind treatment)**	**N (Completers*) per Treatment group (% of Efficacy Pop.*)**	**N (Double Blind Efficacy Pop.) * per Treatment group**	**N (ITT Double Blind Safety Pop.) ** per Treatment group**
SCT-MD-03 36-Week "Prevention Relapse" Study in SCT Responding Patients with MDD	Multicenter, Double blind, Randomized, Fixed dose, Parallel group 53 U.S. sites	Fixed doses of 10 mg/day SCT 20 mg/day SCT Placebo group	SCT: 92 (51%) Placebo: 31 (33%) **Total: 123**	10 mg SCT group: 95 20 mg SCT group: 86 Placebo: 93 **Total: 274**	10 mg SCT group: 95 20 mg SCT group: 86 Placebo: 93 **Total: 274**

* Completers here refer to subjects completing the double-blind treatment phase of the study.
** Double Blind Efficacy Population: randomized subjects having at least one dose of double-blind study drug (during the double-blind phase of the study) who had at least one post-baseline Montgomery Asberg Depression Rating Scale assessment.
*** Double Blind Safety Population: randomized subjects having at least one dose of double-blind study drug (during the double-blind phase of the study).

Note that the double-blind efficacy and safety populations consist of the same number of subjects, such that all subjects of the safety population also received at least one post baseline Montgomery Asberg Depression Rating Scale assessment.

Efficacy and safety populations for the open-label phase which preceded the double-blind phase of Study MD-03 are enumerated in the following table. The treatment groups shown in this table (placebo, SCT or citalopram) correspond to the treatment group to which subjects were previously assigned during participation in a lead-in study preceding Study MD-03. As described in Section VI of this review, subjects of Study MD-03 were required to complete one of the 8-week lead in studies (Studies MD-01 or MD-02) within 72 hours prior to enrollment to participate in Study MD-03.

Table IV.B.2. Populations of the 8-Week Open Label Escitalopram Treatment Phase of Study MD-03		
Treatment During the Lead-in Study upon entry into Study MD-03	**N (Open Label Efficacy Pop.) * per Treatment group**	**N (Open Label Safety Pop.) per Treatment group**
placebo	145	146
Escitalopram	219	220
Citalopram	138	138
Total Subjects:	**502**	**504**
*Open Label Efficacy population: subjects are from the open label safety population (subjects receiving at least one having at least one dose of open label SCT treatment) who also had at least one post-baseline Montgomery Asberg Depression Rating Scale assessment. Note that 2 subjects of the Open Label Safety Population were enrolled in the open label phase but discontinued prior to receiving open label escitalopram and were therefore not included in the Open Label efficacy Population		

Completers of the double-blind safety population consisted of 123 subjects (45%) in which 31 subjects received placebo (33% of the 93 of the placebo treated double-blind safety population subjects) and 92 subjects received SCT (51% of SCT treated double-blind safety population subjects).

C. Post-Marketing Experience

Escitalopram is approved for marketing for the indications of Depression and Panic Disorder in Sweden (submitted by H. Lundbeck A/S). Five applications were submitted in other non-US countries for approval in the market for [redacted]

No non-US application has been withdrawn from the market or declined authorization for the market due to safety or any other reason.

D. Literature Review

Upon request, an updated literature of SCT and citalopram was provided by the sponsor that covers the period of time since their previous NDA 21-323 submission and amendment submissions to the present NDA 21-440 submission. The results of the literature review are described in another section of this review (Section VII.M). However, methods of the search are described in this section, below.

The search databases and terms employed by the sponsor include the following those itemized below.

Databases:

- MEDLINE (1965- present)
- TOXLINE (1965- present)
- BIOSIS (1969 – present)
- International Pharmaceutical Abstracts (1970-present) EMBASE (1974-present)
- Derwent Drug File (1983-present

Terms:

- S()Citalopram + Escitalopram + RN
- citalopram

V. Clinical Review Methods

A. Materials Reviewed.

Refer to Section IV, above, regarding materials utilized for this review and for a summary of the clinical trials described in the submission.

B. Adequacy of Clinical Experience.

In addition to the safety and efficacy information provided in this submission (which cross-references portions of NDA 21-323, as previously described), the sponsor has described other depression trials for short term efficacy claims in a previous NDA 21-323 submission. This information, together with clinical experience with the racemate, citalopram and data submitted under the NDA for Celexa® reflects adequate clinical experience with SCT.

C. Data Quality and Completeness

The submission generally appeared to show adequate accuracy, consistency and content of information. This conclusion is based on the overall general impression as the submission was reviewed and on a few specific comparisons made between some text information and tables (such as in cases when this reviewer examined incidence tables of supplemental sections cited in the text of the study report, such that the description in the study report appeared to accurately described the results of the table that was cited).

D. Evaluation of Financial Disclosure

The sponsor provided a list of investigators with no disclosable financial arrangements and a list of investigators who could not be contacted (listings included subinvestigators, as well as principal investigators). Only 9 investigators had disclosable arrangements, as described in the submission. The potential bias of these financial arrangements was minimized by study methods, as described by the sponsor as follows: use of double-blind, placebo controlled, multi-center methods, independent site monitoring, randomized site auditing, among others.

VI. Integrated Review of Efficacy

Study SCT-MD-03, entitled "Placebo-Controlled Evaluation of the Safety and Efficacy of Lu 26-054 in the Prevention of Depression Relapse."

A. Investigators and Sites

See Table VI.A.1 in the appendix for a listing of investigative sites (a total of 53 sites in the located in the United States).

B. Objectives

- The primary objective of study MD-03 was to compare SCT treated patients to placebo on efficacy on "relapse rates" over 36-weeks of double blind treatment in patients with MDD who responded to 8-weeks of open label SCT treatment. A response was defined as a Montgomery Asberg Depression Rating Scale (MADRS) score of 12 or less. A relapse was defined as a MADRS≥22 or discontinuation for insufficient therapeutic response. The relapse rate is defined as the time from start of double-blind treatment to the time of relapse using survival analysis procedures.
- A secondary objective was to assess safety of "longterm" SCT treatment.

C. Study Design

Study MD-03 was a 36 week double-blind placebo controlled "prevention relapse" study in which subjects (Ss) were recruited from two lead-in studies MD-01 and MD-02. Studies MD-01 and MD-02 were multicenter, double-blind, placebo controlled parallel group studies of outpatients with MDD. These studies involved 8 weeks of double blind treatment of placebo, SCT or citalopram treatment employing flexible dose (10-20 mg/day SCT) or fixed dose (10 mg/day and 20 mg/day groups) designs. Within 72 hours of completing the final dose of treatment in either of these lead-in studies, Ss underwent an 8-week open label SCT treatment phase of Study MD-03. The starting dose of SCT was 10 mg a day, which was increased to a daily dose of 20 mg at the end of weeks 4 and 6 in nonresponders (MADRS>12), while responders were continued on the 10 mg daily dose. At the end of the 8-week treatment period, Ss classified as responders (MADRS ≤ 12) proceeded to the 36-week double blind treatment phase. These Ss were randomized to receive double blind placebo or SCT in a 2:1 ratio. Ss assigned to SCT remained on the same dose of the drug (10 mg or 20 mg, daily) as they were taking at the end of the 8-week open label phase of the study. SCT and placebo Ss were instructed to take the same number of tablets that they were taking at the end of the open label phase. Ss who met relapse criteria (MADRS of ≥22 or considered to have an "insufficient response") at any visit during double-blind treatment were discontinued from the study.

D. Study Population

504 Ss enrolled in the Study MD-03 were generally healthy, 18 to 81 years old, male and female outpatients with DSM-IV MDD. Ss were required to have completed an 8-week lead-in

study within 72 hours prior to entry into Study MD-03. After completing the open-label phase of the study Ss classified as responders (MADRS ≤12 at the end of the 8-week open-label SCT treatment phase) were eligible for the double-blind treatment phase of the study in which a total of 276 Ss were randomized to study drug. A total of 274 out of the 276 received at least one dose of study drug and had at least one post-baseline assessment (the Double-blind Efficacy Population). See Tables IV.B.1-2 in section IV B, above and the subsection on "Patient Disposition", below, for a further breakdown and disposition of Ss of the Open Label and Double-blind treatment phases.

Various inclusion and exclusion criteria were employed as described in the Study Report of the submission.

E. Assessments Employed

Refer to Table VI.E.1 in the appendix for the study flow chart (as provided by the sponsor) regarding efficacy, safety and screening assessments. As shown in Table VI.E.1, various assessments were conducted on the following visits:

- A Baseline visit
- Visits during the Open Label Treatment Phase (weeks 1-8): weeks 1, 2, 4, 6, and 8
- Visits during the 36-week Double-blind Treatment Phase (weeks 9-44 of the study): initially every 2 weeks (on weeks 10 and 12) followed by every 4 weeks (from weeks 16 to 44, or upon early termination).

F. Analysis Plan

Data Sets Analyzed.

The primary efficacy analyses was conducted on data from the Double-blind Efficacy population using the observed cases (OC) dataset. Secondary efficacy analyses were conducted on the same population but included analyses of last observed carried forward (LOCF) dataset.

Primary Efficacy Parameter.

