

CT and placebo groups, respectively. These values are similar to the maximum values observed at baseline within each corresponding treatment group. The maximum change in QTc from baseline to treatment endpoint was 84, 79 and 95 msec for the SCT, CT and placebo groups, respectively.

K.2 Analysis of Outliers

Completed 8-Week Depression Trials (SCT-MD-01, -MD-02, 99001 and 99003)

The incidence rates of outliers for “abnormal” versus “normal” ECG values (the type of abnormality was not specified), as well as the incidence rates of outliers that met PCS criteria on specific ECG parameters were provided in the 120 Update report. The sponsor employed the following outlier criteria: QRS interval ≥ 150 msec, PR interval ≥ 250 msec, and QTc interval > 500 msec. Treatment groups showed similar incidence rates of outliers when using these criteria (incidence rates ranged from 0 to 3% of Ss in each treatment group). None of the Ss met the PCS criterion for prolonged QTc interval, 1 out of 368 CT Ss met the PCS criterion for prolonged QT interval and 1 out of 652 SCT Ss met the PCS criterion for prolonged PR interval. No other information could be found in the update report on these Ss (no narratives or CRFs or line listings with any associated AEs could be found unless otherwise indicated below).

Treatment groups were similar on the incidence of Ss converting from a “normal” to an “abnormal” ECG reading (incidence rates were approximately 7% for each group). There were no SAEs reported as being due to meeting PCS criteria on ECG parameters. However, as described in the SAE section above, S 2232 had tachycardia, that was probably related to the non-accidental overdose of cough cold medication. Another S is described who had an SAE of an overdose of zolpidem and acetaminophen and coma. This S had a nonserious “abnormal” ECG when hospitalized for their SAE, which occurred 6 days after having 4 daily doses of CT. The line listing of ADOs by Preferred Term does not list any ADO specifically due to an abnormal ECG, arrhythmia or to syncope.

The Update Report describes ECG results of 17 Ss who had normal ECGs at baseline and 1 S with a missing baseline ECG who had abnormal ECGs at their last study visit (8 SCT Ss, 5 CT S and 5 placebo Ss) that were considered to be “clinically significant”. Some of these abnormal ECGs were listed as treatment emergent AEs as follows:

- In 2 SCT Ss: Nodal arrhythmia and bradycardia in 1 SCT S and bradycardia in the other S
- In 2 CT Ss: bradycardia in one S and “abnormal ECG” in the other S
- 1 placebo S: ECG abnormal (Wolff-Parkinson-White syndrome).

Upon request the sponsor provided a listing of the type of each “abnormal” ECG at treatment endpoint in Ss with a “normal” ECG at baseline for each of the four depression trials. Upon inspection of the line listings, which are shown as Tables 4-5 in Attachment 1 of this review, it appears that the most common types of abnormal ECGs were due to bradycardia, first degree block and prolonged QTcB “dispersion.” The enumeration of these Ss in each treatment group of the four studies, combined, is summarized in the table below (several conduction defects are also included in this table). This table shows a possible trend for greater incidence rates of first degree block and bradycardia, while noting that the line listings show tachycardia reported in only one CT S and no SCT Ss (refer to Tables 4-5 in Attachment 1 of this review).

The Number (incidence) of Subjects* in Each Treatment Group with Normal ECGs at Baseline and Abnormal ECGs** at Treatment Endpoint			
	Treatment Group		
ECG Abnormality	Placebo (N=537)	SCT (N=644)	CT (N=364)
First Degree Block	5 (0.9%)	10 (1.6%)	3 (0.8%)
Bradycardia	5 (0.9%)	11 (1.7%)	7 (1.9%)
First Degree Block or Bradycardia (the above 2 combined)	10 (1.9%)	21 (3.3%)	10 (2.7%)
QTcB Prolongation***	11 (2.0%)	9 (1.4%)	4 (1.1%)
Right Bundle Branch Block	0	0	1 (0.3%)
Junctional escape rhythm	0	1 (0.2%)	0

*Note that a 4 SCT subjects had more than one type of ECG abnormality and are counted for each type in this table and 1 Placebo S had bradycardia along with ST depression. See text below for a listing of these subjects.
** Only the more common ECG abnormalities and conduction defects are shown in this table (refer to line listings in Tables 4-5 in Attachment 1 for less common ECG abnormalities.
*** 2 Placebo Ss not counted in this table had "borderline" QTcB prolongation.

Additional less common types of ECG abnormalities, not shown in the above table, are provided in the line listings (see Tables 4-5 in Attachment 1). Note the following Ss counted in the above table that had more than one type of ECG abnormality:

- One Placebo S: bradycardia and ST depression
- 4 SCT Ss as follows:
 - 3 Ss had First Degree Block along with bradycardia in 2 of these Ss or with inverted T wave in 1 of these Ss.
 - 1 S had junctional escape rhythm with bradycardia.

K.3. Three PK Trials with Multiple Post Treatment ECG Assessments (single dose trials 98106 and 99166 and multiple dose trial 9817)

The single dose trial 98106 revealed a "slight trend" for a decrease in mean HR at 4 hours postdose for 40 mg CT and 20 mg SCT groups (a mean decrease of 2 bpm and 3 bpm in each study, respectively). In this study 24 healthy males received either the CT or SCT single oral dose and after 21 days washout, they received the alternative drug. 5 females received a single dose of 40 mg CT and 4 females received a single dose of SCT. 4 CT Ss and 7 SCT Ss had sinus bradycardia (HR<50 bpm) at 4 hours post-dosing. The lowest HR in the CT or SCT groups at 4 hours post-dose was 43 and 42 bpm, respectively. None of the Ss had tachycardia (as defined as HR>100 bpm). Other ECG results appeared to be unremarkable. The maximum QTc values at any time during the study were 450 msec in the CT group and 460 msec in the SCT group. An abnormal T wave was observed in one S following SCT treatment, which was considered to be "possibly drug related".

A trend for a decrease in HR was also observed in the multiple dose, crossover study (98107) in 36 healthy male and female Ss. Ss received daily doses of 20 to 60 mg/day of CT for 24 or 18 days respectively or doses of 10 mg to 30 mg/day of SCT for 24 or 18 days, respectively. The incidence of Ss with bradycardia (<50 bpm) in each treatment group was:

- 28% in the 20 mg CT group,
- 17% in the 60 mg CT group,
- 18% in the 10 mg SCT group and

- 18% in the SCT group.

None of Ss in any of the treatment groups had tachycardia (HR>100). ECG abnormalities occurring in more than 1 S in a given group was first degree heart block which was reported in:

- 4 Ss in the 20 mg CT group,
- 1 S in the 10 mg SCT group and
- 1 S in the 30 mg group.

Other ECG abnormalities were as follows:

- Atrial premature contraction (1 60 mg CT S),
- "Coronary sinus rhythm (1 60 mg CT S)
- Left ventricular hypertrophy (1 20 mg CT S)
- Ventricular premature contraction (1 30 mg SCT S).

The mean change from baseline to last dose of study drug of QTc values (no S had a QTc of ≥ 500 msec) in each group was as follows:

- 4 msec in the 20 mg CT group,
- 10 msec in the 60 mg CT group,
- -1 msec in the 10 mg SCT group and
- 11 msec in the 30 mg SCT group.

Small mean decreases in HR were noted from Day -1 to Day 1 of treatment and at 4 hours post dose, in a single dose, crossover trial in young (18-45 years old) and elderly (≥ 65 year old) Ss using 10 mg, 20 mg and 30 mg doses of SCT. However, the sponsor attributes these results to a "relatively high baseline value" on Day -1 that does not reflect an effect of SCT treatment. Other ECG parameters did not appear to show any remarkable or clinically significant findings.

L. Overdose Experience

The sponsor reports a total of 3 intentional overdoses with SCT (Ss R3060, R0060 and R0166 in Study 99002). These overdoses involved doses of 100 mg, 380 mg and in one S, 400 to 600 mg. There were no symptoms reported in all 3 cases and all Ss recovered. However, the S who consumed 400 to 600 mg did not recall the event precisely, as they also consumed 2 bottles of wine, as well as 500 mg of ketoprofen. While there was limited information on this latter S, she reported going to the emergency room on the day after the overdose in a sober state and was discharged "recovered", on the "next day." The sponsor indicates that attempts to obtain information from the emergency room were unsuccessful. The age of each of the 3 Ss that overdosed, were 30, 40 and 22 years old. Symptoms that are often associated with overdose of CT are described in the 120 Update Report and Celexa™ labeling includes additional information.

M. Safety Results from Other Sources

Safety Alert Reports. This section describes selected safety alert reports received since receipt of the 7/12/01 120-Day Safety Update report. Two events were deaths. One death, described as "sudden," occurred in a 49-year-old male who had myocardial infarction. The other death occurred in a 91-year-old female nursing home patient who had a CVA. In addition to these two deaths, a third S is described below who was an 89 year old male with a SAE of syncope resulting in a serious fall that in turn, resulted in a fracture of the neck of the femur. Each of the events involved Ss with risk factors for development of these events. However, given the limited information available, a potential role or interaction effect of SCT treatment cannot be ruled out.

Mfr report # T01-FIN-01573-01 (S# 14999 at a Finland center F1005): AE Terms of Sudden Death, Myocardial Infarction. This S in study 99269 (relapse prevention trial on patients with Social Anxiety Disorder) was an obese (BMI of 30.4) 49 year old male who was reported by his wife to have “suddenly died on 8/6/01 of suspected cardiac infarct.” The S was receiving open label 20 mg/day oral SCT (in the open phase of the relapse prevention trial, prior to randomization). He was initially started on blinded study drug on 5/19/01. Medical history and concomitant medications were unknown or listed as “none reported”. The patient was reported to have “no cardiovascular risk factors” but as above, was reported to be obese. However, this S appears to have several risk factors for this event that included obesity, gender and an age (over 45 years old). While, his age of 49 years appears young for sudden death, his obesity and gender were likely to be significant contributory factors.

Additional information was requested and was provided by the sponsor in 9/27/01 and 10/9/01 submissions, as well as in follow-up MedWatch reports. The later submission revealed a cause of death as death due to aspiration of vomit and alcohol intoxication based on autopsy findings (2.9% blood level and 3.4% vitreous eye level, while therapeutic drug levels). Patient was reported to have taken a trip to Estonia on 8/2/01 and drank herbal alcohol. Autopsy revealed “no signs of myocardial infarction”. On the day of his death, the patient complained of being “very tired” for about 20 minutes and of severe chest pain for about two minutes before he suddenly collapsed onto the floor of his car in parking lot (as reported by his wife). When the ambulance arrived (within a 15-minute period) he was “already dead” (no other clinical data or autopsy data was described). Based on the autopsy results this patient appears to have died due to complications from alcohol intoxication, as above, which does not appear to be drug-related.

