CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-323

MEDICAL REVIEW(S)

Number of Pages Redacted

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Draft Labeling
(not releasable

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
Dates of Submission:	March 23, 2001
Materials Reviewed:	Original NDA 21-323 Four 8-Week Placebo Controlled, Multi-Center, Double-blind, Parallel group, Fixed or flexible dose (includes 10 and 20 mg doses of escitalopram), clinical Trials (SCT-MD-01 and-02, 99001 and 99003) on the Safety and Efficacy of Escitalopram in 1732 Randomized Adults with Major Depressive disorder.
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	10/19/01

EXECUTIVE SUMMARY

Purpose of this review: This review and summary are to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of NDA 21-323. The summary provides a brief overview of the Clinical review of NDA 21-323 (refer to the review for more complete and detailed clinical information and clinical recommendations).

Background and Overview of Clinical Studies. Escitalopram (SCT) is the S-enantiomer of citalopram, a selective serotonin reuptake inhibitor (SSRI). Citalopram is currently marketed under the brand name of Celexa™ for Major Depressive disorder (MDD), which is the indication to which the sponsor is seeking approval for SCT under the current NDA 21-323. The sponsor describes three positive, multicenter, placebo controlled, double-blind depression trials (SCT-MD-01, 99001 and 99003) in the submission and in labeling proposed in the 120 Day Update Report (dated 7/12/01). These studies employed a parallel group design that involved either flexible doses of 10-20 mg of SCT/day and 20-40 mg/day CT or fixed doses of 10 mg/day of SCT and in one study, an additional 20 mg/day SCT in each treatment group. A one-week single-blind placebo run-in phase was followed by an 8-week treatment phase in each study. A fourth flexible dose parallel group trial (10-20 mg/day SCT and 20-40 mg/day CT) of similar design is also described in the submission, but is not included in proposed labeling (Study MD-02).

Study Populations. A total of approximately 1300 randomized Ss were included in the three studies. The study populations were enriched in that subjects (Ss) underwent a placebo run-in phase, had to exceed cut-off scores on various standardized rating scales assessing MDD symptoms and were excluded if they were known to be resistance to treatment with SRRIs, as specified. The majority of Ss were female (approximately 67% of Ss) which is consistent with the known preponderance of women with MDD in the general population. Most Ss were Caucasian (approximately 91%) and non-elderly (mean age of approximately 40 years with approximately 94% under 65 years old). Treatment groups were generally similar on various demographic features and on efficacy measures in each of the studies. Exposure of subjects to SCT in the four studies (N=715) was approximately 51 days (58 patient years).

Primary Efficacy and Safety Results. Each of the three positive studies showed significantly greater improvement on the primary efficacy variable, the Montgomery Asberg Depression Rating Scale (MADRS) score (from baseline to treatment endpoint) in the SCT treatment group compared to placebo, at daily doses of 10 mg or 20 mg of SCT. Study MD-02 failed to show significant treatment group effects on the primary efficacy variable but SCT and CT groups showed small numerical trends in favor of efficacy, which was significant for the observed cases dataset. These findings suggest that MD-02 was a failed rather than a negative study. Significant group differences between the 10 mg/day and 20 mg/day SCT groups were not found on the primary efficacy measure in the fixed dose study MD-01. However, dose-dependent effects appeared to exist between these two groups on overall incidence of adverse events (AEs). At least trends for dose-dependent effects on some of the specific AE categories are described in the review.

The safety profile of SCT generally appears similar to that observed with CT. Vital sign and ECG data showed at least a trend for a decrease in mean heart rate and prolongation of the QT or QTc interval in the SCT group compared to placebo that also appeared to exist with CT. However, the magnitude of these trends was small, such that they do not appear to be clinically significant to the general population. In contrast to the general population, the cardiac results may be clinically relevant for patients at risk of bradycardia, conditions of conduction defect or

arrhythmia, including patients taking medications that decrease heart rate or prolong the QT interval. Other ECG changes, noted in the review, appear to be consistent with this conclusion. Other potential safety issues pertaining to SSRIs, as a class, are also discussed in the review. One issue is a possible association of abnormal bleeding or platelet function with SSRI treatment (as suggested by a recent BMJ 1999;319:1106-9 publication of a possible association with upper gastrointestinal bleeding). Another issue pertaining to SSRIs as a class, is the reported association of AEs with cessation of SSRI treatment (based on reports in the literature). These safety issues and others, along with some recommendations are discussed in the review.