The time between commencement of double-blind treatment to a relapse. Relapse was defined as a MDARS≥22 or "an insufficient clinical response" during the Double-blind Treatment Phase.

Secondary Efficacy Parameters.

Relapse rates (% of Ss who relapse) were determined for each visit using the OC and LOCF datasets. The sponsor also determined relapse rates when relapse is defined as meeting DSM-IV criteria for a depressive episode (DSM-IV relapse). Relapse rates were also determined when defined as meeting both the DSM-IV relapse and the "crude" relapse (MADRS ≥ 22 or an insufficient response) criteria. Additional secondary efficacy parameters that include measures obtained by using MADRS, Hamilton Depression Rating Scale (HAMD), Clinical Global Impression scale (CGI), CGI-Severity score (CGI-S) and other efficacy scores were analyzed by the sponsor. Other secondary measures were also employed, as described in the submission.

Statistical Tests Employed.

Primary Analysis: Survival analysis tests were employed for the primary efficacy variable (time to relapse). A log rank test was conducted to compare treatment groups on hazards ratios. A Cox proportional hazards regression model was conducted with treatment as a covariate. A Kaplan-Meier survival curve of time to relapse was also determined.

Secondary Analyses: Treatment groups were compared on relapse rates (% of Ss that relapsed) using the Mantel-Haenszel Chi-Square test at each double-blind treatment phase visit. A two-way analysis of covariance (ANCOVA) was conducted to test for treatment group and

center main and interaction effects on mean change of efficacy measures from baseline to treatment endpoint or at each visit of the double blind treatment phase. The covariate was the baseline efficacy score.

G. Patient Disposition

Section IV above provides the enumeration of Ss in open label and double-blind, safety and efficacy populations (also enumerates Ss in each treatment group and Ss who were completers).

The following table shows disposition of Ss during the 8-week Open-Label SCT Phase focusing on withdraws due to insufficient response or the classification of Ss on the basis of responders versus nonresponders upon completion of the Open Label Phase. Only 2 out of the 504 Ss in the Open Label Safety Population were not included in the Open Label Efficacy Population (refer to Table VI.G.1 in the appendix for a more detailed breakdown of these Ss).

Disposition and Enumeration of the Open Label Safety Population (N=504) During the 8-Week Open-Label SCT Treatment Phase*	
Withdrawn before the Week 8 Visit because of an insufficient response	13 (3% of the Safety Population)
Completers (Ss completing 8-weeks of open label treatment)	377 (75% of the Safety Population)
Nonresponders at the End of Week 8	88 (23% of completers)
Responders	276 (73% of completers)
*At the end of week 8 Ss were classified as responders and nonresponders in which only the responders were eligible for the next study phase (the double-blind placebo controlled treatment phase), while nonresponders withdrew from the study	

Two of the 276 Ss who completed the Open-Label Phase that were also classified as responders, withdrew before receiving double-blind treatment. Consequently, the remaining 274 Ss received at least one dose of double-blind study drug (the Double-blind Safety Population). These Ss also met criteria for being included in the Double-blind Efficacy Populations had at least one post-baseline MADRS score). The following table shows the disposition of these Ss (274 Double-Blind Safety, and also, Efficacy Population) during the Double-Blind Treatment Phase, similar to that provided by the sponsor.

Disposition of the Double-Blind Safety/Efficacy Population (N=274) during the Double-Blind Phase		
Treatment Groups:	**Placebo (N=93)**	**Escitalopram (N=181)**
Completers	31 (33%)	92 (51%)
Withdrawn for Any Reason	62 (67%)	89 (49%)
Adverse Event	6 (7%)	7 (4%)
Insufficient Therapeutic Response	7 (8%)	5 (3%)
Withdrawal of Consent	14 (15%)	19 (11%)
Lost to Follow-Up	8 (9%)	10 (6%)
Protocol Violation	2 (2%)	12 (7%)
Relapse	22 (24%)	30 (17%)
Other	3 (3%)	6 (3%)

H. Baseline Demographics/Medical/Psychiatric Comorbidity and Baseline Efficacy Measures

Baseline Demographics. Treatment groups (Open-Label and Double-blind Safety Populations) were similar on various demographic parameters (mean age and weight, proportion of Ss by gender and by race: Caucasian versus non-Caucasian). The majority of Ss were female (approximately 61%/group) with slightly more women in each SCT group (67 or 70%/group) and most Ss were Caucasian (85 to 87%/group). The mean age of each group was approximately 42 to 43 ±12 years with only 6% to 8% of Ss over the age of 60 years or older. The mean weight of the study cohort was approximately 180 to 184 pounds. Table VI.H.1. in the appendix

(as provided by the sponsor) summarizes these demographic results including demographic results on Ss receiving SCT treatment for periods exceeding 8 weeks or 16 weeks of daily treatment (the longer term safety populations, refer to Section VII.A. which provides a more detailed definition of longterm safety populations).

Medical and Psychiatric Comorbidity. The incidence rates of non-MDD psychiatric disorders (current and past) in treatment groups of the ITT Safety population (N=274) were generally similar and small in magnitude (generally ranging from 0 to <3% in each group). However, the following disorders were exceptions:

- Dysthymic disorder: 2.8% of SCT Ss (5/181) and 5.4% of Placebo Ss (5/93)
- Anxiety disorders (as a major category): 3.3% of SCT Ss (6/181) and 7.5% of Placebo (7/93)

The majority of the Ss had an abnormal medical history (93%). Treatment groups were generally similar in incidence rates of abnormal medical histories (also categorized by organ system). Treatment groups of each lead-in study (MD-01 and MD-2) were generally similar in incidence rates of current medical or psychiatric disorders. In study MD-01, ongoing anxiety disorders (as a general category encompassing DSMIV anxiety disorders) were reported in 10% of Ss of which most of these Ss had Generalized Anxiety disorder (5% of Ss). All other major psychiatric disorders were reported in 3% of Ss or less. In Study MD-02, 3% of Ss or less reported a given major category psychiatric illness, as ongoing (or when each major category is subcategorized by each specific psychiatric disorder).

Treatment groups (of the Safety Population) of Study MD-03 were also similar on demographic features pertaining to their history of MDD, such as the duration of the disorder (approximately 12 years) and the incidence of Ss having a previous major depressive episode (approximately 66 to 70% of Ss/group). Approximately 30% of Ss had a history of being treatment resistant.

Mean Efficacy Scores at Baseline

The Table VI.H.2 in the appendix shows the mean baseline scores for various efficacy measures (the MADRS, HAMD and the CGI-S) for the Open-Label (N=502) and Double-blind (N=274) Intent to Treat Populations of Study MD-03. Table VI.H.3 in the appendix, shows results of mean change from baseline to treatment endpoint of the open label SCT phase on various efficacy scores (MADRS, HAMD and CGI-S, LOCF dataset). Ss who received placebo during the lead-in studies, showed a numerically greater mean decrease in each of the efficacy scores than Ss receiving SCT or citalopram in the lead-in studies (no statistics were performed).

Table VI.H.2 shows that baseline efficacy scores of the double-blind SCT group were numerically greater than the placebo group of the double-blind phase of the study. These treatment group differences were significant or showed trends for being significant ($p=0.02$ on the MADRS, $p=0.02$ on the HAMD, and $p=0.18$ on the CGI-S). Similar results were revealed on mean baseline HAMA scores (as described in the submission, mean scores of 5.2 and 6.4 in placebo and SCT groups, $p=0.003$). However, the magnitude of these observed differences between the treatment groups were small (approximately one point on the MADRS and HAMD and of only 0.1 point on the CGI-S). Furthermore, these differences were in a direction in which a greater relapse rate in the SCT group than in the placebo group may be anticipated, rather than in the opposite direction as hypothesized for demonstrating efficacy with SCT treatment.

Concomitant Medications.
Treatment groups of the double blind treatment phase were similar in the percentage of subjects taking concomitant medications (approximately 76 to 88%/group) and were generally similar in the distribution of Ss across various medication categories. Common (≥10% in any of the groups) concomitant medications were as follows:

- Analgesics
- Antacids, drugs for treatment for peptic ulcer disease and flatulence
- Systemic Anti-bacterials
- Systemic Anti-histamines
- Anti-inflammatory and anti-rheumatic products
- Cough and Cold preparations
- Nasal preparations
- Sex hormones and modulators of the genital system
- Vitamins

I. Efficacy Results

Primary Efficacy Results (Time to Relapse). The table below shows primary efficacy results similar to Table 3.1 in the submission (volume 3 of the 10/19/01 NDA 21-323 amendment submission). The risk of relapse in the SCT group was 44% lower than the placebo group (hazard ratio of SCT to placebo=0.56, p=0.013).