T01-BEL-01475-01 (S # R5369 at Center BE007, Belgium study): AE term of cerebrovascular accident with the outcome of death. This was a 91 year old female S in an open label extension trial on patients with MDD who received 10 mg oral SCT/day from 12/9/00 (also received in a prior study, 99024) to 7/22/01. This S who was in a “Rest and Care Home for Elderly People” had a cerebral vascular accident (CVA with left-sided paralysis, aphasia) on 7/22/01. Follow-up information on 8/7/01 reported death (date NOS) and no autopsy (per family request). Laboratory results were as follows: neutrophil count of 79.5 (nl 40-75%), platelets of 447 (nl 130-140 GI/L), RBC agglutination present, WBC of 15.1 (nl 3.8-10.8 GI/L). These laboratory results were considered to be potentially inaccurate due to “significant numbers of platelet clumps.” “No examinations or treatment was done between 7/22/01-7/23/01.” No other information was provided. Given this patient’s age, that she suffered from MDD and that she was institutionalized receiving nursing home care, she was likely to have either limited mobility or exercise. Therefore, this S appears to have had several risk factors for developing CVA. The information on this S is limited, but given that this S required nursing home care, it appears that this she may have had additional risk factors or complications, not reported in the MedWatch report. The medical history reported on this S only included a history of fractures (left arm/shoulder, left hip) occurring in 1/99 and 7/99. A history of multiple fractures in an elderly S is strongly suggestive of susceptibility to falls, perhaps due to underlying, undiagnosed or unreported condition(s) that in turn, may be related to the development of her CVA and death.

Therefore, it appears that the events in this S were not likely to be drug-related. Although, without additional information, a possible drug interaction effect cannot be ruled out.

Mfr report # T01-UKI-01263-01 (United Kingdom study, GB001 site, S# R5139): AE Terms of Syncope, Stupor, and Accidental Injury. This 89 year old male S was in an open label extension trial on patients with MDD. He was reported to have “collapsed, was unresponsive, and sustained a fractured neck of femur” on 6/24/01. He was receiving 10 mg/day oral SCT (started on 9/27/01) and Zoladex (goserelin) of an unknown dose and duration. The latter drug is a synthetic analogue of gonadotropin releasing hormone and is an agonist, used in patients with cancer of the prostate. No other concomitant medications were reported (another place in the report indicated that this information was unavailable), and the past medical history section of the safety report indicated prostate cancer in remission. A chest x-ray on examination revealed a “shadow and dilation of the trachea (verbal report).” Fracture of the neck of the femur was also confirmed and surgery was performed. “Further testing NOS was being performed at the time of this report.” There is no other information at this time. Without additional information, one cannot rule-out the possibility that this was drug-related. However, falls are common among the elderly population, which can result in fracture of the neck of the femur, particularly in patients with osteoporosis, which is age-related and may also be associated with goserelin treatment.

Literature: A total of 39 published articles were found with safety information as described by the sponsor provided in Section VII of this review (the Integrated Review of Safety section). According to the sponsor none of these articles provided safety information on SCT. The sponsor upon request provided a list of these publications.

Upon request (refer to a 9/18/01 fax) the sponsor conducted a literature review on the safety of citalopram and summarized the results of this search in a 9/27/01 submission. There were 4 placebo controlled studies of MDD patients and 2 placebo controlled studies of other patient populations revealed by their search (reviews and publications of active controlled and open label studies were also revealed and summarized by the sponsor). According to that described by the sponsor, controlled studies failed to reveal any new or unexpected safety findings that are not already described in current Celexa™ labeling. One study reported a 1.4 to 3 pbm reduction in standing HR in CT treated patients and a study that conducted a meta-analysis of ECG data collected from placebo controlled clinical trials reported a 1 to 3 bpm mean reduction in HR in CT treated patients. Celexa™ labeling describes a mean reduction of 1.7 bpm of HR in CT patients of the placebo controlled trials conducted by the sponsor (refer to labeling for specifics). Results of other non-placebo-controlled studies are difficult to interpret, but did not appear to reveal clear drug-related, unexpected, serious adverse events.

Post Marketing Reports: SCT has not been marketed in any country (see Section IV.C above for details).

N. Conclusions on Safety Results.

Overall safety results appear to show that SCT is adequately safe for treatment of patients with MDD. Several safety issues impacting on recommendations for labeling are discussed in subsequent sections of this review.

One potential safety issue not addressed in other sections of this review, is the possible association between SSRI treatment and upper gastrointestinal bleeding, as suggested in an epidemiological study described in the literature, de Abajo, et al., 1999, also refer to section IC of this review). The safety results described by the sponsor fail to show evidence for an association of SCT with upper GI bleed or with hemorrhage. This conclusion is based on laboratory and safety analysis, as well as upon examination of incidence rates of common AEs in the four 8-week depression trials by use of anti-inflammatory and anti-rheumatic products or by use of analgesics. One S (S2374) had an SAE of "stomach ulcer and hemorrhage" who was not taking a non-steroidal anti-inflammatory agent. This S had a positive history of peptic ulcer disease. The other SCT S (3188) had alcohol abuse disorder and was believed to have been actively consuming alcohol whereby he had a series of events associated with the gastrointestinal (GI) system that included the SAEs of gastritis and hematemesis. These 2 Ss were the only Ss with SAEs involving upper GI bleed out of 2552 SCT Ss and 816 CT Ss. It is also noted that 1 placebo S out of 1199 placebo Ss who had a SAE of gastric ulcer. Consequently, the possible association of the SSRI, SCT and upper GI bleeding is not supported by the safety findings described in the submission. Refer to Section IC above regarding a further discussion of this topic, as it pertains to the class of SSRIs.

VIII. Dosing, Regimen and Administration Issues

A. Initial Treatment. The sponsor recommends 10 mg as the daily starting dose in proposed labeling for SCT. If after a week the patient fails to respond, then the patient may benefit from an increase in the daily dose to 20 mg. The sponsor indicates there may be benefit from an increase to 20 mg based on efficacy results from the fixed dose study (SCT-MD-01) showing a numerically greater improvement in the 20 mg treatment group compared to the 10 mg group. However, this difference is not statistically significant ($p=0.69$) and the least square mean change from baseline to treatment endpoint was only 0.45 higher in the 20 mg group (-14.01 least mean change) than that of the 10 mg group (-13.56 least mean change). These statistical results were provided in communication with the Biometrics reviewer, Ohidul Siddiqui (e-mail dated 9/501). Therefore, the two doses appear to show similar efficacy. Furthermore, the sponsor did not conduct a study to examine the effects of increase the dose from 10 mg to 20 mg in nonresponders. However, it is reasonable to increase the dose to 20 mg in patients that fail to respond to the 10 mg. Therefore, more accurate statements such as those provided below are recommended for labeling regarding increasing the dose to 20 mg:

- A statement that clinical trials showed effectiveness of Name of Product™ in patients dosed in a range of 10 to 20 mg/day.
- A statement that the low and higher dose groups showed no statistically significant difference on the primary efficacy variable.
- The dosage recommendation that an increase from 10 mg to 20 mg is recommended in patients not responding to the 10 mg daily dose. This increase should occur no sooner than one week of treatment on the 10 mg dose.

B. Maintenance Treatment.

Several issues are described in this section regarding the introduction of new language and a new subsection in the proposed SCT labeling, that are not used in approved labeling for Celexa.™ This new language contains references to relapse prevention, prophylactic treatment and continuation treatment which are not clearly defined, are not established, scientifically based

terms in the field. Given various reasons discussed below, it is recommended that the new proposed language is deleted and replaced with standard language, as used in labeling for Celexa.™ By doing so labeling for SCT may convey a more accurate description, less confusing and more conservative interpretation of the results of longterm citalopram clinical trials that would avoid an over interpretation or misinterpretation of the results.

The new proposed language and a new proposed section, “Continuation Treatment” appears under “Dosage Administration” with references of *preventing relapse* of an acute episode that do not exist in current approved labeling for Celexa™. Furthermore, the “Maintenance Treatment” section of the proposed labeling for SCT also introduces new language in reference to *prophylactic maintenance* treatment rather than using the term maintenance treatment. This section describes a long-term citalopram study as being a study on *prophylactic maintenance treatment* in which patients received maintenance treatment for up to 72 weeks after initial 22-25 weeks of treatment. Despite the introduction of this new language and the new section, “Continuation Treatment”, the annotated proposed labeling references the Celexa™ labeling. Two longterm citalopram studies are described in the “Clinical Efficacy Trials” section of current labeling for Celexa™. These studies were reported to show “significantly lower relapse rates” over a 6-month period of treatment (not 72 weeks) that followed the acute treatment phase of the study. Ss that were nonresponders or Ss in the placebo group during treatment in the acute phase did not participate in the 6 month continuation phase of the study. Consequently, it is not clear with this study design whether continued treatment actually prevented recurrence or prevented relapse of an acute episode, which in turn depends on how one defines *relapse* versus *recurrence prevention*. Furthermore, one must define a response. The study does not address the effects of longterm treatment in drug free patients with a history of recurrent Major depressive episodes who are in remission. Consequently, a number of methodological issues exist together with the use of terminology that is not clearly defined or established which can result in confusion regarding the terminology being proposed for labeling. Finally, to avoid confusion or misinterpretation of new language introduced into labeling, it is recommended that the terms being used in labeling are those that are established in the field, clearly defined, scientifically based and are validated.

In conclusion, the introduction of the proposed new language into the labeling for SCT appears to be confusing and open to misinterpretation. Furthermore, a number of methodological concerns exist regarding the interpretation of the results of the longterm Celexa™ trials regarding the issue of prophylaxis and prevention of relapse. It is also noted that the longterm trials in Celexa™ labeling do not describe a 72-week study, as suggested by the annotated version of proposed labeling for SCT. Therefore, it is recommended that standard language, as that employed in Celexa™ labeling be used regarding maintenance therapy and when describing results of long-term trials. It is also recommended that the new language and terms and the new subsection on “Continued Treatment” be deleted from SCT labeling.

IX. Use in Special Populations

A. The Elderly Population

The sample size of elderly Ss was insufficient in the positive trials (studies employed an upper age limit) to conduct a subgroup analysis on safety and efficacy measures. The sponsor conducted an analysis on efficacy when combining a positive study (MD-01) to a study (MD-02) that failed to show significant treatment group effects and did not report age-group effects on efficacy. However, these results are difficult to interpret given that MD-02 failed to show

significant treatment group effects on efficacy. It is not clear why, the sponsor did not pool data from the three positive studies to conduct age group or gender effects. Refer to the Biometric Review (pending at the time of this writing) on this NDA for further details.