Overall Conclusion. In conclusion, three (MD-01, 99001 and 99003) out of the four adequately controlled 8-week trials were positive for demonstrating efficacy of 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 clinical trials described by the sponsor 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. Refer to the Clinical Review, for a complete and more detailed review of the clinical aspects of SCT, as revealed by studies described in this NDA and for some recommendations from a clinical perspective.

I. Introduction and Background.

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.

A. Indication and Proposed Direction of Use

Escitalopram (SCT) 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), which is the indication to which the sponsor is seeking approval for SCT under the current NDA 21-323.

The proposed direction for use of SCT recommends a starting dose of 10 mg administered daily, in the morning or evening, and with or without food. It is also recommended that after one week on the 10 mg daily dose that patients failing to respond may benefit from an increase in the daily dose to 20 mg.

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

Celexa™ NDAs 20-822 and 21-046: A letter to the sponsor (dated 4/27/01), also sent to other sponsors of SSRI agents, requests further safety information and requests a study protocol within 2 months of receipt of this letter (refer to the letter for specifics) regarding "abnormal bleeding/abnormal platelet function" for this SSRI. A request for this information was also made for other SSRIs given the recent BMJ 1999;319:1106-9 publication of a possible association of upper gastrointestinal bleeding possibly being associated with SSRI use which may possibly be linked to concomitant use with non-steriodal anti-inflammatory agents. The concern expressed in the letter is regarding an adequate description in labeling that describes this finding, but before making such a modification furthermore information is needed (as described in the letter dated 4/27/01).

The sponsor submitted a protocol on July 13, 2001. Subsequently, a letter (dated 9/14/01) was sent to the sponsor, as well as to other sponsors of SSRIs. This letter describes a "prototype" protocol to be used as a minimum requirement for analyzing NDA clinical trial databases for hemorrhage-related adverse events (refer to the letter dated 9/14/01 for details).

D. Related Reviews

NDA 20-822s and 21-046 are related NDAs for Celexa™ (citalopram hydrobromide) tablet and oral solution formulations were approved for treatment of MDD. The date of approval for

Celexa™ for this indication was 7/17/98. SCT is the S-enantiomer of the racemate citalopram (CT).

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics, and/or other Consultant Reviews.
The submission provides chemistry information to be reviewed by the Chemistry Reviewer. Refer to the Chemistry Review for a detailed description and for recommendations and conclusions. According to Dr. Paul Roney, Animal Pharmacology and Toxicology Reviewer, SCT and CT have similar animal toxicity profiles except for cardiovascular findings observed in rats (per communication with Dr. Roney on 7/3/01, also refer to his Review of this submission for details). A 13-week study and a 60-day bridging study in rats revealed an association of SCT with progressive cardiomyopathy, myocardial hypertrophy, and papillary muscle ossification, that does not appear with CT.

At the time of this writing the Clinical Pharmacology, Biopharmaceutical Reviewer has no key issues (refer to their review for details and recommendations).

III. Human Pharmacokinetics and Pharmacodynamics
Refer to the Clinical Pharmacology, Biopharmaceutical Review of this NDA regarding the human pharmacokinetics (PK) and pharmacodynamics (PD) sections of the submission. PK and PD properties of SCT as described in clinical volumes of the submission are summarized below.

A. Human Pharmacokinetics
The clinical section of the submission describes PK and some PD results from a total of 8 normal volunteer studies and one clinical trial (conducted by H. Lundbeck A/S and Forest Laboratories, Inc.). The sponsor also references several published articles. The PK results are summarized below.

1. Metabolism
The sponsor reports that the biotransformation of SCT is similar to that of CT based on results of *in vitro and in vivo* studies, in which SCT is metabolized by CYP2C19, CYP2D6 and CYP3A4. However, *in vivo* studies of subjects (Ss) phenotyped as poor mephenytoin or sparteine metabolizers (reported to reflect altered 2C19 and 2D6 metabolism, respectively) are reported to show evidence for involvement of CYP2C19 as the primary enzyme involved with SCT metabolism. 3A4 and 2C19 are indicated in the proposed labeling, as being the primary isozymes responsible for SCT metabolism based on results of *in vitro* human liver microsome studies.

Interconversion of SCT to the R-Enantiomer of CT. No interconversion from SCT to the R enantiomer of CT was observed in single or multiple dosing studies of SCT tablets in Phase I trials.