Primary Efficacy Results (Time of Relapse) of the Double-blind Efficacy Population		
	Placebo (N=93)	Escitalopram (N=181)
Cumulative Rate (%) of Relapse*	40	26
25% Quantile (days)	56	188
Hazard ratio of Escitalopram TO Placebo**	0.56	
95% C.I. for the hazard ratio	(0.35, 0.89)	
p-value***	0.013	
*Relapse defined as MADRS≥22 or discontinued due to an insufficient response ** based on Cox proportional hazards regression model with treatment as the covariate *** level of significance based on the log-rank test		

Secondary analyses included relapse rates by visit during the Double-blind Phase (visit weeks 10 through 44) with results summarized in Tables VI.I.1 (for the LOCF dataset) and VI.I.2 (for the OC dataset) of the appendix (as provided by the sponsor). The following are some preliminary observations which are primarily based on numerical comparisons of the results in these tables, unless otherwise specified. Upon examination of Table IV.I.1 of the LOCF dataset results, the incidence of relapse appears to peak at week 20 in the placebo group and at week 36 in the SCT group. The greatest difference between treatment groups appeared to occur on visit weeks 12, 16 and 20 (a 10-15% difference, p value ranging from 0.004 to 0.025). Only trends for greater relapse in placebo Ss compared to SCT Ss were observed in later weeks (on visit weeks 28, 32, 36, 40, and 44, p values of 0.05-0.06).

Upon visual examination of relapse rates of the OC dataset in Table VI.I.2, trends (p values of 0.02 to 0.06) for a greater relapse rate in placebo Ss compared to SCT Ss were observed on visit weeks 10, 12, and 20. These results may be reflecting a larger relapse rate occurring early in the

double blind phase (prior to week 20) and a smaller sample size of Ss remaining in the study, as the accumulative number of dropouts (due to multiple reasons) increases with time (over the 36 week double blind treatment phase). It is noted that the majority of relapses in each treatment group occurred prior to week 20 (23 out of 93 placebo Ss and 25 out of 181 SCT Ss relapsed).

Secondary Efficacy Results.

DSM-IV and Full Relapse Rates. Results of relapse rates (defined by various criteria) over the Double-blind treatment phase are summarized in the following table.

Relapse Rates (defined by various criteria) During the Double Blind Treatment Phase of the Intent to Treat Population			
	Placebo (N=93)	Escitalopram (N=181)	p-value
Crude Relapse**	33%	23%	0.06
DSM-IV Relapse***	35%	23%	0.03
Full Relapse****	29%	20%	0.10
** Relapse defined as a MADRS ≥ 22 or an insufficient response *** Relapse defined as meeting DSM-IV criteria for a depressive episode **** Relapse defined as Ss who meet both the crude relapse and the DSM-IV criteria.			

Mean Change in the MADRS, HAMD and CGI-S Scores at Treatment Endpoint and Over Each Visit in the Double-Blind Phase of the Study.

Table VI.I.3 in the appendix (as provided by the sponsor) shows that in the LOCF dataset, there were at least trends for (or significantly) less mean increases (or worsening of symptoms) from baseline to treatment endpoint in SCT Ss compared to placebo on each efficacy variable (MDRS, HAMD and CGI-S) during the Double-blind Phase of the study. A mean increase in each efficacy score (worsening of symptoms) observed in each treatment group may be reflecting high scores in Ss that relapsed who were included in the LOCF dataset analysis (the high scores were carried forward), as suggested by the sponsor. Consistent with this interpretation, the OC dataset, which excludes these Ss (excludes Ss that relapse at subsequent time-points), reveals mean changes on efficacy scores in the opposite direction (an improvement) in each treatment group. The SCT group in this dataset showed at least trends for greater improvement than the placebo group (p=0.05 for MADRS and HAMD and p=0.01 for the CGI-S).

When examining the mean change of efficacy scores from baseline to each visit of the double-blind phase, a numerically greater improvement in SCT Ss compared to placebo appears to exist for most time-points. However, these numerical group differences generally appear to be smaller between visit weeks 16 through 40 (p values generally range from 0.2-0.9), than that observed on the first few visits of treatment (visit weeks 10, 12, and possibly week 16) and on the final study visit (visit week 44).

Time to Relapse Adjusted for MADRS Baseline score, Age, Gender, Race and Depression History

The majority of Ss were Caucasian and the number of Ss in other groups of ethnic origin were insufficient to provide meaningful results from an analysis of the primary efficacy variable (Time to Relapse) on the basis of ethnic origin. However, the sponsor conducted an analysis on time to relapse for Caucasians versus Non-Caucasian subgroups and for gender subgroups in which the sample sizes in these subgroups were adequate. Other variables of interest could be

analyzed as continuous variables. The results of these analyses are summarized in the following table.

Time to Relapse* Adjusted for MADRS Baseline Score, Age, Gender, Race and Depression History of the Double Blind ITT Population			
	Risk Ratio**	**95% CI for Risk Ratio**	**p-value*****
SCT vs. Placebo	0.53	(0.33,0.85)	0.008
Baseline MADRS Score	1.08	(1.01,1.15)	0.022
Age	1.01	(0.99,1.03)	0.29
Male vs. Female	1.03	(0.64,1.67)	0.901
Caucasian vs. Non-Caucasian	0.78	(0.4,1.52)	0.473
Single Episode vs. Recurrent	1.31	(0.8,2.15)	0.288

This table is similar to Table XI.2.3 in the submission

* Relapse = MADRS ≥ 22 or discontinuation due to an insufficient clinical response during the double-blind phase

** Risk rations were calculated from Cox proportional hazards regression model comparing SCT vs. placebo, respectively

*** p-values are based on Wald statistics from proportional hazards regression model

J. Conclusions of Efficacy Results of Study MD-03.

The results of Study MD-03 show a significantly longer mean survival time to relapse (or rate of relapse) in SCT treated Ss relative to placebo Ss (pending final confirmation by Biometrics). According to the Biometrics Reviewer (per communication on 2/20/02) the mean survival time was 176 days in the SCT group compared to 147 days in the placebo group. While a number of relapses appeared to occur before Day 56 in the placebo group of the double-blind treatment phase (22 relapses out of a total of 31 relapses, or 71%), several relapses occurred at later time points (with the last relapse on Day 204). Treatment groups did not show significant differences on the time-to censorship or on the rates of censored Ss during the double-blind treatment phase (per communication with the Biometric reviewer). Therefore, treatment group differences on mean survival time, appear to primarily reflect the rate of relapse, rather than rate of censored Ss or time to censorship.

No gender effect was observed by the sponsor on the primary variable, except for the mean baseline MADRS score ($p=0.022$). Nevertheless, when adjusting for potential confounding variables a significant hazard ratio of 0.53 was revealed ($p<0.01$) in which there was a 47% lower risk of relapse rate in the SCT Ss than placebo Ss. The effect of gender on time to survival the risk ratio was 1.03 ($p>0.05$) as shown previously in the above table. Other confounding variables included in the sponsor's analyses in the above table, were age, baseline MADRS score, Caucasian vs. non-Caucasian, Single episode versus recurrent. However, these results are considered preliminary, given the sample size and the number of variables analyzed.

Other factors or caveats impacting on the interpretation of the efficacy results of Study MD-03 are discussed below.

Potential caveats regarding efficacy results of Study MD-03.

One potential consideration regarding the efficacy results of Study MD-03 is if higher relapse rates in the first few weeks of double blind placebo Ss were reflecting undetected adverse events (or adverse dropouts) associated with treatment cessation. There are reports of adverse events (AEs) associated with treatment cessation of various SSRIs. However, the AEs (i.e. parasthesias, abnormal dreams, sweating, nausea, dizziness and others) are typically clinically

distinct from symptoms of major depressive disorder. Hence, the investigator may generally be anticipated to make an adequate, clinical distinction between a relapse of the major depressive disorder and the appearance of AEs associated with treatment cessation. Furthermore, the placebo group had a mean survival time of147 days and an apparent peak period of relapse of approximately 12 weeks of double-blind treatment (based on numerical comparisons). These time periods appear to exceed that anticipated for the emergence of AEs associated with treatment cessation. This conclusion is based on the known half-life of SCT and major active metabolites, together with observed AEs associated with treatment cessation of other SSRIs, including several years of postmarketing experiences with Celexa,® the racemate of SCT (refer to the Safety Section VII of this review for safety results pertaining to this topic). Furthermore, the use of a double-blind treatment study design minimizes a potential for treatment group bias in classifying Ss as having a relapse of major depressive disorder versus AEs associated with the assigned study drug or with treatment cessation of SCT.

Another consideration regarding efficacy results, is that the study population was enriched. Given that Ss not only successfully completed treatment in a lead-in study, but also were responders to short term SCT treatment, it would be anticipated that these Ss are less likely to dropout due to an AE or due to an insufficient response. Despite this possibility, the relapse rate was greater in the placebo group compared to SCT group in which a double-blind, randomized design was employed. However, labeling should reflect that the study population examined was that of SCT treatment responders.

Group differences in mean efficacy scores at baseline (prior to double-blind treatment) were observed in which the SCT group had higher mean scores. However, for reasons already provided under subsection I (above) these differences do not appear to account for the positive results of Study MD-03 on time to relapse (or on relapse rates). A mean worsening of efficacy scores (a mean increase from baseline to each visit) at various time-points was observed in both treatment groups during the Double-blind Phase with the LOCF dataset but not with the OC dataset, in which the later showed a numerical improvement in each treatment group. However, these results appear to reflecting the inclusion of Ss that relapse in the LOCF dataset who are excluded from subsequent time points during the double-blind phase in the OC dataset, as previously discussed. Furthermore, the SCT Ss appeared to show at least a numerically greater improvement on efficacy measures than placebo Ss in the OC dataset. However, secondary efficacy results involving multiple treatment group comparisons, small sample sizes, and multiple dependent variables are considered preliminary.