The sponsor recommends a daily dose of 10 mg in elderly populations with titration to 20 mg in those who do not respond to the 10 mg dose. This recommendation is similar to that for the general population in the "Dosage and Administration" section of the proposed labeling. Yet PK findings in elderly compared to non-elderly adult Ss, show that AUC is 50% greater in the elderly and the elimination half life of SCT is 41 hours compared to 27 hours in non-elderly Ss (approximately 70% greater). Consequently, consideration may be given to recommending a 5 mg dose. If well tolerated than 10 mg is a reasonable dose with titration to 20 mg in the absence of a response to the 10 mg dose. This recommendation is also consistent with that recommended for Celexa™ treatment in elderly (20 mg which may be titrated to 40 mg in nonresponders) given that the potency and bioequivalence of SCT appears to be approximately twice that of CT. It is also noted that Celexa™ labeling describes the inclusion of over 1000 elderly Ss in clinical trials.

B. Patients with Impaired Renal or Hepatic Function

The proposed dose recommendation of SCT for elderly is also recommended for hepatically impaired patients and is consistent with that recommended for Celexa™, when considering SCT as having twice the potency and bioequivalence to that of Celexa™. Since a small proportion of SCT is excreted in urine as the parent compound or active metabolites, based on that described in the submission, dose adjustment for patients with mild to moderate renal impairment does not appear necessary. However, as proposed, caution should be employed for patients with severe renal impairment. These recommendations are also consistent with that described for Celexa™ in which PK studies of CT treatment were conducted on patients with mild to moderate renal impairment and yielded only a 17% reduction in oral clearance of CT compared to normal Ss (as described in current labeling for Celexa™).

C. Male and Female Populations

No gender effects are reported on SCT and S-DCT PK parameters following multiple daily dosing of SCT at doses within the dose range being recommended for treatment of patients with MDD. These findings are consistent with those described for CT. Consequently dose adjustment by gender is not indicated on the basis of PK results. See section D below regarding gender effects on efficacy and safety.

Gender effects were not reported on primary efficacy measures for each of the individual positive trials (MD-01, 99001 and 99003). However, failure to show an influence of gender in each trial may be due to a sample size effect, in which the number of males was small (approximately 40 male Ss per group), as the prevalence of MDD is known to be greater in women compared to men. Sample sizes were also insufficient to conduct gender subgroup analysis on safety results.

D. Ethnic Populations

Ss were primarily Caucasian and the sample size of other ethnic subgroups were insufficient to conduct a subgroup analysis on the basis of ethnicity for each study. Since MD-02 failed to show significant treatment effects such that the results of an analysis of pooled data from MD-01 and MD-02 as described in the submission is difficult to interpret. Pooling of data from the three positive studies was not conducted for unclear reasons (refer to Biometrics review for details).

E. Other Special Populations.

One special patient population to consider regarding SCT treatment is the population with existing bradycardia, or with a pre-existing conduction defect or patients that are at risk for developing a conduction defect. The safety section of this review describes small trends that appear to be reproducible for a decrease in heart rate and small trends for QT and QTc interval prolongation with SCT treatment. The trends for decreased HR were observed in both vital sign and ECG parameters. ADOs involving bradycardia and conduction defects on ECG such as junctional nodal rhythm escape and others are also described. Three PK studies that employed multiple ECG assessments including some assessments at approximately Tmax, also revealed trends for bradycardia, as well as Ss meeting outlier criteria for bradycardia. Furthermore, several Ss had first degree heart block in the controlled depression trials and in PK studies (refer to sections VII K 2 and 3 of the Integrated Safety Summary section, above). It is also noted that Ss meeting PCS for bradycardia (in the PK trials) tended to have HRs in the low normal range at baseline (approximately 64 to 76 bpm) such that patients with low normal HRs or bradycardia at baseline appear to be at greater risk of bradycardia during SCT treatment. There are also reports in the literature (Nyth et al, 1992, Nyth & Gottries, 1990) of possible worsening of bradycardia in elderly depressed patients with or without dementia or in patients with psychopathology associated with dementia being treated with CT. Given these observations caution may be needed regarding SCT treatment in patients with existing bradycardia, or a conduction defect or for patients that are at risk for conduction defect. One must consider the possibility that an exacerbation or development of bradycardia and other possible sequelae, such as an arrhythmia may occur with SCT treatment in this special patient population.

The magnitude of a potential effect of SCT on prolong QT interval, decreasing HR or increasing incidence of bradycardia was small for each parameter such that these results do not appear to be of clinical significance for the generally healthy patient. The reports of arrhythmias described above occurred in only a few patients in a large number of trials with a large number of Ss with extensive SCT exposure. The 4 Ss with arrhythmias that were ADOs described in two ongoing trials (SCT-MD-03 and 99002) in Section VII F of this review occurred out of a total of 1098 SCT Ss. The above described PK trials did not include placebo Ss for comparison such that results must be interpreted with caution. Nevertheless, a precaution statement is recommended for labeling regarding patients with pre-existing bradycardia, conduction defects or arrhythmias before considering SCT treatment. Similarly, elderly individuals may also be at risk since they may be on concomitant medications or may be at risk for development of bradycardia and/or arrhythmias.

Given the above described cardiac results, it is recommended that the Precautions section of proposed labeling is modified to reflect these safety results. Current labeling for Celexa™ and proposed labeling for SCT has a section on “Use in Patients with Concomitant Illness” under “Precautions”, which explains that experience with the drug in “certain concomitant systemic illnesses”... “myocardial infarction or unstable heart disease”... “is limited”. This section also indicates that 1116 patients receiving Celexa™ failed to show an association with the drug and “development of clinically significant ECG abnormalities.” As a result of the cardiac findings, it is recommended that the sponsor modify this section of labeling for at least the SCT product to reflect the cardiac results on HR and QT interval and to include a precautionary statement, accordingly. Since CT is the racemate compound, consideration for changing this section in the Celexa™ labeling is also recommended.

Additional modifications of proposed labeling regarding "Use in Patients with Concomitant Illness" under "Precautions" and regarding reported events under "Other Events Observed ... Premarketing Evaluation" sections of labeling are also recommended. Several reports of cerebral ischemia and cardiovascular events were observed in the clinical trials on SCT. It is important to consider noting these reports in labeling, although they occurred in only 7 Ss out of 2552 SCT Ss (0.3%) in completed and ongoing trials (see section VII E above). Consequently, the concomitant illness section under Precautions may include a statement that patients at risk of cardiovascular and cerebrovascular disease have not been systematically examined and that the "Other Events in Premarketing..." section include rare reports of cerebrovascular and cardiovascular events during the premarketing evaluation of SCT. As a side note, the 7 cerebral or cardiovascular events occurred mostly in elderly female Ss. However, this observation is likely reflecting the preponderance of female patients with MDD, and a greater proportion of females in the geriatric population (due to greater longevity in women compared to men).

X. Conclusions and Recommendations

A. Conclusions

Three (MD-01, 99001 and 99003) of the four studies showed significant treatment group effects on efficacy in favor of SCT treatment (pending confirmation by Biometrics) and support the sponsor's overall claim for efficacy in treatment MDD patients. One study, Study MD-02 failed to show significant treatment group effects. Given the numerical mean values on the primary efficacy measure for various treatment groups (LOCF dataset) and results of the OC dataset, this study appears to be a failed study, rather than a negative study. Possible reasons for failing to show positive results in this study are discussed in Section VI.C.8. and are also provided by the sponsor upon request in a 8/13/01 submission. Also refer to the Biometrics review regarding this issue.

Regarding the overall safety of SCT in MDD patients, SCT treatment appears to be adequately safe in this population. The safety profile generally appears to be similar to that observed for other SSRIs and for CT. However, possible small effects on decreasing HR and prolonging QT interval and development of bradycardia are described and there were reports of first degree heart block and junctional nodal arrhythmias in a few patients. A small decrease in HR is also noted in Celexa™ labeling. Given the cardiac results on SCT, it is recommended that there is a precautionary statement in labeling regarding patients at risk for development of bradycardia and conduction defects or that have these conditions. Based on PK results of SCT and CT, along with exposure of over 1000 elderly Ss to CT in controlled trials (as described in Celexa™ labeling) the recommended starting dose of 10 mg appears to be adequately safe for elderly patients, in patients with hepatic impairment or with mild to moderate renal impairment, as described in the proposed labeling. However, consideration may be given to starting elderly on a 5 mg dose, as previously described. Since there is inadequate information regarding patients with severe renal impairment, a cautionary statement in labeling as proposed by the sponsor is appropriate. There were no clear gender differences in PK or PD properties, as described in the submission.

One area regarding safety that is not addressed in other sections of this review, is that consideration may be given to potential discontinuation effects of SCT, as with other selective serotonin reuptake inhibitors. Spontaneous reports in the literature suggest that discontinuation, particularly upon abrupt cessation, may lead to various adverse events as described in the current

labeling for various SSRIs. These adverse events are described in the "Postmarketing Reports" section of the current labeling for various SSRIs and include the following: dizziness, sensory disturbances, agitation, anxiety, nausea and/or sweating which are "generally self-limiting." Also refer to Dr. Andrew Mosholder's review of Lilly's NDA18-936 SLR-055 submission regarding results studies of adverse events associated with treatment interruption of various selective serotonin reuptake inhibitors, that have been on the market for several years.

The potential safety issue of withdrawal-like effects with CT or SCT has not been systematically investigated. However, this SCT submission does not provide evidence for a withdrawal-like effect and there were no SAEs or ADOs described that were due to this phenomenon. However, consideration may be given to describing postmarketing reports of AEs associated with cessation of treatment regarding this class of drugs, the SSRIs, similar to that in the labeling of other SSRIs. Alternatively, the sponsor may wish to conduct well designed controlled studies that provide evidence refuting the possibility for withdrawal effects associated with abrupt cessation of paroxetine treatment.

B Recommendations

Three (MD-01, 99001 and 99003) out of the four trials are positive for the efficacy of SCT in treating MDD, while Study MD-02 for unclear reasons appears to be a failed study, but does not appear to show evidence refuting an efficacy effect. SCT appears to be adequately safe within the proposed dose range. The clinical trials demonstrate a benefit to risk ratio in favor of the use of SCT in treating patients with MDD. When considering the risk to benefit ratio of drugs for treating MDD, it is important to note that MDD can be life threatening and is a debilitating chronic disorder typically with a course of recurrent acute episodes over many years in a patient's life. From a Clinical perspective and pending confirmation of the efficacy results by Biometrics, it is recommended that this NDA be given an approvable status.