2. Absorption
Based on results of Phase I studies the following PK parameters are summarized in the following tables.

Approximate PK Results of Single Oral Dosing Phase I Studies

Drug Administered	Mean Tmax (range) of SCT	Mean Tmax (range) of S-DCT*	Cmax (ng/ml) of SCT	Cmax (ng/ml) of S-DCT
SCT	4 hours (1-8 hours)	13 hours (2-48 hours)	10 (post 10 mg SCT) 20 (post 20 mg SCT)	1.7 (post 10 mg SCT 3.5 (post 20 mg SCT
CT	Similar to above	Similar to above	10 (post 20 mg CT) 20 (post 40 mg CT)	1.7 (post 20 mg CT) 3.5 (post 40mg CT)

*S-DCT is S-desmethyl-CT (a major metabolite of SCT). S-didesmethyl-CT a secondary metabolite was only measurable in plasma after multiple dosing which showed Tmax of 1 to 48 hours.

Cmax values following 3 weeks of daily 10 and 30 mg SCT oral administration show dose proportionality. A multiple dose fixed dose range study of racemic CT showed linearity between dose of CT and SCT Cmax and SCT AUC. Dose proportionality was observed between the Cmax of S-DCT and the dose of SCT administration in a multiple dosing study. Results of multiple oral dosing studies of SCT are shown in the following tables.

Approximate PK Results of Multiple Oral Dosing Phase I Studies

Drug Administered	Cmax (ng/ml) of SCT	Cmax (ng/ml) of S-DCT*	Cmax (ng/ml) of S-DDCT**
SCT (daily dose)	21 (post 3 weeks of 10 mg SCT) 64 (post 3 weeks of 30 mg SCT)	7.4 (post 10 mg SCT) 19.4 (post 30 mg SCT)	1 (post 10 mg SCT) 1 (post 30 mg SCT)

* S-DCT is S-desmethyl-CT, a major metabolite of SCT.
** S-DDCT is S-didesmethyl-CT, a secondary metabolite of SCT.

AUCs (ng*hr/ml of SCT and S-DCT in Phase I Multiple Oral Dosing Studies of Daily SCT Treatment		
	Daily Dosing Regimen	
	10 mg/day SCT	30 mg/day SCT
AUC of SCT	360	1100
AUC of S-DCT*	152	396

* S-DCT is S-desmethyl-CT, a major metabolite of SCT.

Steady state levels of SCT in multiple dosing Phase I studies of daily oral SCT were achieved within 7 to 10 days. Steady state plasma levels of SCT after daily multiple dosing of 10 mg or 20 mg of SCT in depressed patients were 17 ng/ml and 31 ng/ml respectively, which according to the sponsor shows a dose proportionality of SCT. Steady state levels of SCT ranged from 11 to 92 ng/ml in a study of depressed patients who received 10 mg/day of CT for 3 days followed by 20 mg/day of CT for 2 weeks. Phase I multiple dosing studies of SCT and CT treatment in healthy Ss and of CT treatment in one study of depressed patients show that S-DCT and S-DDCT plasma levels are generally one third to one twentieth, respectively, of SCT levels. This conclusion is based on AUC and Cmax values that were observed in these studies.

Fasted versus Fed Conditions of SCT Administration. Administration of 20 mg oral SCT in fasted or fed states (following a high fat meal for the fed state) did not affect the rate and extent of absorption of SCT or Tmax, which was 4.5 hours in each condition. Based on Cmax and AUC results, the relative bioavailability of SCT or S-DCT in the fed to fasted conditions was approximately 108% or 93%, respectively.

3. Distribution

The volume distribution of racemic CT in healthy volunteers is 13-20 L/kg. 82% of racemic CT and 74% of racemic DCT is reported to be protein bound. The sponsor indicates that similar values are expected for the enantiomers, SCT and S-DCT, respectively.

4. Elimination

SCT has a biphasic elimination profile and a terminal half-life of approximately 27 to 32 hours. Based on results of Phase I studies, approximately half of SCT is eliminated daily. The table below shows the results of Phase I studies regarding the T1/2 of SCT. In comparison to that shown, the T1/2 of CT is 34.8 hours. These results are generally from studies of healthy non-elderly Ss.