One potential issue regarding the positive efficacy results of Study MD-03, is the possibility of pseudospecificity of SCT treatment in patients with MDD. This potential issue was previously addressed in a Clinical review of the short term trials under NDA 21-323 in which it was concluded that pseudospecificity did not appear to account for the positive results observed in the short term trials. In addition to that previously described, the following are additional reasons for making a similar conclusion regarding the positive results of MD-03. Firstly, few Ss in Study MD-03 had other concomitant psychiatric and were Ss who completed a short term trial. Anxiety disorders, which commonly coexist with MDD, were reported in only a few Ss in Study MD-03 (approximately 3% of SCT Ss and 8% of Placebo Ss). Secondly, a greater relapse was observed in the Placebo Ss compared to SCT Ss, using various criteria for relapse, including one definition in which Ss must meet DSMIV criteria for a major depressive disorder to be given a relapse classification (35% of placebo compared to 23% of SCT met the DSMIV criteria). These observations, in addition to the rationale provided in the Clinical

review of the short term MDD trials (NDA 21-323), support the conclusion that potential psuedospecific effects of SCT do not appear to account for significant treatment effects on time to relapse in patients with MDD in study MD-03.

VII. Integrated Safety Information

A. Background Information

A review of serious AEs (SAEs), adverse dropouts (ADOs) and common AEs of Study MD-03 was previously conducted under NDA 21-323 (see Clinical Review Amendment 1, completion date of 11/19/01 under NDA 21-323). For the convenience of the Team Leader and Division Director, these sections of the previous review are also provided in corresponding sections below. Results on the incidence rates of outliers and descriptive statistics (no statistical tests were conducted) on laboratory, vital sign and ECG measures are also summarized.

The sponsor examined safety data from the following safety populations (Ss must have at least one dose of study drug in a given study phase to be included in the safety population for that phase of the study):

- Open Label Safety population
- Double-blind Safety population
- The following longterm SCT safety groups:
  - SCT > 8 week longterm safety group: Ss that received at least 8 weeks of open-label SCT and were randomized to the SCT group of the double-blind phase of Study MD-03. Inclusion of Ss into this longterm safety group was independent of what study drug Ss received (placebo, SCT or citalopram) during the lead-in study (Studies MD-01 and MD-02).
  - SCT > 16 week longterm safety group: Ss who received SCT during the lead-in study (8 weeks of double-blind treatment), followed by the 8-weeks of SCT of the open label phase of Study MD-03, and were also assigned to the SCT group of the double-blind phase of Study MD-03. Therefore, this group is a subset of the SCT >8 week longterm safety group in that this subset had 16 weeks of SCT treatment prior to receiving SCT treatment during the double-blind phase of Study MD-03.

This paragraphs raises several key points regarding the safety results, as provided by the sponsor for various safety populations (as above) that impact on how results may be interpreted. First, the Open Label phase of the study was not placebo controlled and was not double-blind. While, a placebo group was employed during the double-blind phase of the study "baseline" values used for descriptive statistical results for this phase, were obtained while Ss were receiving open label SCT. That is, "baseline" for the double-blind phase was the last assessment of the open label phase of the study (after 6 weeks or 8 weeks of open label treatment). Consequently, while there was a placebo group to allow for treatment group comparisons on safety measures of the double-blind phase, the baseline measures that were examined did not reflect a true pre-dose baseline value. Instead, results of the double-blind phase, are more likely to reflect the effect of continued treatment of SCT compared to cessation of open label SCT treatment and continued treatment with placebo. In contrast to baseline values employed for these analyses, "baseline" for safety results of the open label phase and each of the two longterm SCT safety populations (> 8 weeks and >16 weeks) did reflect a pre-drug exposure measure. Baseline for these safety populations and for the Open Label phase of the study was defined as prior to randomization to double-blind drug in the lead-in studies. Yet, a caveat to using these

"baseline" values is that they were obtained from separate, independent studies (two lead-in studies which are compared to a third study, Study MD-03). Therefore, these comparisons may only be considered preliminary. Finally, the sponsor employed time-windows for each study visit that ranged over a number of days or weeks. The time window for the last visit of the double-blind treatment phase of the study (week 44) occurred between Days 239-278 (with Day 252 corresponding to 36 weeks of double-blind treatment). Despite this caveat, no pre-randomization visit was considered a double-blind visit and no post-randomization visit was considered an open-label visit. While taking these caveats under consideration safety results are described below.

B. Demographic Characteristics

Demographic features of the study populations of MD-03 are described in a previous section of this review (under section IV). In summary, treatment groups in the double-blind phase of Study MD-03 and safety populations across study phases and longterm safety populations (open label, double-blind phases and >8 week and >16 week longterm SCT safety populations) were generally similar on each demographic feature. The demographic features of the safety population of MD-03 also appeared to be generally similar to the safety population of the four short term (8-week) depression trials studies (MD-01, MD-02, 99001 and 99003), combined, noting that two of these short-term trials were lead-in studies of MD-03 (Studies MD-01 and MD-02 were the lead-in studies).

C. Extent of Exposure

The total exposure of the ITT Safety Population: 151 patient years (32 patient years for placebo Ss) and exposure of the Safety population by study phase or by longterm safety groups was as follows:

- In the Open Label Phase: 69 patient years in SCT Ss
- In the Double Blind Phase: 82 patient years in SCT Ss
- The SCT > 8 week longterm safety group (as defined above): 123 patient years
- The SCT > 16 week longterm safety group (as defined above): 58 patient years

The dose assignment of SCT Ss of the ITT Safety population (also the Efficacy population) during the 36 week double-blind treatment phase of Study MD-03 (N=181) was as follows:

- 10 mg/day group: 95 Ss (53%)
- 20 mg/day group: 86 Ss (48%).

SCT exposure expressed in mean duration was as follows:

- In the Open Label Phase: 50 days
- In the Double Blind Phase: 24 weeks in SCT Ss (18 weeks in placebo randomized Ss)

The mean daily dose of SCT at the end of the open label phase of the study was 14.5 mg/day. Out of the 504 Ss in the Open Label phase Safety population (Ss who received at least one dose of open label drug), 55% of these Ss were taking 10 mg/day and 45% were taking 20 mg/day.

Exposure of Completers (mean duration in weeks) of the Double-blind Treatment Phase of Study MD-03.

SCT completers (N=92): 36±0.6 weeks (median of 36 weeks, range of 34-38 weeks)

SCT completers of each treatment group (note that a fixed dosed design was employed for the double-blind phase of the study):

10 mg SCT group (N=50): 36±0.7 weeks (median of 36 weeks, range of 34-38 weeks)

20 mg SCT group (N=42): 36±0.6 weeks (median of 36 weeks, range of 34-37 weeks)

Placebo completers (N=31): 36±0.8 (median of 36 weeks, range of 35 to 39 weeks)

Additional Exposure information of Longterm Safety Populations.

The enumeration of Ss exposed to at least (approximately) 6 months (>24 weeks) or one year (>48 weeks) of SCT (during open-label and double blind phases) was a total of 125 Ss and 39 Ss, respectively, out of 179 Ss randomized to double-blind SCT treatment.

Exposure of the longterm safety groups expressed as mean daily dose was as follows:

- The SCT > 8 week longterm safety group (as defined above): 13.8 mg/day
- The SCT > 16 week longterm safety group (as defined above): 14.1 mg/day

D. Deaths

There were no deaths reported.

E. Serious Adverse Events (SAEs)

There were 9 serious adverse events (SAEs). 8 of the 9 SAEs were in SCT Ss and occurred during either the open label phase (5 SAEs out of 504 SCT Ss) or the double blind treatment phase (3 out of 181 SCT Ss) of the study. A listing of these Ss is provided in the appendix, as Table VII.E.1. Most of these SAEs occurred in Ss with a history of a pre-existing condition in which the event did not appear to be drug-related. Other events were conditions that were likely not to be drug-related (tonsillitis, appendicitis), that are known to occur in the general population. The only possible exception, was in S1306 who was a 26 year old female reported to have a migraine requiring hospitalization. Given the S's age and gender, she may have been at risk of migraine. Migraine is listed as a frequent event under the "Other Events Observed During the Premarketing Evaluation..." section of proposed labeling for escitalopram submitted under this NDA.

F. Dropouts due to Adverse Events

Results on ADOs in Study MD-03 did not reveal any new or unexpected findings from that previously described in clinical reviews of NDA 21-323. These results are described below.

A total of 46 Ss withdrew from treatment due to an AE and are enumerated as follows:

- During the Open-Label SCT Treatment Phase of the MD-03: 33 out of 504 SCT Ss (6.5%) were adverse dropouts (ADOs). Note that there were no placebo Ss during the Open Label phase of the study.
- During the Double-Blind Placebo Controlled Phase: 7 of 181 SCT Ss were ADOs (3.9%) compared to 6 out of 93 placebo Ss (6.5%).