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

cc: IND
HFD 120
HFD 120/
P Andreason
K Brugge
D Bates
T Laughren

APPENDIX

**APPEARS THIS WAY
ON ORIGINAL**

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

20 pages

Table VI.B.5. Study Flow Chart and Assessment Schedule for the 8-Week Depression Study MD-01

			<i>Double-Blind Treatment: End of Week</i>				
Visit Name	Screen	Baseline	1	2	4	6	8 ^a
Visit Number	1	2	3	4	5	6	7
ASSESSMENT							
Informed Consent	X						
Inclusion / Exclusion	X	X					
Patient History	X						
Physical Exam	X						X
Laboratory Tests	X						X
Pregnancy Test	X						
Thyroid Function Test	X						
Urine Drug Screen	X						
ECG	X						X
Plasma Sample							X
Vital Signs	X	X	X	X	X	X	X
MINI	X						
MADRS	X	X	X	X	X	X	X
HAMD	X	X	X	X	X	X	X
CGI		X	X	X	X	X	X
HAMA		X					X
CES-D		X					X
Quality of Life Questionnaire (QOL)		X					X
Adverse Events		X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Drug Dispensed/Returned	X	X	X	X	X	X	X

a: or when the patient discontinued prior to week 8

Table VI.B.6. Subject Disposition for the 8-Week Depression Study MD-01

	Placebo	Escitalopram		Citalopram	Total
		10 mg/day	20 mg/day		
Patients Randomized	127	124	128	127	506
Did not receive study drug	5	5	3	2	15
Safety Population	122	119	125	125	491
No postbaseline MADRS assessment	3	1	2	0	6
ITT Efficacy Population	119	118	123	125	485
Cross-reference: Table 1.1					

Table VI.B.7. The Number (%) of Subjects in the Safety Population Who Completed or Discontinued (Categorized by Reason) for Study MD-01

Reason	Placebo (N=122)	Escitalopram		Citalopram (N=125)	Total (N=491)
		10 mg/day (N=119)	20 mg/day (N=125)		
Total Completers	91 (74.6%)	95 (79.8%)	94 (75.2%)	93 (74.4%)	373 (76.0%)
Total Withdrawn For Any Reason	31 (25.4%)	24 (20.2%)	31 (24.8%)	32 (25.6%)	118 (24.0%)
Adverse Event	3 (2.5%)	5 (4.2%)	13 (10.4%)	11 (8.8%)	32 (6.5%)
Insufficient Therapeutic Response	6 (4.9%)	3 (2.5%)	0	1 (0.8%)	10 (2.0%)
Withdrawal of Consent	10 (8.2%)	2 (1.7%)	6 (4.8%)	3 (2.4%)	21 (4.3%)
Lost to Follow-Up	10 (8.2%)	11 (9.2%)	8 (6.4%)	15 (12.0%)	44 (9.0%)
Protocol Violation	1 (0.8%)	3 (2.5%)	3 (2.4%)	1 (0.8%)	8 (1.6%)
Other	1 (0.8%)	0	1 (0.8%)	1 (0.8%)	3 (0.6%)

Percentages are relative to number of patients (N) in safety population.
Cross-reference: Table 1.2, Table 1.3, and Appendix IX, Listing 1.

Table VI.B.8. Demographic Characteristics of the Safety Population in Study MD-01

Characteristic		Placebo (N = 122)	Escitalopram		Citalopram (N = 125)
			10 mg/day (N = 119)	20 mg/day (N = 125)	
Age, years	Mean (SD)	40.3 (10.6)	40.6 (12.3)	39.6 (12.1)	40.0 (11.5)
	Median	39.0	40.0	40.0	41.0
	Min, Max	18, 63	19, 65	19, 63	18, 65
Sex, n (%)	Female	72 (59.0%)	84 (70.6%)	84 (67.2%)	78 (62.4%)
	Male	50 (41.0%)	35 (29.4%)	41 (32.8%)	47 (37.6%)
Race, n (%)	Caucasian	105 (86.1%)	103 (86.6%)	103 (82.4%)	101 (80.8%)
	Noncaucasian	17 (13.9%)	16 (13.4%)	22 (17.6%)	24 (19.2%)
Weight, lbs	Mean (SD)	179.7 (48.11)	168.0 (43.34)	177.1 (43.95)	178.2 (41.54)
	Median	173.3	159.0	170.9	177.0
	Min, Max	99.0, 336.5	86.0, 304.5	112.0, 326.5	98.0, 331.5

Percentages are relative to number of patients (N) in safety population.
Cross-reference: Table 2.1 and Appendix IX, Listing 2.

Table VI.B.9. Mean Baseline Scores on Various Efficacy Measures of the ITT Efficacy Population in Study MD-01

Efficacy Parameter	Placebo (N = 119)	Escitalopram		Citalopram (N = 125)
		10 mg/day (N = 118)	20 mg/day (N = 123)	
MADRS	29.5 (5.0)	28.0 (4.9)	28.9 (4.6)	29.2 (4.5)
HAMD	25.8 (5.9)	24.3 (6.2)	25.8 (5.7)	25.9 (5.9)
CGI-S	4.2 (0.5)	4.2 (0.5)	4.3 (0.6)	4.3 (0.6)

ITT population

Cross-reference: Table 2.4 and Appendix IX, Listings 8 and 9.

Table VI.B.10. Primary Efficacy Results (Mean MADRS Scores) in Study MD-01

Primary Efficacy
Change from Baseline in MADRS after 8 Weeks
ITT population - LOCF

					Primary Analysis Escitalopram vs. Placebo(1)			Secondary Analysis Citalopram 40mg vs. Placebo(2)	
	Placebo	Escitalopram 10mg	Escitalopram 20mg	Citalopram 40mg	Overall P-value Treatment (Interaction)	10mg vs. Placebo LSMD [95% CI] P-value	20mg vs. Placebo LSMD [95% CI] P-value	LSMD [95% CI]	P-value (Interaction)
Baseline									
Mean	29.5	28.0	28.9	29.2					
N	119	118	123	125					
SD	5.04	4.86	4.57	4.53					
SEM	0.46	0.45	0.41	0.40					
Median	29.0	27.0	28.0	29.0					
Range									
Week 8									
Mean	20.0	15.2	15.0	17.2					
N	119	118	123	125					
SD	10.47	9.23	8.32	10.62					
SEM	0.96	0.85	0.75	0.95					
Median	21.0	15.0	15.0	17.0					
Range									
Week 8 - Baseline									
Mean	-9.4	-12.8	-13.9	-12.0	<0.0001	-3.9 [-6.2, -1.7]	-4.6 [-6.9, -2.4]	-2.5 [-5.0, -0.1]	0.0414 (0.773)
N	119	118	123	125	(0.221)	0.0007	<0.0001		
SD	9.37	8.53	8.87	10.49					
SEM	0.86	0.79	0.80	0.94					
Median	-9.0	-13.0	-14.0	-12.0					
Range									

Note: (1) Based on an ANCOVA model with three treatment groups - escitalopram 10mg, escitalopram 20mg and placebo.
 (2) Based on an ANCOVA model with two treatment groups - citalopram 40mg and placebo.
 P-values are from ANCOVA models with treatment, center, and treatment by center as factors and baseline score as covariate.
 The interaction term was dropped if not significant at the 10% level.
 LSMD indicates the difference of least-squares means. CI = Confidence Interval.

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Table VI.B.11. (continued on the next page) Efficacy Results for Study MD-01

Summary of Change from Baseline for Efficacy Parameters
MADRS
ITT Population - LOCF

					Escitalopram vs. Placebo(1)		Citalopram 40mg vs. Placebo(2)		
	Placebo	Escitalopram 10mg	Escitalopram 20mg	Citalopram 40mg	Overall P-value	10mg vs. Placebo	20mg vs. Placebo	P-value	
						LSMD [95% CI] P-value	LSMD [95% CI] P-value		
Baseline									
Mean	29.5	28.0	28.9	29.2					
N	119	118	123	125					
SD	5.04	4.86	4.57	4.53					
SEM	0.46	0.45	0.41	0.40					
Median	29.0	27.0	28.0	29.0					
Range									
Week 1 - Baseline									
Mean	-4.4	-5.1	-5.1	-4.0	0.2772	-1.1 [-2.5, 0.4] 0.1401	-0.9 [-2.3, 0.5] 0.1992	0.3 [-1.0, 1.7]	0.6184
N	119	118	123	125					
SD	5.52	5.48	6.73	5.22					
SEM	0.51	0.50	0.61	0.47					
Median	-4.0	-4.0	-4.0	-3.0					
Range									
Week 2 - Baseline									
Mean	-6.8	-8.2	-8.3	-7.9	0.0409	-2.0 [-3.8, -0.2] 0.0256	-1.9 [-3.6, -0.2] 0.0311	-1.3 [-3.1, 0.4]	0.1315
N	119	118	123	125					
SD	6.63	6.89	7.39	7.50					
SEM	0.61	0.63	0.67	0.67					
Median	-6.0	-9.0	-7.0	-8.0					
Range									

Note: (1) Based on ANCOVA model with three treatment groups, escitalopram 10 mg, escitalopram 20 mg and placebo.
(2) Based on ANCOVA model with two treatment groups, citalopram 40 mg and placebo.
P-values are from additive ANCOVA models with treatment and center as effects and baseline score as covariate.
LSMD indicates the difference of least-squares means.
CI = Confidence Interval.

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Table VI.B.11, continued. Efficacy Results for Study MD-01

Summary of Change from Baseline for Efficacy Parameters
MADRS
ITT Population - LOCF

	Placebo	Escitalopram vs. Placebo(1)			Citalopram 40mg vs. Placebo(2)				
		Escitalopram 10mg	Escitalopram 20mg	Citalopram 40mg	Overall P-value	10mg vs. Placebo LSMD [95% CI] P-value	20mg vs. Placebo LSMD [95% CI] P-value	LSMD [95% CI]	P-value
Week 4 - Baseline									
Mean	-9.1	-11.1	-11.1	-10.2		-2.5	-2.3	-1.3	
N	119	118	123	125	0.0242	[-4.5, -0.5]	[-4.2, -0.3]	[-3.4, 0.9]	0.2491
SD	7.92	7.77	7.74	9.23		0.0145	0.0224		
SEM	0.73	0.72	0.70	0.83					
Median	-8.0	-12.0	-10.0	-11.0					
Range									
Week 6 - Baseline									
Mean	-9.4	-12.9	-12.9	-11.7		-3.9	-3.6	-2.2	
N	119	118	123	125	0.0005	[-6.1, -1.7]	[-5.8, -1.5]	[-4.6, 0.2]	0.0672
SD	8.73	7.79	8.82	10.16		0.0005	0.0009		
SEM	0.80	0.72	0.80	0.91					
Median	-9.0	-13.0	-13.0	-11.0					
Range									
Week 8 - Baseline									
Mean	-9.4	-12.8	-13.9	-12.0		-3.9	-4.6	-2.5	
N	119	118	123	125	<0.0001	[-6.2, -1.7]	[-6.9, -2.4]	[-5.0, -0.1]	0.0414
SD	9.37	8.53	8.87	10.49		0.0007	<0.0001		
SEM	0.86	0.79	0.80	0.94					
Median	-9.0	-13.0	-14.0	-12.0					
Range									

Note: (1) Based on ANCOVA model with three treatment groups, escitalopram 10 mg, escitalopram 20 mg and placebo.
(2) Based on ANCOVA model with two treatment groups, citalopram 40 mg and placebo.
P-values are from additive ANCOVA models with treatment and center as effects and baseline score as covariate.
LSMD indicates the difference of least-squares means.
CI = Confidence Interval.