Approximate T1/2 of SCT in Single and Multiple Dosing Phase I Studies	
Treatment Regimen	**T1/2**
Single dose of 20 mg SCT:	21-25 hours
10 mg/day SCT x 3 weeks:	27 hours
30 mg/day SCT x 18 days	32 hours

The T1/2 of S-DCT ranged from 53-60 hours after a single dose and from 45-54 hours after multiple doses of SCT in healthy non-elderly Ss. Accumulation of SCT and its metabolites is reported to occur by a factor of approximately 2.2 to 2.5 with daily administration of SCT.

8%, 10% and 2% of a single dose of 20 mg SCT is excreted in the urine as SCT, S-DCT and S-DDCT, respectively. Oral clearance of SCT in young Ss after a single 20 mg dose was 34-41 l/hr with similar clearance rates observed with multiple dosing of SCT. Renal clearance after a single dose of 20 mg SCT was 2.6 l/h for SCT and 6.9 l/hr for S-DCT. Similar results were obtained after a single dose of 40 mg racemic CT. Higher values for renal clearance of SCT and S-DCT were observed after 21 days of daily dosing of 40 mg CT (4.90 l/hr for SCT and 8.0 l/hr for S-DCT).

5. Drug-Drug Interaction Results.

In vitro studies of the human hepatic P-450 cytochrome enzyme system revealed negligible inhibitory effects of SCT and S-DCT on the following isoenzymes: CYP1A2, 2C9, 2C19, 2D6, 3A4 and 2E1 such that clinically significant drug-drug interactions due to inhibition of the P450 system is not likely.

However, drug-drug interactions may be anticipated by drugs that are substrates of at least the 3A4 and 2C19 isoenzymes or that may induce or inhibit these isoenzymes, which are the primary isoenzymes responsible for the N-demethylation of SCT. The submission describes results of various drug-CT interaction studies.

Drug-drug interaction PK *in vivo* clinical studies (SCT-PK-03, -PK-01 and –PK-02) examined potential interaction effects between multiple dosing with SCT and single dose of metoprolol, ritonavir or desipramine on PK and safety parameters. These studies did not reveal any remarkable safety findings, but did show some interaction effects on PK parameters when SCT was coadministered with metoprolol or desipramine. Refer to the Clinical Pharmacology and Bipharmaceutical Review (pending at the time of this writing) of this NDA for details.

6. Special Populations.

The Elderly Population

While T max is reported to show no age-group effect when comparing old (mean age of 69.7 years, N=18) to young (mean of 30.1 years, N=18) Ss following 3 weeks of treatment with 10 mg/day of SCT, Cmax and AUC values are found to be greater in the elderly group by approximately 34 % and 50%, respectively. The $T_{1/2}$ of SCT in elderly Ss is reported to be 50% longer than that observed in young Ss ($T_{1/2}$ of 41 compared to 27 hours). These age-groups did not show differences in apparent volume of distribution of SCT. The oral clearance is 35% lower in elderly (21 l/hr) compared to young Ss. PK results of S-DCT also showed Cmax and AUC values of approximately 50% greater in the elderly group compared to the young group following 3 weeks of 10 mg/day of SCT. Similar age-group differences on various PK results following CT treatment are also reported. Given these results the sponsor recommends the dose of 10 mg in the elderly, which is half of that recommended for non-elderly adults.

Male and Female Populations. In the same study described above, contrasting elderly to non-elderly Ss on various PK parameters after 3 weeks of daily 10 mg of SCT treatment, gender effects on SCT and S-DCT PK parameters were also examined. No differences were reported (with or without weight normalization of the PK parameters) between the female Ss (N=18, 9 elderly and 9 young Ss) and males Ss (N=18, 9 elderly and 9 young Ss). With weight normalization of SCT and S-DCT PK parameters, no gender effects were observed in a study that examined the effects of ritonavir on PK of SCT (10 male Ss and 8 female Ss).

Hepatic and Renal Impaired Populations. Based on "the common PK characteristics observed for SCT when administered alone or as part of racemic citalopram", the sponsor expects hepatic or renal impairment to have similar effects on PK parameters of SCT following SCT, to those observed with CT administration. Consequently, impaired hepatic function, but not impaired renal function is expected to decrease systemic clearance and increase T½ of SCT. Impaired renal function is not expected to show a significant effect on PK parameters of SCT.