Three of the 46 ADOs were due to a SAE and are described above under the SAE section. See the complete list of ADOs, as provided by the sponsor, in Table VII.F.1 in the appendix of this

review. The ADOs were similar to those described in previous reviews under NDA 21-323 (four 8-week depression trials, ongoing and Phase I trials).

Selected Ss are described in Table VII.F.2 of the appendix (as described in previous clinical reviews, the10/19/01 Clinical review and the 11/19/01 Addendum 1 Review of NDA 21-323). The selected events listed in Table VII.F. 2 involve cardiac arrhythmias, syncope and a S with markedly elevated liver enzyme levels in which a role of SCT must be considered based on the information provided (noting that some Ss also received citalopram prior to SCT). These events include those also described in labeling for Celexa®. Refer to various sections of the 10/19/01 Clinical review of NDA 21-323 for a discussion regarding bradycardia and cardiac conduction defects observed in some Ss in the SCT clinical trials and various ECG and vital sign observations. In conclusion results of ADOs in Study MD-03 failed to reveal any new safety findings.

G. Specific Search Strategies

No specific search strategies were described in this submission.

H. Adverse Events

Treatment Emergent Adverse Events in Study MD-03.

Incidence rates of AEs for Open Label and Double-blind phases and longer term SCT safety populations of Study MD-03 are described in the submission. The most common AEs during the double-blind phase of the lead-in studies no longer appeared to meet the following criteria during the double-blind phase of Study MD-03: an incidence rate of greater than 5% in SCT Ss with a rate of at least twice that of placebo. However, rhinitis, back pain and influenza-like symptoms which did not meet these incidence rate criteria in the lead-in studies, did in the double-blind phase of Study MD-03. Given that these comparisons were made across different studies and were numerical comparisons, these observations are only considered preliminary. In general, those AEs that did meet the incidence rate criteria during the double-blind phase of MD-03 (of greater than 5% of SCT Ss with an incidence rate of twice that of placebo) were not unexpected for the class of SSRIs or for the MDD population. These observations are described in more detail below.

Common AEs (defined as ≥5% incidence rate in SCT Ss) that occurred in the four 8-week depression trials with an incidence in SCT Ss of at least twice that of placebo included the following (taken from the Clinical Review under NDA 21-323):

- Nausea (7% of Placebo, 15% of SCT, 17% of citalopram)
- Ejaculation disorder (0 in placebo, 9% in SCT, 9% of citalopram)
- Insomnia (4% of placebo, 9% of SCT, 9% of citalopram)
- Somnolence (2% of placebo, 6% of SCT and 4% of citalopram)

The double-blind phase of Study MD-03 revealed that the above AEs did not have an incidence rate of at least 5% of SCT Ss and twice that of placebo Ss. Ejaculation disorder and somnolence did not meet the ≥5% criterion, but appeared to show numerical trends for greater rates in SCT Ss compared to placebo Ss and met the 2 times greater than placebo criteria, as follows:

- Ejaculation disorder (0 in placebo, 4.2% in SCT)
- Somnolence (1.1% of placebo, 2.2% of SCT)

The table below shows common AEs (≥5% in SCT Ss) and were reported in SCT Ss with a rate of at least twice that of placebo in Study MD-03, but did not meet these incidence rate criteria in the short term lead-in trials (MD-01 and MD-02).

Incidence of Selected Common Treatment Emergent Adverse Events in Each Treatment Group (≥5% Incidence in Escitalopram subjects with ≥2 time placebo rates) during the Double-Blind Phase of Study MD-03*		
Preferred Term	**Placebo (N=93)**	**Escitalopram (N=181)**
Subjects with at least 1 AE	60%	69%
Rhinitis	1%	9%
Back Pain	1%	6%
Influenza-Like Symptoms	1%	6%
*These adverse events were selected on the basis that they did not meet the ≥5% and twice that of placebo criteria during in the short term depression trials (8-week trials). The results of this table are generated from Panel 18 in the Study Report for MD-03 submitted under NDA 21-440).		

Sinusitis did not meet criteria to be included in the above table but occurred in 4% of Placebo Ss compared to 7% of SCT Ss. It is not clear why the AEs in the above table and sinusitis, did not meet the common AE twice that of placebo incidence rates criteria in SCT Ss during the 8-week lead-in trials, with the exception that Ss in the double blind phase of Study MD-03 were exposed to SCT longer (had completed 8 weeks of open label SCT). Similar observations appear to exist when making numerical comparisons between the open label phase and the placebo versus SCT groups of the double blind phase of Study MD-03. Sinusitis, back pain and influenza-like symptoms were not common AEs in the Open Label SCT Phase but were common in SCT Ss of the double-blind phase (as shown in the above table). Some of these common AEs (back pain, influenza-like symptoms and others) were also observed in the longterm SCT safety populations and appeared to show numerically greater incidence rates in female Ss compared to male Ss (see subsequent sections). The clinical significance of these observations is not clear and the above comparisons are considered preliminary. It is also noted that vague symptoms such as the above AEs are not uncommon symptoms in the MDD population. The sponsor also shows incidence rates of newly emergent common AEs over time-intervals (weeks 1-8, 9=16, 17-24 and 25-52) in which there were no apparent numerical trends for an increase in the incidence rates of the above described common AEs, but rather many common AEs appeared to show numerical trends for a decrease in incidence rates over time.

Other common AEs appeared to decrease in incidence rates with increasing treatment exposure when making similar numerical comparisons of results of the safety populations, as above. When making numerical comparisons between the Open Label SCT phase and the Double-blind Placebo-controlled phase of Study MD-03, AEs that were common in the Open Label phase were no longer common in SCT Ss of the double-blind phase. These AEs were as follows: dry mouth, diarrhea, fatigue, somnolence and decreased libido. For reasons already described these results are considered preliminary.

Longer Term Treatment Populations of AEs over Time

The incidence rates of AEs in the >8 week SCT safety population over time were described by the sponsor. The AEs with incidence rates of at least 3% higher during the final 28 weeks of double-blind treatment compared to the initial 8 weeks of treatment were as follows (incidence rates correspond to those of the final 28 weeks compared to the initial 8 weeks, respectively):

- Influenza-like symptoms: 8% compared to 4%
- Pain in limb: 5% compared to 1%
- Weight increase: 8% compared to 3%
- Back Pain: 6% compared to 2%
- Sinusitis: 7% compared to 3%

Upon visual inspection of the incidence tables of the >8 week SCT safety population (Table 7.8 in volume 3 of the submission) the following AEs appeared to show consistent numerical trends for increasing incidence rates over time (time intervals examined were 1-8, 9-16, 17-24 and 25-52 weeks):

- Weight increase (3%, 4%, 6%, and 8% over corresponding time intervals)
- Musculo-skeletal system (MSS) disorders (7.7%, 9.9%, 10.8% and 16%, respectively)
  Two subcategories under the MSS disorders category:
  - Arthralgia (1.7%, 2.2%, 3.2% and 4.0%, respectively).
  - Back Pain (1.7%, 4.4%, 3.2%, 6.4%, respectively)

In contrast to the above results on weight increase, weight decrease was reported in only 0.6% of the >8 week SCT safety population in the first eight weeks and 0% at subsequent time intervals.

The sponsor describes some AEs that appeared to show a decrease in incidence rates over time in the >8 week safety population. Incidence rates of newly emergent AEs over time in this population were also described in the submission. These results are shown in Table VII.H.1 in the appendix (as provided by the sponsor).

It is notable that the AE of abnormal ECG was reported in only 1 S of the >8 week SCT longterm safety population between weeks 1 and 8, while no Ss had this AE on subsequent time-intervals.

Subgroup Analyses of AE's on the Basis of Gender, Age-group or Race.

Due to insufficient sample size of Ss over 65 years old and an insufficient number of non-Caucasian Ss, subgroup analyses for treatment effects on treatment emergent AEs on the basis of race or age are not described in this review. The number of male Ss in the placebo group of the double-blind phase of the study was only 35, such that the sample size for subgroup analysis for treatment group effects on the basis of gender was also insufficient. The following are preliminary observations described by the sponsor.

The sponsor reported that a higher percentage of female Ss had treatment emergent AEs than male Ss of the Double-blind phase of Study MD-03 in each treatment group (SCT Ss: 72% compared to 64%, respectively, placebo Ss: 64% compared to 54%, respectively). Among the ten most common treatment emergent AEs in the double-blind phase, the following AEs showed incidence rates in females that were twice that of males in each treatment group:

- Upper respiratory tract infection
- Back pain
- Influenza-like symptoms
- Insomnia
- Nausea

I. Laboratory Findings

Results of the Incidence of Outliers. The incidence rates of Ss meeting potentially clinically significant criteria (PCS) on laboratory parameters in the Double-blind phase of the study are shown below. The parameters with at least 1% of SCT Ss and that also appeared to be numerically greater than placebo are described (these results are based on a visual inspection of the sponsor's summary incidence Table 9.2B). Refer to Table VII.I.1 in appendix for the PCS criteria employed. In summary, the percentages and group differences shown below are small. There were no SAEs due to laboratory results. One treatment emergent AE was due to elevated SGPT levels during open label SCT. Treatment was discontinued due this event (see above section on adverse dropouts).