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Table VI.B.12. Results of Gender Subgroup Analysis: Study MD-01

MADRS: Treatment by Gender Analysis
ITT Population - LOCF

Visit	Statistic	Placebo		Escitalopram 10 mg		Escitalopram 20 mg		p-value		
		Male	Female	Male	Female	Male	Female	Treatment	Gender	Interaction
Baseline	N	48	71	35	83	40	83			
	MEAN	28.8	30.0	27.6	28.1	30.0	28.4			
	SD	5.11	4.97	4.65	4.96	4.94	4.32			
	MEDIAN	28.5	30.0	27.0	27.0	30.0	28.0			
	MIN	14	22	15	15	22	22			
	MAX	38	52	37	40	39	43			
Endpoint	N	48	71	35	83	40	83			
	MEAN	21.9	18.8	14.9	15.3	15.3	14.9			
	SD	8.82	11.34	9.03	9.37	8.89	8.08			
	MEDIAN	24.0	19.0	14.0	15.0	15.5	15.0			
	MIN	0	0	1	0	0	0			
	MAX	39	59	36	36	32	30			
Endpoint-Baseline	N	48	71	35	83	40	83			
	MEAN	-6.8	-11.2	-12.7	-12.8	-14.7	-13.5	0.0000	0.2802	0.0924
	SD	7.90	9.91	8.17	8.73	9.49	8.59			
	MEDIAN	-6.0	-11.0	-13.0	-13.0	-14.5	-14.0			
	MIN	-24	-33	-30	-34	-36	-38			
	MAX	8	9	5	5	0	5			

Table VI.C.1. Disposition of Subjects in Study MD-02

Reason	Placebo (N=127)	Escitalopram (N=125)	Citalopram (N=123)	Total (N=375)
Total Completers	105 (82.7%)	96 (76.8%)	99 (80.5%)	300 (80.0%)
Total Withdrawn For Any Reason	22 (17.3%)	29 (23.2%)	24 (19.5%)	75 (20.0%)
Adverse Event	4 (3.1%)	11 (8.8%)	5 (4.1%)	20 (5.3%)
Insufficient Therapeutic Response	1 (0.8%)	2 (1.6%)	1 (0.8%)	4 (1.1%)
Withdrawal of Consent	6 (4.7%)	5 (4.0%)	6 (4.9%)	17 (4.5%)
Lost to Follow-Up	6 (4.7%)	7 (5.6%)	10 (8.1%)	23 (6.1%)
Protocol Violation	3 (2.4%)	3 (2.4%)	2 (1.6%)	8 (2.1%)
Other	2 (1.6%)	1 (0.8)	0	3 (0.8%)

Percentages are relative to number of patients (N) in safety population.
Cross-reference: Table 1.2 and Appendix IX, Listing 1.

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Table VI.C.2. Efficacy Results on the MADRS Score for Study MD-02 (continued on the next page).

Summary of Change from Baseline for Efficacy Parameters
MADRS
ITT Population - LOCF

	Placebo	Escitalopram	Citalopram	Escitalopram vs. Placebo (1)		Citalopram vs. Placebo (1)	
				LSMD [95% CI]	P-value	LSMD [95% CI]	P-value
Baseline							
Mean	28.8	28.7	28.3				
N	125	124	119				
SD	4.97	4.27	4.98				
SEM	0.44	0.38	0.46				
Median	28.0	28.5	27.0				
Range							
Week 1 - Baseline							
Mean	-3.8	-4.4	-3.2	-0.6	0.406	0.4	0.539
N	125	124	119	[-1.9, 0.8]		[-0.9, 1.8]	
SD	5.65	5.19	5.13				
SEM	0.51	0.47	0.47				
Median	-3.0	-4.0	-2.0				
Range							
Week 2 - Baseline							
Mean	-6.7	-6.9	-6.5	-0.1	0.914	0.1	0.954
N	125	124	119	[-1.9, 1.7]		[-1.7, 1.8]	
SD	7.28	7.45	6.58				
SEM	0.65	0.67	0.60				
Median	-6.0	-6.0	-6.0				
Range							

Note: (1) Based on ANCOVA model with two treatment groups.
P-values are from additive ANCOVA models with treatment and center as effects and baseline score as covariate.
LSMD indicates the difference of least-squares means.
CI = Confidence Interval.

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Table VI.C.2, continued. Efficacy Results on the MADRS Score for Study MD-02
(continued on the next page).

Summary of Change from Baseline for Efficacy Parameters
MADRS
ITT Population - LOCF

	Placebo	Escitalopram	Citalopram	Escitalopram vs. Placebo (1)		Citalopram vs. Placebo (1)	
				LSMD [95% CI]	P-value	LSMD [95% CI]	P-value
Week 3 - Baseline							
Mean	-7.9	-8.8	-7.9	-0.8	0.462	-0.2	0.875
N	125	124	119	[-2.8, 1.3]		[-2.2, 1.9]	
SD	8.60	8.71	7.71				
SEM	0.77	0.78	0.71				
Median	-6.0	-8.0	-7.0				
Range							
Week 4 - Baseline							
Mean	-10.2	-10.4	-10.0	-0.0	0.994	0.0	0.996
N	125	124	119	[-2.2, 2.1]		[-2.1, 2.2]	
SD	8.37	9.58	8.84				
SEM	0.75	0.86	0.81				
Median	-10.0	-9.5	-9.0				
Range							
Week 6 - Baseline							
Mean	-10.5	-12.5	-11.7	-1.7	0.141	-1.4	0.246
N	125	124	119	[-4.1, 0.6]		[-3.8, 1.0]	
SD	9.77	9.91	9.53				
SEM	0.87	0.89	0.87				
Median	-9.0	-13.0	-12.0				
Range							

Note: (1) Based on ANCOVA model with two treatment groups.
P-values are from additive ANCOVA models with treatment and center as effects and baseline score as covariate.
LSMD indicates the difference of least-squares means.
CI = Confidence Interval.

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Table VI.C.2, continued. Efficacy Results on the MADRS Score for Study MD-02
(continued on the next page).

Summary of Change from Baseline for Efficacy Parameters
MADRS
ITT Population - LOCF

	Placebo	Escitalopram	Citalopram	Escitalopram vs. Placebo (1)		Citalopram vs. Placebo (1)	
				LSMD [95% CI]	P-value	LSMD [95% CI]	P-value
Week 8 - Baseline							
Mean	-11.2	-12.9	-13.0	-1.4	0.251	-1.9	0.151
N	125	124	119	[-3.9, 1.0]		[-4.4, 0.7]	
SD	10.35	10.03	9.79				
SEM	0.93	0.90	0.90				
Median	-10.0	-13.0	-14.0				
Range							

Note: (1) Based on ANCOVA model with two treatment groups.
P-values are from additive ANCOVA models with treatment and center as effects and baseline score as covariate.
LSMD indicates the difference of least-squares means.
CI = Confidence Interval.

Report Generated by Program: /usr5/biostat/sct/sct02/programs/tables/effvisit.sas

Table VI.D.1. Disposition of Subjects in Study 99001

Number of Patients Planned and Analysed			
• A minimum of 320 patients were planned.			
• Patient disposition is tabulated below:			
	Placebo	Escitalopram	Total
	n (%)	n (%)	n (%)
Patients randomised	189	191	380
Patients treated	189	191	380
Patients completed	160 (84.7%)	160 (83.8%)	320 (84.2%)
Patients withdrawn	29 (15.3%)	31 (16.2%)	60 (15.8%)
Primary reason for withdrawal:			
Adverse event	2 (1.1%)	9 (4.7%)	11 (2.9%)
Lack of efficacy	13 (6.9%)	7 (3.7%)	20 (5.3%)
Patient Data Sets:			
All Patients Treated Set	189	191	380
Full Analysis Set	189	188	377

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Table VI.D.2. Adjusted Mean Change (Using Least Square Means) from Baseline to Treatment Endpoint on the MADRS Score in Each Treatment Group for Study 99001

Treatment Group	n	Least Squares Mean	SE	95% Confidence Limits	
				Lower	Upper
PBO	189	-13.60	0.69	-14.96	-12.24
ESC	188	-16.27	0.69	-17.63	-14.92
99001	ET11A	12JAN2001:14:53:28	Final		

Table VI.D.3. Mean MADRS Score at Each Visit in Each Treatment Group for Study 99001

Last Observation Carried Forward (LOCF)									
Treatment Group	Visit #	n	Mean	SD	Median	Minimum	Maximum	MADRS<=12	
								n	%
PBO	Baseline	189	28.7	3.7	29.0	21	40	0	(0.0)
	Week 1	189	25.1	5.8	25.0	3	40	4	(2.1)
	Week 2	189	22.5	6.5	23.0	0	36	14	(7.4)
	Week 3	189	20.2	8.1	21.0	0	43	39	(20.6)
	Week 4	189	18.4	8.3	18.0	0	43	47	(24.9)
	Week 6	189	17.9	9.0	18.0	0	43	56	(29.6)
	Week 8	189	16.7	9.2	17.0	0	43	66	(34.9)
	ESC	Baseline	188	29.2	4.2	29.0	22	39	0
Week 1		188	24.9	6.1	25.0	7	40	7	(3.7)
Week 2		188	21.1	7.5	21.5	0	42	26	(13.8)
Week 3		188	17.9	7.9	18.0	1	37	47	(25.0)
Week 4		188	15.9	8.2	15.0	0	36	65	(34.6)
Week 6		188	14.6	8.8	13.0	0	38	84	(44.7)
Week 8		188	14.3	9.1	13.0	0	38	89	(47.3)
@ nominal visits									
99001	ET01	12JAN2001:14:47:56	Final						