B. Pharmacodynamics

SCT is an (S)-(+)-enantiomer of CT (the racemate). CT is an SSRI, as demonstrated by *in vitro* and *in vivo* preclinical studies and is currently being marketed for treatment of MDD, as Celexa™. CT is reported to be selective for reuptake inhibition for serotonin, while showing little to "virtually" no effect on reuptake inhibition of catecholamines. SCT was found to be an active enantiomer of CT and reported to be primarily responsible for various pharmacological properties of CT, such as its SSRI effects, as well as showing little to no affinity for adrenergic, dopaminergic, serotonergic and muscurinic receptors based on results of *in vitro* studies of rat and human brain preparations. SCT or CT, but not R-CT are reported to inhibit neuronal activity in cell bodies of the dorsal raphe nucleus, suggesting an indirect effect on somatodendritic 5HT1A receptors.

The antidepressant effects of CT and SCT were initially anticipated because of positive results in studies employing rodent behavioral models of depression, the forced swim test and the agonistic behavior model. Potential anxiolytic effects of SCT were demonstrated using a foot shock-induced ultrasonic vocalization model. The relative potency of SCT to CT in these various animal models is reported to be approximately two-fold greater with SCT, whereas the R-CT enantiomer is reported to be inactive in most animal models of depression or anxiety.

Other Pharmacodynamic Properties of SCT.

Arrhythmogenic properties. SCT is described as lacking arrhythmogenic properties based on results of studies in which SCT fails to bind to cardiac ion channels, and does to have an effect on repolarization or depolarization currents, and on the QT interval (does not prolong QT).

Effects on Psychomotor Function.

According to the sponsor a study (SCT-PK-01) on the interaction effects of desipramine and fluoxetine or SCT treatment on PK supports their conclusion that SCT does not appear to show a "clinically relevant influence on psychomotor function in healthy subjects." However, this study failed to employ a placebo group and appeared to be confounded by a differential effect of the PK of desipramine (an agent associated with sedative effects) between the fluoxetine and SCT treatment groups. Consequently, the results of this study are difficult to interpret. Finally, a clear rationale for the use of a visual analog scale for measuring psychomotor function, such as a the validity, reliability and other psychometric properties of this scale cannot be found in volume 104 of the submission where the study is described. Another study (SCT-PK-03) is also reported to show similar results to those of Study SCT-PK-01. However, this study poses similar problems to those of Study SCT-PK-01 in the interpretation of the results.

A third study (94303) employed the Critical Flicker Fusion test (CFF) among other measures (Choice Reaction Time, Short Term Memory, Compensatory Tracking Task, Milford Epworth Sleepiness Scale and others) as the dependent variables. CT treatment was compared to placebo and a sedative antidepressant medication (dothiepin) administered as single or 7-daily multiple oral doses of CT using a 5-way crossover design. This study showed that CFF threshold was "raised" with CT treatment, while the sedative antidepressant medication was associated with "significant impairment" on most measures. CT "at all doses" is reported to show no impairment of psychomotor function (no data shown and no description of results on measures other than results of the CFF were provided in the "Final Report" of volume 104). However, drowsiness was one of the main adverse events reported in CT, as well as in dothiepin treated Ss, yet each treatment group was reported to be similar to placebo on the rates of adverse events.

The submission also described results of a study using subjective rating scale of sleep quality to assess treatment effects of SCT or fluoxetine. Since this study is an active drug comparative study, without use of a placebo control group, the results of this study are difficult to interpret and are therefore, not described in this review.

IV. Description of Clinical Data and Sources

A. Overall Data: Materials from NDA/IND

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

Documents Utilized in Clinical Review	
DATE	DESCRIPTION
March 23, 2001	• NDA 21-323, Hard copy clinical volumes 1, 102-153, a total of 53 hard copy volumes. Case Report Tabulations as SAS Transport files and Case Report Forms are on Compact Disk . • 120-Day Safety Update Report dated 7/12/01 • N(BM) submissions: dated 8/13/01 (response to questions faxed to the sponsor on 7/26/01, dated 9/27/01&10/9/01 (response to questions faxed or sent to the sponsor on 9/18/01and 9/27/01) • N(SU) submission dated 5/24/01 (5/29/01)