Incidence rates of Ss meeting PCS criteria during the double-blind treatment phase for selected parameters were as follows (only those with at least 1% incidence rates in SCT Ss that appeared to be numerically greater than the incidence rates in placebo Ss):

- Low Hemoglobin: 1.2% of placebo Ss and 4.1% of SCT Ss
- Low Hematocrit: 0% of placebo Ss and 1.2 % of SCT Ss
- High Eosinophils: 0% of placebo Ss and 1.2 % of SCT Ss
- Increased Protein on Urinalysis: 0% of placebo Ss and 1.8 % of SCT Ss

It is noted that the incidence rates of Ss meeting PCS criteria among SCT Ss of the > 8 week and > 16 week SCT longterm safety populations were as follows:

- 2.8% and 3.9%, respectively for low hemoglobin
- 5.5% and 6.6%, respectively for low hematocrit.
- 3.3% and 5.3%, respectively for high total cholesterol

These observations can only be considered preliminary given the absence of a placebo comparison group (no placebo group during the open-label phase). These results may be reflecting an increase in incidence rates of Ss meeting outlier criteria over time secondary to having increasingly longer periods of monitoring and multiple assessments. Furthermore, a review of the line listings appears to reveal that many of the above outliers in hemoglobin and hematocrit among the longterm safety populations met PCS criteria on these parameters at baseline. The next section on central tendency provides results consistent with this observation. The incidence rates of outliers on other laboratory parameters were generally less than 1%.

Results on Central Tendency Analyses

Mean changes from baseline to treatment endpoint of the open-label phase and the double-blind phase on various laboratory parameters failed to reveal any changes of a magnitude to be considered clinically significant (noting that baseline for the double-blind phase was at time-point during open label SCT treatment and that baseline for the open label phase was at pre-randomization to double-blind treatment of the lead-in study).

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J. Vital Signs and Body Weight

Results of Incidence of Outliers

PCS criteria for vital sign (VSS) and weight parameters are shown in Table VII.J.1 of the appendix (as provided by the sponsor). The results on incidence of outliers failed to reveal any

remarkable results or treatment group differences that are considered clinically significant except for possibly the incidence of outliers on weight gain. During the Open Label Phase of the study 6.6% of the 504 SCT Ss of the safety population met PCS criteria for weight gain (≥7% gain), while only 2.8% met PCS criteria for weight loss (≥7% loss). Given that there was no placebo group for comparison, these results are difficult to interpret. However, incidence rates during the double-blind Phase, as shown in the following table (similar to Table 8.1B, provided by the sponsor), are consistent with a possible greater incidence in weight gain with SCT treatment compared to placebo. Also note that the percentage of Ss with weight gain shows a numerical increase with increasing duration of SCT treatment. However, there is no long term placebo group for comparison to the long term SCT groups.

Incidence of Subjects of the Safety Population Meeting PCS Criteria for Weight Change During the Double-Blind Treatment Phase and With Long Term Open Label and Double-Blind SCT Treatment				
	Double-blind Treatment Groups		**Long Term Open Label and Double Blind Escitalopram Treatment**	
	Placebo (N=92)	**Escitalopram (N=181)**	**> 8 Weeks (N=181)**	**> 16-Weeks (N=76)**
Increased weight	3.3%	11.0%	27.6%	35.5%
Decreased weight	8.7%	1.1%	5.0%	3.9%

None of the Ss meeting PCS criteria on any of VSS or weight parameters were classified as SAEs. Two SCT Ss discontinued double-blind treatment due to weight gain, but this gain did not meet PCS in either S. The following ADOs regarding VSS or weight parameters were observed during the open-label SCT phase:

- ADOs due to weight gain: 4 Ss (0.8%)
- ADOs due to hypertension: 1 S (0.2%)
- ADOs due to bradycardia: 1 S (0.2%)

Treatment emergent AEs related to VSS parameters in SCT Ss were as follows:

- Open Label Phase (N=504):
  - Weight gain in 16 Ss (3.2%)
  - Hypertension in 12 Ss (2.4%)
  - Tachycardia in 2 Ss (0.4%)
  - Bradycardia in 1 S (0.2%)
- Double-blind Phase (N of SCT Ss=181):
  - Weight gain in 8 Ss (4.4%)
  - Hypertension in 1 S (0.6%)
  - Tachycardia in 1 S (0.6%)

The incidence rates of outliers for decreased heart rate in the open label phase of the study and in SCT Ss of the double-blind phase were less than 1%. This observation is based on using the following outlier criteria: ≤50 bpm and a decrease from baseline of ≥ 15 bpm (noting that baseline for the double-blind phase was at time-point during open label SCT treatment and that baseline for the open label phase was at pre-randomization to double-blind treatment of the lead-in study).

Results on Central Tendency Analyses

Results of mean changes (from baseline to endpoint, as previously defined) on vital sign parameters failed to reveal any clinically remarkable or significant findings, except for results on weight gain. A possibly clinical relevant numerical increase in mean weight of 5 pounds was observed with longterm safety populations of over 8 weeks and over 16 weeks of SCT treatment. However, these results must be interpreted with caution for several reasons. There was no placebo group for comparison and some of the treatment was open-label. These results may be reflecting a non-treatment related weight gain over time, as weight gain is prevalent in the general adult population. However, results of the placebo controlled double-blind phase revealed mean weight changes of 3.2 lbs. in SCT Ss compared to a mean increase of 0.6 lbs. in placebo Ss which suggests an effect of SCT treatment on weight gain.

A small mean decrease in heart rate also was revealed in the open-label and double-blind phases of the study, as well as in the longer term safety populations, as described in more detail in this paragraph. These results are not new or unexpected from that described in pervious clinical reviews of SCT trials (under NDA 21-323) and as described in labeling of the approved racemate, Celaxa®. The mean change of heart rate in the open label phase of the study was –2.1 bpm. The >8week and >16 week longterm SCT safety populations also showed mean decreases (numerical decreases) ranging from –1.6 to –3.9 bpm over study visits (at weeks 8, 16, 24, 36 and 44). Note that the baseline measures for the open label phase of the study and for the longterm safety populations are measures obtained prior to randomization to double-blind treatment in the lead-in studies. Mean changes in heart rate in the double blind phase of the study (baseline assessments were obtained during open label SCT treatment) failed to show numerical mean decreases with continued SCT treatment. Also the placebo and SCT treatment groups appeared to be similar on this parameter (a mean change of 0.9 bpm for placebo Ss and 1.1 bpm for SCT Ss). Note that the magnitude of the above numerical decreases in heart rate was small.

K. Electrocardiographic Results

Results of Incidence of Outliers

PCS criteria for ECG parameters are as follows:

- PR Interval ≥250 msec
- QTc Interval > 500 msec

None of the ECG findings were classified as an SAE. None of the Ss met PCS criteria for ECG parameters during open-label or double-blind treatment, except for one S (S 2055)who had a QTc interval longer than 500 msec (QTc=517 msec compared to a QTc interval of 414 msec prior to randomization in the lead-in study). This PCS outlier occurred during the open-label SCT phase of the study and the S continued treatment of the study drug, with a final QTc interval of 517 msec on the final study visit.

Open Label phase ADOs due to ECG related findings:

Abnormal left axis deviation and left anterior fascicular block in 1 S (0.2%)
Bradycardia in 1 S (0.2%)

Open Label phase treatment emergent AEs due to ECG related findings:

Abnormal ECG in 5 Ss (1%)
Bradycardia in 1 S (0.2%)
Atrial arrhythmia in 1 S (0.2%)
Nodal arrhythmia in 1 S (0.2%)

No ADOs during the Double-blind phase were due to ECG related findings and 1 SCT S of the Double-blind phase had an AE due to an abnormal ECG.

Results on Central Tendency Analyses

As with results on central tendency analyses of laboratory data, the results for ECG parameters are using baseline values obtained at the end of the 8-week open-label SCT treatment phase, such that these values do not reflect true pre-dose baseline values. Overall, the results of central tendency for various ECG parameters were generally unremarkable for numerical or clinically relevant treatment group differences, except for possible QT and QTc interval results. Ventricular rate failed to show a mean decrease from baseline of Study MD-03 to treatment endpoint of the double-blind treatment phase of the ITT Safety population. However, there appeared to be a numerically greater mean increase in the placebo Ss compared to the SCT Ss (a mean increase of 5.3 bpm compared to 1.0 bpm, respectively). This numerical difference does not appear to be of a magnitude to be of clinical significance, particularly within the SCT Ss. It is important to note that these results do not reflect a true mean change from a pre-dose baseline value, since baseline values came from the end of the open-label SCT phase of the study. However, they suggest that heart rate does not appear to show a mean decrease in heart rate with continuous treatment with SCT, similar to that observed with the vital sign results on pulse rate of the double-blind treatment phase.

The QT and QTc interval results are suggestive of QT prolongation with SCT treatment, but such an interpretation can only be considered preliminary given a number of reasons described later in this section. Perhaps the most remarkable observation are the results on QTc (and QT) interval data from the Open Label SCT safety population and the SCT >8 week and SCT > 16 week longterm safety populations, as shown in the table below. This table shows mean baseline and treatment endpoint QTc values in these populations, as well as treatment endpoint results for the double-blind phase of the study.