Table VI.D.4. The Disposition of Subjects in Study 99003

Number of Patients Planned and Analysed				
• A minimum of 360 patients were planned for the study (120 patients in each of 3 treatment arms).				
• Patient disposition is tabulated below.				
	Placebo	Citalopram	Escitalopram	Total
	N (%)	N (%)	N (%)	N (%)
Patients randomised	154	161	156	471
Patients treated	154	160	155	469
Patients completed	139 (90.3)	152 (95.0)	146 (94.2)	437 (93.2)
Patients withdrawn from APTS	15 (9.7)	8 (5.0)	9 (5.8)	32 (6.8)
Primary reason for withdrawal:				
Adverse Event(s)	4 (2.6)	6 (3.8)	4 (2.6)	14 (3.0)
Lack of efficacy	5 (3.2)	1 (0.6)	0 (0.0)	6 (1.3)
Patient data sets:				
All Patients Treated Set (APTS)	154	160	155	469
Full Analysis Set (FAS)	154	159	155	468

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Table VI.D.5. Mean Change from Baseline on the MADRS Score at Each Visit in Study 99003

Last Observation Carried Forward (LOCF)									
Treatment Group	Visit #	n	Mean	SD	Median	Minimum	Maximum	>=50% reduction	
								n	%
PBO	Week 1	154	-3.4	5.2	-3.0	-24	9	7	(4.5)
	Week 2	154	-6.8	7.3	-7.0	-28	12	24	(15.6)
	Week 3	154	-8.8	7.9	-9.0	-28	12	45	(29.2)
	Week 4	154	-8.9	8.8	-8.5	-28	12	43	(27.9)
	Week 6	154	-11.1	8.8	-11.0	-31	12	55	(35.7)
	Week 8	154	-12.5	9.5	-13.0	-35	12	68	(44.2)
CIT	Week 1	159	-4.0	4.5	-3.0	-21	4	6	(3.8)
	Week 2	159	-7.4	6.6	-7.0	-32	20	20	(12.6)
	Week 3	159	-9.6	7.9	-9.0	-32	20	40	(25.2)
	Week 4	159	-10.6	8.5	-9.0	-34	20	53	(33.3)
	Week 6	159	-12.5	8.8	-12.0	-37	20	66	(41.5)
	Week 8	159	-14.2	8.9	-14.0	-37	20	81	(50.9)
ESC	Week 1	155	-4.4	5.2	-4.0	-19	10	8	(5.2)
	Week 2	155	-8.1	6.3	-8.0	-29	6	27	(17.4)
	Week 3	155	-10.5	6.9	-10.0	-28	3	41	(26.5)
	Week 4	155	-11.5	7.6	-10.0	-31	3	60	(38.7)
	Week 6	155	-13.8	7.8	-14.0	-34	4	77	(49.7)
	Week 8	155	-15.3	8.4	-16.0	-36	2	95	(61.3)

@ nominal visits
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Table VI.D.6. Mean Scores of Each Treatment Group on the MADRS at Each Visit in Study 99003

Last Observation Carried Forward (LOCF)									
Treatment Group	Visit #	n	Mean	SD	Median	Minimum	Maximum	MADRS<=12	
								n	%
PBO	Baseline	154	28.7	4.0	28.0	22	40	0	(0.0)
	Week 1	154	25.3	6.2	25.0	3	39	2	(1.3)
	Week 2	154	21.9	8.0	22.0	0	45	21	(13.6)
	Week 3	154	19.9	8.3	19.5	2	45	30	(19.5)
	Week 4	154	19.8	9.3	20.0	0	45	40	(26.0)
	Week 6	154	17.6	9.1	18.0	0	45	44	(28.6)
	Week 8	154	16.2	9.8	16.0	0	45	63	(40.9)
	CIT	Baseline	159	29.2	4.2	29.0	22	39	0
Week 1		159	25.2	5.7	25.0	10	39	4	(2.5)
Week 2		159	21.8	7.0	23.0	4	43	14	(8.8)
Week 3		159	19.6	7.9	19.0	0	43	31	(19.5)
Week 4		159	18.6	8.6	19.0	0	43	42	(26.4)
Week 6		159	16.7	8.8	16.0	0	45	53	(33.3)
Week 8		159	15.0	8.7	14.0	0	45	66	(41.5)
ESC		Baseline	155	29.0	4.3	29.0	20	39	0
	Week 1	155	24.6	5.6	24.0	10	36	3	(1.9)
	Week 2	155	20.9	6.8	21.0	3	36	17	(11.0)
	Week 3	155	18.5	7.4	18.0	1	36	35	(22.6)
	Week 4	155	17.4	8.3	17.0	0	36	44	(28.4)
	Week 6	155	15.2	8.2	14.0	0	35	64	(41.3)
	Week 8	155	13.7	8.3	12.0	0	36	78	(50.3)

@ nominal visits
99003 ET01 10JAN2001:16:51:11 Final

Table VII.D.1. Summary of Deaths Occurring in Completed and Ongoing Trials (see Section VII D of this review).

S 5302: This 77 year old male S was in study 99024 (a geriatric depression trial) with a history of suicide attempt (within the previous 6 months), who committed suicide (hanging) 4 days after completing blinded treatment. The S was on several concomitant medications including oxazepam and had multiple medical conditions including ischemic heart disease and stroke with left hemiparesis. The suicide appears to be due to underlying MDD in a patient with at least several risk factors for depression that include his age, gender, and previous history of a suicide attempt.

S 5370: This 81 year old female had previously completed Study 99258 (8 weeks of blinded treatment) followed by 10 days of 10 mg/day SCT in Study 99258 when she was hospitalized for CVA and ultimately was in a coma and died. Her medical history includes IDDM, previous CVA and seizure. Given this medical history and the patient's age it appears the CVA was due to underlying disease. While a possible interaction effect between SCT and the patient's preexisting condition cannot be ruled out, it appears that the CVA was not likely to be drug-related.

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Table VII.E.1. Serious Adverse Events in 14 Completed Trials (Includes the Four 8-Week Depression Trials)

Treatment	Study Number	Patient Number	Age (years)/ Sex	Adverse Event Preferred Term	Day of SAE Start	Severity/ Relationship to Study Medication
Placebo	99001	0026	48/F	Gastric Ulcer	42	Severe/Not Related
	99001	0074	37/F	Vein Varicose	59	Moderate/Not Related
	99001	0124	34/F	Vein Varicose	55	Moderate/Not Related
	99001	0201	26/F	Accidental Overdose	32	Mild/Not Related
	99001	0275	38/F	Pregnancy Unintended, Abortion	57	Severe/Not Related
	99003	3349	37/M	Psychosis	7	Severe/Not Related
	SCT-MD-01	1106	52/F	Gall Bladder Stones	4	Severe/Not Related
	SCT-MD-01	1265	26/M	Non-Accidental Overdose	8	Severe/Not Related
Escitalopram	99001	0176	42/F	Insomnia*	47	Severe/Not Related
	99001	0356	47/F	Suicide Attempt	49	Severe/Not Related
	99003	3302	29/F	Pelvic Inflammation	32	Moderate/Not Related
	99003	3360	22/F	Pregnancy Unintended, Abortion	76	Moderate/Not Related
	SCT-MD-01	1095	35/F	Anaphylaxis	52	Severe/Not Related
	SCT-MD-01	1392	31/F	Suicide Attempt*	9	Severe/Not Related
				Non-Accidental Overdose ¹	9	Severe/Not Related
	SCT-MD-02	2021	29/F	Suicidal Tendency*	13	Severe/Not Related
				Suicide Attempt	25	Moderate/Not Related
				Suicidal Tendency	27	Severe/Not Related
	SCT-MD-02	2232	19/F	Tachycardia	39	Moderate/Not Related
Non-Accidental Overdose*				39	Moderate/Not Related	
Suicide Attempt				39	Moderate/Not Related	
Citalopram	99003	3350	19/F	Miscarriage*	61	Severe/Not Related
	SCT-MD-01	1041	45/M	Intestinal Fistula	40	Moderate/Not Related
	SCT-MD-01	1401	63/M	Non-Accidental Overdose*	10	Severe/Not Related
				Coma	10	Severe/Not Related
	SCT-MD-02	2350	30/F	Cholestasis Intrahepatic* Dehydration*	2 2	Severe/Not Related Severe/Not Related

* Discontinued due to SAE

¹ Initially reported as suicide attempt only (ISS) and subsequently reclassified as both suicide attempt and non-accidental overdose.

Initially reported as accidental (ISS) and subsequently reclassified as non-accidental.

Based on Studies SCT-MD-01, SCT-MD-02, SCT-PK-01, SCT-PK-02, SCT-PK-03, SCT-PK-04, SCT-PK-05, SCT-PK-06, 99001, 99003, 98106, 98107, 98113, and 99166.

Day of SAE start = SAE start date - start date of study medication + 1.

M = Male; F = Female.

Cross reference: Table 4.1.

**Table VII.E.2. SAEs in 4 SCT Subjects and 2 CT in the 14 Completed Trials
SCT Ss described in Section VII E of the Review:**

- **Tachycardia** in S 2232 who also had the SAE of non-accidental overdose of cough-cold medication 8 days after her last dose of SCT during which she had tachycardia. Consequently, it appears tachycardia was secondary to overdose of cough-cold medication.
- **Unintended pregnancy (abortion)** in S3360. This S stopped taking her oral contraceptive agent (OCA) on 4/16/01 and had completed the 8 week trial of SCT on 4/10/00 with a negative pregnancy test on 4/11/01. On 5/1/01 in a follow-up visit her pregnancy test was positive (last menstrual period occurred in mid March). It appears that the S's pregnancy was due to her cessation of OCA. She then had an abortion induced with mifepristone treatment.
- **Pelvic inflammatory disease (PID)** in S 3302 who was 22 year old female who underwent elective hysterectomy for "recurrent" PID. Given that the PID was indicated as recurrent, the S's age and that she may be sexually active, this SAE appears to be due to a pre-existing or non-drug related underlying condition. SSRIs are not known to be associated with development of infectious diseases, including PID.
- **Anaphylaxis** in S 1095 who had known latex allergy and was exposed to latex gloves on her 52nd day of SCT treatment. It appears that this S had an allergic reaction to exposure to latex.
- **Insomnia** reported by S 0176 who was hospitalized and recovered. She had a history of a sleep disorder and was withdrawn from the study due to the SAE. Given the S's history, this event may not be drug-related. However, insomnia is among known adverse events associated with SSRIs and CT.

CT Ss:

- **Cholestasis intrahepatic with dehydration:** S 2350 had nausea and diarrhea during the placebo run-in phase, followed by vomiting on Day 1 of CT treatment. On Day 2 he was hospitalized for intrahepatic cholestasis and dehydration. CT was discontinued. Resolution of SAEs occurred within 3 days of hospitalization. Since the S was symptomatic during the placebo run-in phase, this SAE appears to be due to a preexisting non-drug-related condition.
- **Intestinal fistula** in S 1041 who had a positive history of anal fissure and hemorrhoidectomy 6 months prior to study entry.