B. Tables Listing the Clinical Trials

Table IV.B.1. Clinical Studies Reviewed from this Submission

Protocol No	Study Design	Treatment Groups	N (Completers) per Treatment group (% of ITT Efficacy Pop.*)	N (ITT Efficacy Pop.) * per Treatment group	N (ITT Safety Pop.) ** per Treatment group
SCT-MD-01 Fixed Dose US 8-Week Trial	Multicenter, Double blind, Randomized, Fixed dose, Parallel group 35 U.S. sites	10 mg/day SCT 20 mg/day oral SCT groups 40 mg/day oral CT group Placebo group	95 (80%) 94 (75%) 93 (74%) 91 (75%) **Total: 373**	118 123 125 119 **Total: 485**	119 125 125 122 **Total: 491**
SCT-MD-02 Flexible Dose US 8 Week Trial	Multicenter, Double blind, Randomized, Flexible dose, Parallel group 22 U.S. sites	10-20 mg/day oral SCT group 20-40 mg/day oral CT group Placebo group	96 (77%) 99 (81%) 105 (83%) **Total: 300**	124 119 125 **Total: 368**	125 123 127 **Total: 375**
99001 Fixed Dose European 8-Week Trial	Multicenter, Double blind, Randomized, Fixed dose, Parallel group 40 sites in 5 non-US countries	10 mg/day SCT Placebo group	160 (85%) 160 (85 %) **Total: 320**	189 188 **Total: 377**	189 191 **Total: 380**
99003 Flexible Dose European 8 Week Trial	Multicenter, Double blind, Randomized, Flexible dose, Parallel group 69 sites in 8 non-US countries	10-20 mg/day oral SCT group 20-40 mg/day oral CT group Placebo group	146 (94%) 152 (96%) 139 (90%) **Total: 437**	155 159 154 **Total: 468**	155 160 154 **Total: 469**

*ITT Efficacy population: randomized subjects having at least one dose of double blind study drug and at least one post-baseline Montgomery Asberg Depression Rating Scale assessment.

**ITT Safety Population: randomized subjects having at least one dose of double blind study drug.

C. Post-Marketing Experience

According to the sponsor, SCT is not being marketed. H. Lundbeck A/S in Sweden submitted an application for marketing of SCT, in which the outcome of this submission is still pending. No other information regarding this application could be found in the submission.

D. Literature Review

For the purposes of this review, the sponsor appears to have conducted an adequate literature search for SCT, given the number of databases, the start dates and the search terms employed as shown below.

The sponsor conducted the literature search on January 11, 2001 using the terms and databases 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
- enantiomer and citalopram
- escitalopram or LU()26()054

A total of 39 published articles were found with safety information (as described by the sponsor) in Section VII of this review (the Integrated Review of Safety section). A listing of these 39 publications was provided upon request by the sponsor.

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. The search term used by the sponsor was citalopram and 5 electronic databases were searched (including MEDLINE and others). The results of this search are described in a later section of this review (see Section VII).

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.

The sponsor makes their claim for the efficacy of SCT in the treatment of MDD in which they describe three positive, multicenter, placebo controlled 8 week depression trials (SCT-MD-01, 99001 and 99003) in the proposed labeling of the 120 Day Update Report (dated 7/12/01). These studies involved either flexible dose parallel group or fixed dose parallel group designs and included a total of approximately 1300 randomized Ss (see previous Section IV for table of all clinical trials). A fourth trial is also described (MD-02) in the submission, but not in proposed labeling. Section VII of this review (Integrated Safety) provides more information on the demographic features and the extent of drug exposure in the study population. Given these trials, along with previous clinical trials of citalopram supporting the approval of Celexa®, the data described in the submission is adequate to review.

C. Data Quality and Completeness

This section describes various comparisons made between listings, tables, Case Report Forms (CRFs), and/or narratives. The results of these comparisons are described in more detail below, but generally appear to show adequate accuracy, consistency and content of information. On the basis of these observations, the quality and completeness of the data described in the submission appears to be adequate.

Each item below describes various comparisons made of listings, CRFs and narratives in the 120-Safety Update Report.

- The listing of CRFs matched the listing of narratives (by S and study number for Ss with serious adverse events) and the serious adverse event (SAE) listing on Panel 5 (for all 14 completed studies, as specified under VII of this review).
- Preferred Terms of approximately 10 SCT Ss with SAEs in the SAE line listing (Table 4.2 in volume 3) generally matched Preferred Terms provided in corresponding narratives.
- Narratives of approximately 6 SCT Ss with SAEs were assessed for consistency with selection of Preferred Term used in the narrative form and line listing, which appeared to be generally consistent with events described within the narrative description of Ss. However, narratives tended to be brief (refer to Section VII regarding specific SAEs). Therefore, the possibility of the event being drug-related could not be ruled out in some cases, without having additional information or given the limited information that was provided (see S #3263

described in section VII E of this review as an example). Nevertheless, these narratives provided medical history, concomitant medication use, and dates of events relative to drug exposure, among other pertinent and important clinical information (also see next item). There also did not appear to be any inconsistencies within narratives reviewed (see Section VII E describing information from narratives on specific Ss).