Mean QT_C (±SD) Values (in msec) of Open Label, Double-Blind and SCT Longterm Safety Populations in Study MD-03 (ITT Safety Population)*

	Baseline Prior Double-blind Randomization of the Lead-in Study (studies MD-01 and MD-02)	Treatment Endpoint**
Open Label SCT Population (N=446)	393±23	415±24
Double-Blind Population		
Placebo Group (N=78)	not provided	416±20
SCT Group (N=151)	not provided	415±24
> 8 Week SCT Population (N=181)	394±24 (N=179)	415±24 (N=179)
> 16 Week SCT Population (N=76)	395±23 (N=75)	414±23 (N=75)

* These results were obtained from Tables 10.4A, 10.4 B, and 10.4 C in the submission (volume 4 of 121 of the 10/19/01 NDA 21-323 submission (cell sizes of Table 10.4 C were corrected by the sponsor upon request in a 2/15/02 NC submission).

**Endpoint corresponds to the endpoint of the given population. Open label endpoint is the endpoint visit of the Open label phase, Double-blind population endpoint is the endpoint of the Double-blind phase of Study MD-03, etc.

Mean QTc interval results were similar to those of the above QTc interval results. Note that the above table does not include results in the mean change from baseline to endpoint in QTc interval (or QT interval). Results of mean changes in ECG parameters were not provided due to methodological differences ("for the derivation of ECG parameters") between the lead-in studies and Study MD-03, according to the sponsor. While there may be possible mean QT prolongation when comparing mean QTc interval values before SCT treatment to mean values at treatment endpoint for the above populations, it is not clear when the increase occurred and if it occurs continuously over time. Within-subject comparisons were not made. Hence, it is not clear if the above results reflect a within-subject increase in the QTc interval.

Mean changes in QTc and QT intervals of SCT treated Ss between the last assessment during the open-label treatment (baseline) to the end of double-blind treatment (treatment endpoint) in Study MD-03 were examined by the sponsor (the double blind phase safety analyses). These results suggest no QTc or QT prolongation during continuous dosing of SCT, as described in the following. The mean change in QTc or QT intervals in SCT group of the double blind phase from baseline to treatment endpoint were –0.9±23 msec (N=151) and –3.5±26 msec (N=151), respectively. The placebo group (N=93) of the double blind phase showed a mean change of QTc and QT intervals of 2.3 and –11.3, respectively (N=78). These results suggest that QTc or QT interval prolongation did not occur with continuous SCT treatment. However, there were no comparisons made between pre-dose assessments to assessments during treatment or at treatment endpoint on these ECG parameters.

While a dynamic prolongation of QTc and QT interval with continued SCT treatment did not appear to be revealed in the double-blind phase safety results, a potential treatment group effect on QT or QTc interval needs consideration, given the results of short term MDD trials (under NDA 21-323) and results of the open-label and SCT longterm safety populations of Study MD-03 (as in the above table). However, the lack of placebo groups for comparison to the Open-Label and SCT longterm safety populations is problematic in interpreting whether or not the apparent QT prolongation in these populations is a real effect of SCT treatment. Other caveats in the interpretation of the results also need to be considered. Consequently, the conclusion of a possible SCT effect of prolonging the QT or QTc interval is considered a preliminary. For example, the findings suggestive of QT prolongation are observations based on a numerical comparisons between mean baseline and mean treatment endpoint and was not based on the mean change in QT from pre-dose (prior to entry to double-blind phase of the lead-in study) to treatment endpoint of Study MD-03. Other caveats are previously described.

Incidence of ECGs Classified as Abnormal.

ECGs were categorized as "abnormal" or "normal" "regardless of clinical significance" at the baseline and treatment endpoint of each S. The incidence rates of the safety populations for the open label phase and the double blind phase of the study and for longterm SCT safety populations (>8 week and > 16 week SCT safety populations) were provided (noting the definition for baseline employed for each of these safety populations, as previously described). These results did not appear to reveal any apparent differences between treatment groups during continued treatment in the double-blind phase or differences between the longer term populations (over 8 weeks and over 16 week SCT populations). The results are described in more detail in the following.

The incidence of Ss in each of the safety populations with normal ECGs at baseline and abnormal ECGs at treatment endpoint for each safety population was as follows:

- Open Label Phase Safety Population: 28% (127/449)
- Double-blind Phase Safety Population: 17% (13/78) of Placebo and 14% (21/153)of SCT Ss in the double-blind phase.
- > 8 week safety population: 28% (50/180)
- > 16 week safety population: 26% (20/76)

The incidence of each of the following treatment emergent AEs in the open label phase safety population was: abnormal ECG (1%), bradycardia (0.2%), atrial arrhythmia (0.2%), and nodal arrhythmia (0.2%). One ADO in this population was due to abnormal axis deviation and left anterior fascicular block and bradycardia on ECG. Four Ss in the open label phase were considered as having "clinically significant" ECGs as follows: 3 Ss with bradycardia and 1 S with "inferior infarction." One if 3 Ss with bradycardia was also an ADO due to bradycardia. See the above section of ADOs (Section VII F). Only 1 SCT S in the double-blind phase of MD-03 (double-blind safety population) had an abnormal ECG reported as an AE and none of the Ss in this population discontinued treatment due to an abnormal ECG.

L. Overdose Experience

This submission does not include a section on overdose experience. Refer to Clinical reviews under NDA 21-323 for overdose experience with SCT.

M. Safety Results from Other Sources

Refer to Clinical Reviews under NDA 21-323 for additional safety information pertaining to SCT and for results of a review of the literature on SCT. Upon request the sponsor conducted an updated review of the literature on SCT and citalopram and submitted results under the present NDA (NDA 21-440), as described below.

Literature:

The results of an updated literature search conducted by the sponsor (see Section IV.D. for the search methods employed) yielded four new published articles on SCT, since the sponsor's previous NDA 21-323 submission. Only one of these four articles is reported by the sponsor to provide safety information. No other articles of controlled or non-controlled SCT trials, review articles or case reports were found. According to the sponsor no new or unexpected AEs were revealed.

An updated literature search on citalopram was also provided upon request. According to the sponsor no new or unexpected safety results were revealed from this search. Although, the sponsor described one event in a patient following an overdose of citalopram and "heavy alcohol consumption." The patient had a seizure and abnormal ECG findings (left axis deviation, sinus tachycardia, and left bundle branch block) but recovered. The bibliography in the submission, included an article describing a review of the literature and a case report, on the topic of a potential association of QTc interval prolongation with overdoses of citalopram (Catalano, G., Catalano, M., et al., 2001). The contents of this paper are summarized in Attachment 1 of this review.

Post Marketing Reports: No post marketing reports are described in the submission (see Section IV.C above for details regarding applications for marketing of SCT in non-US countries).

N. Conclusions on Safety Results.

Overall safety results of Study MD-03 together with established safety of Celexa® with longer term use, appear to show that continued treatment with SCT is adequately safe in generally healthy patients with MDD at the recommended doses for periods of up to approximately 36 weeks. Refer to previous clinical review (Amendment 1 and the Clinical Review of NDA 21-323) regarding cardiac observations and a discussion about SCT treatment in patients at risk for bradycardia and cardiac conduction defects. The following paragraphs focus on safety issues pertinent to Study MD-03.

There are several limitations to the interpretation of the sponsor's safety results of Study MD-03 for reasons already described. Nevertheless the safety results are generally consistent with the observed safety profile described for short-term (8 weeks) SCT treatment (refer to Amendment 1 Clinical Review of NDA 21-323). Possible exceptions to this conclusion are results on weight gain and on treatment emergent AEs of muscoloskeletal symptoms (arthralgia, back pain), influenza-like symptoms, sinusitis and rhinitis. Based on these results, these AEs may be associated with longterm treatment, as they do not commonly occur during short term treatment at a rate of at least twice that of placebo.

Regarding results on weight gain, a small numerical trend for a greater incidence in outliers on increased weight was previously observed in SCT Ss and citalopram Ss compared to placebo Ss in the short term trials (see NDA 21-323 Clinical Review). The results on weight gain in Study MD-03 appear to reveal consistent results across datasets examined. The datasets examined (no statistical tests were conducted) included the incidence rates of weight gain as AEs, the incidence of increased weight outliers (in contrast to outliers of decreased weight) and the mean change in weight for each of the safety populations (including a numerical comparison between placebo and SCT groups in the double-blind phase). However, results of safety populations such as the longer term SCT populations and results of the Open Label phase of the study are difficult to interpret. There were no placebo groups for comparison to these safety populations and incidence rates of at least some AEs could be reflecting a spontaneous increase over time that could be independent of treatment.