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Table VII.E.3. The Number of Subjects with Serious Adverse Events for All Completed and Ongoing Trials (as of 2/1/01 cut-off date)

<i>SAE Category</i>	<i>Escitalopram</i>	<i>Citalopram</i>	<i>Placebo</i>	<i>Blinded</i>	<i>Total</i>
Suicide/Overdose	11	2	2	6	21
Depression worsened	4	0	0	4	8
Other psychiatric disorder	2	0	1	3	6
CNS disorder	4	1	0	5	10
Cardiovascular disorder	7	0	2	7	16
Respiratory disorder	4	0	0	5	9
Gastrointestinal disorder	5	2	2	4	13
Reproductive disorder, female	8	1	1	3	13
Neoplasm	3	0	0	2	5
Blood disorder	0	0	0	1	1
Injury	3	0	0	3	6
Miscellaneous	11	1	0	8	20
Total Patients	57	5	8	44	112
Total Patient Years	644.7	65.2	82.6	478.8	--

Notes:

Based on Studies 98106, 98107, 98113, 99166, 99001, 99002, 99003, 99012, 99022, 99024, 99258, 99269, 99270, SCT-PK-01, SCT-PK-02, SCT-PK-03, SCT-PK-04, SCT-PK-05, SCT-PK-06, SCT-MD-01, SCT-MD-02, SCT-MD-03, SCT-MD-04, SCT-MD-05, SCT-MD-09, SCT-MD-11, and SCT-MD-17.

Patient years = Total duration of exposure to study medication for all subjects pooled, in years.

One patient may have experienced more than one event within a serious adverse event category.

Two patients had serious adverse events reported under more than one treatment group and are counted only once in the total.

Two serious adverse events that occurred in one fluoxetine-treated patient, a gastrointestinal disorder and a female reproductive disorder, are not represented.

Cross references: Table 4.2 and Appendix I, Table A.1.

Cutoff date: February 1, 2001.

Table VII.F.1. Incidence Rates of Adverse Events (with an n≥3 subjects in any treatment group) Associated with Discontinuation of Treatment in Placebo, Citalopram and Escitalopram Subjects in the Four 8-Week Depression Trials

<i>Preferred Term</i>	<i>Placebo (N=592) n (%)</i>	<i>Escitalopram (N=715) n (%)</i>	<i>Citalopram (N=408) n (%)</i>
Patients discontinued due to AEs	13 (2.2)	42 (5.9)	22 (5.4)
Nausea	1 (0.2)	12 (1.7)	6 (1.5)
Headache	0	4 (0.6)	5 (1.2)
Anxiety	1 (0.2)	2 (0.3)	4 (1.0)
Dizziness	1 (0.2)	5 (0.7)	1 (0.2)
Depression Aggravated	3 (0.5)	2 (0.3)	1 (0.2)
Ejaculation Disorder ^a	0	5 (2.2)	0
Insomnia	0	4 (0.6)	1 (0.2)

^a Percentages are relative to the number of male patients (escitalopram N = 226; citalopram N = 159; placebo N = 188).

Based on Studies SCT-MD-01, SCT-MD-02, 99001, and 99003.

Cross reference: Table 4.3.

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Table VII.H.1. Incidence Rates of Common Treatment Emergent Adverse Events ($\geq 5\%$ of Escitalopram Subjects) in Placebo, Citalopram and Escitalopram Subjects in the Four 8-Week Depression Trials

<i>Preferred Term</i>	<i>Placebo (N=592) n (%)</i>	<i>Escitalopram (N=715) n (%)</i>	<i>Citalopram (N=408) n (%)</i>
Patients with at least one TEAE	379 (64.0)	520 (72.7)	312 (76.5)
Headache	97 (16.4)	113 (15.8)	81 (19.9)
Nausea	44 (7.4)	105 (14.7)	68 (16.7)
Ejaculation Disorder ^a	0	21 (9.3)	14 (8.8)
Insomnia	23 (3.9)	65 (9.1)	36 (8.8)
Diarrhea	31 (5.2)	58 (8.1)	44 (10.8)
Dry Mouth	27 (4.6)	44 (6.2)	33 (8.1)
Somnolence	11 (1.9)	43 (6.0)	18 (4.4)
Upper Resp Tract Infection	42 (7.1)	42 (5.9)	16 (3.9)
Dizziness	16 (2.7)	37 (5.2)	15 (3.7)
Influenza-Like Symptoms	24 (4.1)	36 (5.0)	25 (6.1)

^a Percentages are relative to the number of male patients (escitalopram N = 225; citalopram N = 159; placebo N = 188).

Based on Studies SCT-MD-01, SCT-MD-02, 99001, and 99003.

Cross reference: Table 4.6.

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Table VII.J.1. Treatment Group Mean Values for Vital Sign and Body Weight Parameters in the Four 8-Week Depression Trials.

		Placebo (N=573)	Escitalopram (N=699)	Citalopram (N=402)
Systolic BP (mm Hg)	Baseline	124	123	125
	Change	-1.3	-1.7	-1.6
Diastolic BP (mm Hg)	Baseline	77	77	78
	Change	-0.6	-1.1	-0.3
Pulse Rate (bpm)	Baseline	73	73	74
	Change	-0.4	-1.9	-2.4
Body Weight (lb)	Baseline	168	167	174
	Change	0.7	0.0	-0.3

Notes:

Based on Studies SCT-MD-01, SCT-MD-02, 99001, and 99003.

N = number of treated patients with both baseline and at least one post-baseline assessment.

Pulse was missing for one citalopram patient.

Body weight was missing for one escitalopram patient and one citalopram patient.

BP = blood pressure.

Change = mean change from baseline at endpoint.

Table VII.J.2. The Incidence Rates of Placebo, Escitalopram and Citalopram Subjects with Potentially Clinically Significant Changes in Vital Sign and Body Weight Parameters in the Four 8-Week Depression Trials.

Parameter	PCS Criteria	Placebo (N=573) n (%)	Escitalopram (N=699) n (%)	Citalopram (N=402) n (%)
Systolic BP (mm Hg)	≥ 180 and increase ≥ 20	0	0	1 (0.2)
	≤ 90 and decrease ≥ 20	4 (0.7)	0	3 (0.7)
Diastolic BP (mm Hg)	≥ 105 and increase ≥ 15	1 (0.2)	1 (0.1)	2 (0.5)
	≤ 50 and decrease ≥ 15	0	2 (0.3)	0
Pulse (bpm)	≥ 120 and increase ≥ 15	0	0	0
	≤ 50 and decrease ≥ 15	0	3 (0.4)	2 (0.5)
Body Weight (lb)	Increase ≥ 7%	8 (1.4)	13 (1.9)	9 (2.2)
	Decrease ≥ 7%	6 (1.0)	5 (0.7)	5 (1.2)

Notes:

Based on Studies SCT-MD-01, SCT-MD-02, 99001, and 99003.

N = Number of treated patients with both baseline and at least one post-baseline assessment.

Pulse was missing for one citalopram patient.

Body weight was missing for one escitalopram patient and one citalopram patient.

Cross reference: Table 5.1.

ATTACHMENT 1.

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Exposure in Completers in MDD Trials
 (note that regarding Table 2 below, that 10 mg SCT and 20 mg CT capsules were used in studies MD-02 and 99003)

Table 1 - Duration of Treatment (days) for Completers by Protocol and Treatment Group

Protocol	Treatment	N	Mean	SD	Median	Minimum	Maximum
SCT-MD-01	Placebo	91	57.2	3.6	56	48	76
	Escitalopram 10 mg	95	57.4	3.3	56	50	70
	Escitalopram 20 mg	94	57.9	3.5	57	51	72
	Citalopram	93	57.4	3.2	56	53	70
SCT-MD-02	Placebo	105	57.1	3.4	56	47	69
	Escitalopram	96	57.1	4.0	56	42	70
	Citalopram	99	57.1	2.9	56	50	67
99001	Placebo	160	56.7	3.0	56	47	66
	Escitalopram	160	56.3	2.8	56	49	66
99003	Placebo	139	57.1	4.0	56	48	76
	Escitalopram	146	57.1	3.5	56	49	70
	Citalopram	152	57.2	4.7	56	31	71

Table 2 - Mean Daily Dose (capsules/day) for Completers by Protocol and Treatment Group

Protocol	Treatment	N	Mean	SD	Median	Minimum	Maximum
SCT-MD-02	Placebo	105	1.5	0.18	1.6	1.0	1.7
	Escitalopram	96	1.5	0.23	1.6	0.9	1.7
	Citalopram	99	1.5	0.24	1.6	0.9	1.7
99003	Placebo	139	1.2	0.24	1.3	1.0	1.6
	Escitalopram	146	1.2	0.24	1.0	1.0	1.6
	Citalopram	152	1.2	0.24	1.0	1.0	1.6

Table 3 - Mean Daily Dose (mg/day) for Completers by Protocol and Treatment Group

Protocol	Treatment	N	Mean	SD	Median	Minimum	Maximum
SCT-MD-02	Placebo	105					
	Escitalopram	96	14.7	2.3	15.8	8.9	17.0
	Citalopram	99	29.1	4.8	31.5	18.9	33.9
99003	Placebo	139					
	Escitalopram	146	11.9	2.4	10	9.8	16.0
	Citalopram	152	24.0	4.7	20	20.0	32.1

Table 4.

List of Patients with Normal ECG at Screen and Abnormal ECG at Endpoint

Protocol Number	Treatment Group	Patient Number	Screen Date	Endpoint Date	Abnormality at Endpoint	
SCT-MD-01	Placebo	1126	2/7/00	4/12/00	First Degree Block	
		1421	2/28/00	5/2/00	T waves: Flat	
		1450	3/20/00	5/24/00	First Degree Block	
	Escitalopram	1139	11/9/99	1/11/00	First Degree Block	
		1250	1/28/00	3/31/00	T waves: Flat	
	Citalopram	1185	12/2/99	2/9/00	T waves: Flat	
		1206	11/22/99	1/26/00	First Degree Block	
		1405	1/27/00	3/31/00	Sinus Bradycardia *	
	SCT-MD-02	Placebo	2024	10/19/99	12/20/99	T waves: Flat
			2164	10/28/99	12/30/99	Flat T waves
2285			2/14/00	4/25/00	Flat, inverted T waves	
2333			2/10/00	4/13/00	First Degree Block	
2340			2/10/00	4/13/00	Conduction: WPW *	
				4/24/00	Normal	
2430		3/24/00	5/9/00	First Degree Block		
Escitalopram		2062	11/9/99	1/11/00	ST Segment: Depressed T Waves: Flat	
		2254	1/5/00	3/20/00	Junctional Escape Rhythm; Sinus Bradycardia *	
		2345	3/3/00	4/27/00	Sinus Bradycardia *	
		2410	3/2/00	5/4/00	Sinus Bradycardia, First Degree Block	
Citalopram		2086	11/8/99	1/12/00	Right Bundle Branch Block	
		2090	12/15/99	2/21/00	First Degree Block	
		2104	11/10/99	1/21/00	ST Segment: Depressed T Waves: Flat	
		2297	2/21/00	3/20/00	First Degree Block	
		2357	3/20/00	5/22/00	ST Segment: Elevated *	
5/30/00	ST Segment: Elevated *					

Table 5.