- The following narratives and CRFs were compared for consistency and accuracy: S1055 in Study SCT-MD-01, S2138 in Study SCT-MD-02, S 0028 in Study 99001. The contents of these narratives were also compared to that of the CRF to assess completeness. These assessments showed adequate consistency, accuracy and completeness.

D. Evaluation of Financial Disclosure

Six investigators out of a total of 166 investigative sites (with multiple investigators at each site) of the four 8-week clinical depression trials (MD-01 and MD–02, 99001 and 99003) were listed as having financial arrangements that required disclosure, whereas the majority of investigators were listed as having no disclosable financial arrangement. The sponsor was unable to reach a small subset of investigators after a number of attempts, such that the financial disclosure from these investigators was not obtained. It is noted that any potential bias in the clinical trials was minimized for reasons such as the following: studies were double-blind, multi-center and conducted by multiple investigators. Sites were independently monitored, and randomly audited by Forest, regarding the two US trials (MD-01 and MD-02). Studies were also conducted with IRB approval and supervision, according to regulations. H.Lundbeck sponsored the foreign studies 99001 and 99003. According to the submission, none of the investigators of the trials sponsored by H. Lundbeck have disclosable financial arrangements with Lundbeck.

A few discrepancies between various investigator listings provided in various sections or locations of the submission were noted and inquired about to the sponsor (in a fax with questions to the sponsor dated 9/18/01). The sponsor provided explanations regarding these discrepancies. The sponsor explained that a single investigator may have multiple sites but listed only once in one listing or a given investigator may not have enrolled Ss and was not listed in a particular listing (refer to specifics in their response submitted on 9/27/01). Upon request, the sponsor confirmed in a statement in their 9/27/01 response, that the investigator listings in the financial disclosure section of the NDA submission are complete, with one exception. They accidentally excluded one investigator (accidentally used another name) who they certified "had no disclosable financial arrangements." Refer to the 9/27/01 submission for specifics.

VI. Integrated Review of Efficacy

A. Review of Studies for Which Efficacy Claims Are Made

The efficacy claim that SCT is indicated for treatment of "depression" is based, according to the sponsor's proposed labeling submitted in the 120-Day Update report, on results of three 8-week trials in adult outpatients with MDD (by DSM-IV criteria). One study was an 8-week, parallel group, fixed dose, multicenter, double blind, randomized, placebo controlled US study (Study SCT-MD-01) examining 10 mg and 20 mg daily fixed doses in patients with MDD. This study also had a 40 mg/day CT group, as an active comparator. The other two studies were primarily European Studies 99001 and 99003. Study 99001, was a fixed dose parallel group study with a design similar to that of Study SCT-MD-01 (MD-01) but employed only two groups as follows: a 10 mg SCT group and a placebo group. Study 99003 employed a flexible dose design and was similar to a fourth study, Study SCT-MD-02 (MD-02). Study MD-02 is a US flexible dose study

that is described in the submission but is not in the proposed labeling of the 120-Day Update report. Both of these multi-center flexible dose trials (studies MD-02 and 99003) used a parallel group, randomized, double blind, placebo controlled design with the following treatment groups: placebo, 10-20 mg/day SCT and 20-40 mg CT. These studies are described in more detail below.

B. Study SCT-MD-01, Fixed Dose Comparison of the Safety and Efficacy of Lu 26-054 (SCT), Citalopram, and Placebo in the Treatment of Major Depressive Disorder

1. Fixed Dose Study SCT-MD-01: Investigators and Sites

See Table VI.B.1 in the appendix (as provided by the sponsor, also see Tables VI.B.2-4 of site listings for Studies MD-02, 99001 and 99003) for a listing of 35 investigative centers in the United States.

2. Fixed Dose Study SCT-MD-01: Objectives

The objective of study SCT-MD-01 (MD-01) was to compare 10 mg/day (low dose) and 20 mg/day (high dose) SCT treatment to placebo on safety and efficacy in patients with MDD.