While Study MD-03 did not appear to reveal any other new, clinically significant findings, not already described in previous Clinical Reviews under NDA 21-323, it is important to comment on cardiac related safety results in SCT trials. Cardiac related safety results described in the Clinical review of short term MDD trials of SCT (8 weeks) under NDA 21-323 included bradycardia, conduction defects of a potential QT interval prolongation and of reports of junctional nodal arrhythmias in some Ss (including reports of AV block, bundle branch block and others). Study MD-03 does not appear to reveal any new cardiac findings. However, the study provides additional evidence supporting a possible QT and QTc interval prolongation, previously observed in the short-term SCT trials. A potential QTc or QT interval prolongation was observed in the Open Label phase of Study MD-03 (8-weeks of open label SCT treatment) and in long term SCT safety populations (the > 8week and > 16 week SCT longterm safety populations). The long term populations showed QTc means after over 8 weeks or 16 weeks of treatment of approximately 10 msecs greater than their mean QTc prior SCT exposure (prior to randomization to double-blind treatment of the lead-in study). Yet, a number of methodological

issues exist (such as comparing results across independent studies or the absence of a placebo group) that impact on the interpretability of these results, as previously described. While, the short-term trials (under NDA 21-323) showed evidence for a potential treatment group effect on prolonging the QTc interval, treatment group differences were small in magnitude. Furthermore, examination of results of the placebo controlled double-blind phase of Study MD-03 showed evidence that mean changes in QTc and QT intervals do not increase with continued treatment within the SCT group. Also, a numerical comparison between the treatment groups (SCT compared to placebo) of the double-blind phase failed to show evidence for a treatment group effect of continued treatment on mean change in the QTc interval in the direction of prolongation with continued SCT treatment.

[redacted] under NDA 21-323 and this NDA (NDA 21-440) are currently being examined by the Division Safety Group, with recommendations to follow. Given the problems in the interpretability of the QTc and QT interval results of Study MD-03, the Safety Team might consider other ways of analyzing existing data (e.g. using baseline line assessments of the lead-in studies for comparisons to assessments at various time-points during the open label, as well as during the double-blind phase of the Study MD-03). Perhaps, data from subsets of safety populations may be analyzed over various time-points, such as Ss who received placebo during the lead-in studies as one subset versus Ss who received SCT during the lead-in studies, among other possible ways of analyzing the data. Another area to consider for further examination by the Safety group is regarding the "abnormal" ECG results of Study MD-03. While treatment groups did not differ on the incidence rates of "abnormal" ECGs in the double blind phase of the study, these results may be misleading since abnormal ECGs were not categorized by type. The examination of ECG abnormalities in each treatment group, classified by type, particularly in Ss with normal ECGs at baseline prior to treatment in the lead-in study may shed further light regarding the cardiac safety of SCT.

Given the difficulties in interpreting the results of the Open Label phase and the longterm safety populations of Study MD-03, these results are not considered by this reviewer as adequate evidence for changing the conclusion that SCT treatment at the recommended doses and duration is adequately safe for the generally healthy MDD outpatient population (as described in previous Clinical Reviews under NDA 21-323). However, the cardiac results of the short-term and longterm trials may be clinically pertinent for populations at risk of bradycardia, QT prolongation and conduction defects. Another important consideration is the cardiac risk and safety in the case of off-label use of SCT either at doses or treatment periods that exceed that recommended. Cases of patients with citalopram overdose, as described in this review, also suggest potential cardiac conduction or other related effects of citalopram, the racemate of which SCT is an enantiomer. The examination of these issues is currently underway by the Division Safety Group.

Safety issues not previously addressed in this review are potential AEs associated with cessation of SCT, given reports of a potential association of AEs with cessation of SSRIs. Study MD-03 was not designed to address this issue. However, Ss assigned to placebo during the double-blind phase of the study underwent SCT treatment cessation, since an 8-week open label SCT phase was employed that was followed by the double-blind phase. The incidence rates of ADOs in the SCT group was 4% compared to 7 % in the placebo group during the double-blind phase. Examination of these ADOs (see Table VII.F.1 in the appendix) shows that ADOs in the placebo group generally occurred between Days 2-15 of the double-blind phase, while ADOs

among the SCT group primarily occurred between days 19 to 174. While these observations suggest that the appearance of ADOs in the placebo group occurred within a few weeks of terminating the open-label SCT treatment, many of the reported AEs appeared to be due the emergence of underlying psychopathology and lack of efficacy (sleep disturbances, energy level, anxiety, etc.). AEs reported upon SSRI treatment cessation include abnormal dreams, parasthesias and other symptoms. These AEs appear to be generally distinguishable from symptoms of MDD, and were not reported in placebo ADOs of in Study MD-03. However, one cannot rule out the possibility that some of the AEs reported by some of these placebo ADOs could have been symptoms associated with cessation of SCT treatment.

According to the sponsor, the study showed no evidence for treatment cessation AEs. Yet, the sponsor did not examine the incidence rates of AEs in each treatment group during the first several weeks of the double-blind phase, a time period when possible treatment cessation effects may be more likely to occur. This is an area to consider for further exploration. Nevertheless, the above results are difficult to interpret and are considered preliminary, as the Open Label phase was not blinded and the study was not designed for the purpose of examining possible treatment cessation effects of SCT. The issue of potential treatment cessation associated AEs is under consideration by the Division for the class of SSRIs.

Another potential issue related to the class of SSRIs under consideration by the Division is the potential association between SSRI treatment and upper gastrointestinal bleeding, as suggested in an epidemiological study described in the literature (de Abajo, et al., 1999). The short term SCT trials submitted under NDA 21-323 revealed no clear evidence for this possible association (refer to the Clinical Reviews). While Study MD-03 appeared to show outliers on low hemoglobin and low hematocrit values and numerical trends for greater incidence rates in SCT Ss compared to placebo Ss, many Ss had low values at baseline and the treatment groups did not differ on measures of central tendency, as previously described. Therefore, the safety results of Study MD-03, in addition to the 8-week short term trials under NDA 21-323 do not appear to show evidence supporting a potential association between SCT treatment and bleeding disturbances.

VIII. Dosing, Regimen and Administration Issues

The sponsor's claims on dosing and administration were previously described under Section I A of this review. The study provides positive results that appear to support [redacted]

IX. Use in Special Populations

There is no new information regarding special populations submitted under this NDA. Refer to previous clinical review of NDA 21-323 regarding special populations and [redacted]

X. Conclusions and Recommendations

A. Conclusions

Study MD-03 provides evidence for continued efficacy for up to approximately 36 weeks of treatment with SCT in outpatients with MDD who respond to acute (8-weeks) of SCT treatment (pending confirmation by Biometrics). This conclusion is also supported by established efficacy for longer term treatment of citalopram (as described in Celexa® labeling). However, Study MD-03 was not in the opinion of this reviewer designed to examine the prevention of relapse with SCT treatment.

SCT treatment appears to be adequately safe for periods of up to approximately 36 weeks at daily doses of 10 to 20 mg in generally healthy outpatients with MDD. This conclusion is based on results of Study MD-03, the short term MDD trials of SCT (under NDA 21-323), along with the known safety of citalopram (as described in Celexa® labeling for both short term and longer term treatment). However, there appears to be a small signal for cardiac conduction effects of SCT. It is not known if these potential effects are enhanced at higher than recommended doses or over longer periods of treatment in this population. Reported cases of citalopram overdoses include cardiac observations suggestive of a potential effect at higher doses. Patients at risk for bradycardia, QT prolongation or conduction defects may have greater risk for these conditions when receiving SCT treatment (also consider concomitant medication use and elderly). This conclusion is based on the cardiac results of the short term and longterm SCT trials (refer to Clinical reviews under NDA 21-323 and previous sections of this review), cardiac conduction changes reported in cases of CT overdose (the racemate of SCT), together with preclinical results of SCT and CT (refer to the Pharmacology and Toxicology Review under NDA 21-323). The Division Safety Team is currently reviewing these data.

A 13-week toxicology study of SCT in rats submitted under NDA 21-323 revealed cardiac injury (i.e. cardiomyopathy). Clinical trials of short term (8-week) treatment under NDA 21-323 and the longer trial described in this review failed to show evidence for an association of adverse events or clinical signs of cardiomyopathy associated with SCT treatment at the doses and treatment periods employed. Nevertheless, one cannot completely rule out a possible effect of cardiac injury with SCT treatment in humans similar to that observed in the rat study.

Safety results of study MD-03 also revealed some evidence for weight gain associated with longterm treatment. Furthermore, some AEs appeared more prominent in the SCT group compared to placebo in the double-blind phase of the study that did not appear prominent in short term MDD trials (such as some musculoskelatal symptoms, influenza-like symptoms and possibly rhinitis and sinusitis).

B Recommendations

It is recommended that NDA 21-440 be granted approvable status, pending confirmation of efficacy results by Biometrics. Before SCT is approved for either short term (8-week) or longterm (up to 6 months) treatment (noting that NDA 21-440 will administratively become NDA 21-323), it is recommended that the Division Safety Group examine the cardiac safety of SCT. There are other class related concerns with SSRIs (upper gastro-intestinal bleeding or other related conditions, AEs associated with treatment cessation) that are currently under review by the Division, that may impact on this labeling, as well as that of other SSRIs.

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Draft Labeling
(not releasable

(from the Amendment 1 NDA 21-323 Clinical review) is provided in Attachment 2 of this review.

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Medical Review Officer, DNDP
FDA CDER ODE1 DNDP HFD 120

cc: IND
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HFD 120/
K Brugge
P David
T Laughren

APPEARS THIS WAY
ON ORIGINAL

APPENDIX

APPEARS THIS WAY
ON ORIGINAL

Table VI.A.1. List of Investigators of Study MD-03

Center No.	*Investigator*	*Center Address*
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