List of Patients with Normal ECG at Screen and Abnormal ECG at Endpoint

Protocol Number	Treatment Group	Patient Number	Screen Date	Endpoint Date	Abnormality at Endpoint		
99001	Placebo	0005	9/22/99	12/1/99	QTcB dispersion prolonged*		
		0012	10/8/99	12/10/99	QTcB dispersion increased		
		0031	9/27/99	12/3/99	QTcB dispersion prolonged*		
		0044	10/28/99	1/5/00	QTcB dispersion prolonged		
		0074	10/11/99	12/14/99	Sinus Bradycardia		
		0124	10/14/99	12/13/99	QTcB dispersion prolonged		
		0130	11/24/99	2/2/00	First Degree Block		
		0191	1/24/00	3/29/00	QTcB dispersion prolonged		
		0278	1/24/00	3/30/00	Short PR		
		0289	2/11/00	4/12/00	QTcB dispersion prolonged*		
		0291	2/11/00	2/25/00	Short PR		
		0302	3/20/00	5/22/00	Sinus Bradycardia		
		0310	4/17/00	6/16/00	Borderline QTc		
		0359	4/3/00	6/6/00	Sinus Bradycardia		
		0428	5/16/00	7/18/00	First Degree Block		
		0442	5/19/00	6/6/00	Sinus Bradycardia; ST Segment: Depressed*		
		Escitalopram		0013	10/21/99	12/23/99	QTcB dispersion increased
				0042	9/29/99	12/7/99	QTcB dispersion prolonged
				0075	10/29/99	1/4/00	Short PR
				0094	11/16/99	1/20/00	Short PR
				0150	11/29/99	2/2/00	QTcB dispersion increased*
				0163	3/17/00	5/22/00	T Wave: Inverted
				0173	11/17/99	1/18/00	LAH
0183	11/23/99			1/20/00	QTcB dispersion prolonged		
0190	1/11/00			3/15/00	QTcB dispersion prolonged*		
0222	4/3/00			6/5/00	Short PR		
0250	4/7/00			6/13/00	T Wave: Flat		
0284	3/2/00			5/4/00	Short PR		
0340	4/10/00			6/14/00	First Degree Block		
0427	5/12/00			7/17/00	Sinus Bradycardia		

Table 5, continued.

(continued) - List of Patients with Normal ECG at Screen and Abnormal ECG at Endpoint

Protocol Number	Treatment Group	Patient Number	Screen Date	Endpoint Date	Abnormality at Endpoint	
99003	Placebo	3092	11/23/99	1/25/00	QTc Borderline	
		3128	10/13/99	12/15/99	QTc dispersion increased	
		3235	10/28/99	1/11/00	ST Segment: Depressed	
		3273	2/9/00	3/8/00	ST Segment: Depressed	
		3301	10/26/99	1/3/00	QTcB dispersion increased	
		3306	11/10/99	1/13/00	Sinus Tachycardia; QTcB dispersion prolonged	
		3321	1/14/00	3/17/00	Short PR	
		3434	11/16/99	1/19/00	QTcB dispersion prolonged	
		3450	4/13/00	6/16/00	Sinus Bradycardia	
		3534	3/1/00	5/4/00	ST Segment: Depressed; T Wave: Inverted	
		Escitalopram	3029	3/22/00	5/26/00	Sinus Bradycardia
		3035	9/29/99	12/1/99	> 100% increase in QTcB dispersion*	
		3041	10/6/99	12/8/99	Sinus Bradycardia; First Degree Block	
		3044	10/29/99	1/3/00	Sinus Bradycardia	
		3055	10/11/99	12/15/99	Sinus Bradycardia	
		3075	10/6/99	12/16/99	ST Segment: Depressed; T wave: Inverted	
		3091	11/22/99	1/25/00	First Degree Block	
		3136	10/30/99	12/30/99	Short PR	
		3162	3/30/00	6/14/00	QTc prolonged	
		3187	12/2/99	2/28/00	Sinus Bradycardia	
		3247	10/21/99	12/22/99	First Degree Block	
		3259	10/25/99	12/29/99	First Degree Block	
		3312	12/14/99	2/21/00	QTcB dispersion prolonged	
		3424	4/14/00	6/30/00	T Wave: Biphasic	
		3452	12/15/99	2/22/00	Short PR	
		3462	2/16/00	4/19/00	QTcB dispersion prolonged	
		3502	1/19/00	3/22/00	First Degree Block	
		3505	1/25/00	3/28/00	Sinus Bradycardia	
		3519	2/7/00	4/7/00	ST Segment: Depressed; T wave: Inverted *	
		3541	2/7/00	4/14/00	First Degree Block; T Wave: Inverted *	
		3546	2/28/00	5/11/00	Sinus Bradycardia	
		4279	2/9/00	4/20/00	First Degree Block	
	Citalopram	3026	9/16/99	11/22/99	T Wave: Biphasic	
	3052	1/27/00	4/3/00	ST Segment: Depressed; T wave: Inverted *		
	3068	10/4/99	12/15/99	> 100% increase in QTcB dispersion*		
	3077	11/30/99	2/11/00	Ectopic Atrial Rhythm		
	3080	10/2/99	12/9/99	Sinus Bradycardia*		
	3193	11/23/99	1/26/00	Sinus Bradycardia		
	3223	10/12/99	12/14/99	Short PR		
	3230	11/13/99	1/17/00	Sinus Bradycardia		
	3255	12/3/99	2/4/00	First Degree Block		
	3278	10/20/99	1/5/00	QTcB dispersion prolonged		
	3304	11/3/99	1/10/00	QTcB dispersion prolonged		
	3322	2/19/00	4/22/00	Sinus Bradycardia		
	3376	12/10/99	2/11/00	Sinus Bradycardia		
	3405	2/25/00	4/28/00	T Waves: Flat		
	3415	11/18/99	1/21/00	Sinus Tachycardia		
3460	1/27/00	4/3/00	QTcB dispersion increased			
3490	2/15/00	4/20/00	Sinus Bradycardia			

* Clinically significant

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Karen Brugge
10/22/01 03:05:17 PM
MEDICAL OFFICER

Thomas Laughren
12/27/01 07:09:14 PM
MEDICAL OFFICER
I agree that this NDA is approvable; see memo
to file for more detailed comments.--TPL

**APPEARS THIS WAY
ON ORIGINAL**

ADDENDUM 1: REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 21-323

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 encapsulated tablets (also 20 and 40 mg citalopram encapsulated tablets and placebo were employed)

Indication: Major Depressive Disorder

Date of Original Submission: March 23, 2001

Date of Amendment Submission: October 19, 2001

Materials Reviewed: Amendment N(BM) submission to NDA 21-323 dated 10/19/01: 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: 11/19/01

I. Purpose of this review: 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.

II. Background. The original submission, together with a 120-Safety Update report described efficacy and safety results of four completed 8-week multicenter trials (Studies SCT-MD-01, SCT-MD-02, 99001 and 99003) of outpatients with Major Depressive disorder (MDD) which employed a double blind, placebo controlled, parallel group, flexible or fixed dose design. Three (MD-01, 99001 and 99003) out of the four adequately controlled trials were positive for demonstrating efficacy of escitalopram (SCT) in treating outpatients with MDD. For unclear reasons Study MD-02 failed to show significant treatment group effects, but the study did not appear to be a negative study. The Executive Summary of the review of the original submission (completed review date of 10/19/01) is provided in the appendix of this Addendum 1 Review and summarizes the efficacy and safety results. From a Clinical perspective and pending confirmation of the efficacy results by Biometrics, it was recommended in the 10/19/01 review that this NDA be given an approvable status.

The present submission (dated 10/19/01), is an amendment N(BM) to NDA 21-323 and contains safety results from a recently completed study (Study SCT-MD-03) that was ongoing at the time of the 2/1/00 cut-off date for the 120-Day Safety Update submission. Study SCT-MD-03 (referred to as MD-03) is entitled "Placebo-Controlled Evaluation of the Safety and Efficacy

of Lu 26-054 in the Prevention of Depression Relapse.” The purpose of this amendment submission was to provide the safety results from this study to support escitalopram safety only. The sponsor plans to submit a second NDA 21-440 to support a efficacy claim based on the results of Study MD-03 (the sponsor references the Division’s Letter dated 12/19/00).

III. Materials Reviewed. This amendment submission was reviewed for the purpose of determining if new and unexpected safety results were revealed by Study MD-03 that would potentially impact on NDA 21-323. To accomplish this task, the following materials provided in the 10/19/01 amendment submission were reviewed:

- Cumulative List of Treatment Emergent Adverse Events (pages 141-150)
- Information on Serious Adverse Events and Adverse Dropouts as described in volume 2 (MD-03 Study Report volume) and in selected narratives (in volume 4) of the submission.

Other more detailed safety information (e.g. laboratory, ECG and other data) will be reviewed as part of the NDA 21-440 submission that the sponsor plans to submit.

IV. Safety Results of MD-03.

Summary of the 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, which were briefly described above. Upon completion of either of the lead-in studies, Ss underwent an 8-week open label treatment phase of SCT starting at a 10 mg daily dose increased to a daily dose of 20 mg in nonresponders (MADRS>12) at the end of weeks 4 and 6. At the end of the 8-week treatment period, Ss classified as responders (MADRS ≤ 12) proceeded to the 36-week double blind treatment phase of placebo or SCT (2:1 SCT:placebo random assignment 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) at any visit during double-blind treatment were discontinued from the study.

Serious Adverse Events and Deaths.

There were no deaths and 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. 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.

Adverse Dropouts.

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

- During the Open-Label Phase of the MD-03: 33 out of 504 SCT Ss (6.5%) were adverse dropouts (ADOs) and no placebo Ss were reported as ADOs
- During the Double-Blind Phase: 7 of 181 SCT Ss were ADOs (3.9%) compared to 6 out of 93 placebo Ss (6.5%).