3. Fixed Dose Study SCT-MD-01: Study Population

The study population consisted of 501 randomized generally healthy 18 to 65 year old male and female outpatients with DSM-IV MDD. 485 of the 501 randomized Ss were included in the ITT Efficacy population (119 placebo Ss, 118 low dose SCT Ss, 123 high dose SCT Ss and 125 CT Ss). See Tables IV.B.1 in section IV B, above and subsection 7 below, for a further breakdown and disposition of Ss).

Some of the key criteria for inclusion in the study were the following (refer to study report in the submission for a complete list) in which Ss were required to have:

- MDD (DSM-IV) for at least 4 weeks at the baseline visit
- The following rating scores at baseline and screening:
  - Montgomery Asberg Depression Rating Scale (MADRS) score ≥ 22
  - Hamilton Depression Rating Scale (HAMD) score on Item 1 of ≥ 2

Some of the key criteria leading to exclusion of Ss were the following (refer to the study report of the submission for a complete list):

- Met DSM-IV criteria for any of the following disorders:
  - Bipolar disorder
  - Schizophrenia or any Psychotic disorder
  - Obsessive Compulsive disorder
  - Mental Retardation, Pervasive Developmental disorder, or Cognitive disorder
  - Substance Abuse/Dependence within 6 months of study entry
- Has a principal diagnosis of any personality disorder or Axis I disorder (DSM-IV) except MDD
- Has any history of a Psychotic disorder (DSM-IV)
- Has psychotic features
- Restrictions on concomitant medications (see section below on concomitant medications)
- Failed to respond to a "adequate trials" of an SSRI or of two or more other antidepressants
- Received ECT therapy within 6 months prior to study entry

- Has initiated or terminated psychotherapy (including behavioral therapy) within 3 months of the study or will be initiating or terminating psychotherapy during the study
- Positive urine drug screen or was positive for alcohol at screening

Permitted and Prohibited Concomitant Medications
The following were prohibited, as specified:

- Depot neuroleptic within 6 months prior to study entry
- Psychotropic medications except zolpidem for sleep including drugs with a psychotropic component
- Any neuroleptic, antidepressant or anxiolytic agent within 2 weeks (5 weeks for fluoxetine) prior to start of double blind treatment phase of the study
- Refer to the submission for a complete listing of prohibited, as well as permitted concomitant medications.

4. Fixed Dose Study SCT-MD-01: Design

This was a randomized, double blind, placebo controlled, multi-center, fixed dose, parallel group study involving a one-week single blind placebo lead-in phase followed by an 8 week treatment phase upon which Ss were randomized (1:1:1:1) to one of the following treatment groups (oral administration):

- 10 mg/day referred to as low dose (LD) SCT group
- 20 mg/day referred to as high dose (HD) SCT group
- 40 mg/day CT group
- Placebo

Study medication was in the form of encapsulated tablets (capsules) which were identical in appearance for all doses and study medications. Ss who still met eligibility criteria following a one-week single blind placebo run-in phase were randomized to one of the four double blind treatment groups. Ss assigned to the LD SCT or placebo groups were started and continued on 10 mg/day SCT or placebo (one capsule taken daily in the evening), respectively, for 8 weeks. Ss randomized to the HD SCT and CT groups were titrated to their assigned dose starting with 10 mg/day SCT or 20 mg/day CT (one capsule a day), respectively during the first week of the double blind treatment phase. At the end of Week 1 these Ss were increased to their assigned doses of 20 mg/day SCT and 40 mg/day CT, respectively (one capsule daily), which were continued for the remainder of the 8-week treatment phase. No dose adjustment was permitted throughout the study. Refer to Table VI.B.5 in the appendix (as provided by the sponsor) for a flow chart of visits and time-points for obtaining safety and efficacy measures. A listing of these measures are provided in the next section (section 5).

5. Fixed Dose Study SCT-MD-01: Assessments Employed

Refer to Table VI.B.5 in the appendix for the study flow chart regarding efficacy, safety and screening assessments. As shown in Table VI.B.5, various assessments were conducted at screening, baseline (following a one-week single blind placebo run-in phase), and on weeks 1, 2, 4, 6 and 8 during the 8 week treatment phase (or upon early termination).

Primary Efficacy Assessments.

- MADRS

Secondary Efficacy Measures:

- HAMD 24-item
- HAMD Depressed mood item score
- Clinical Global Impressions Scale for Improvement (CGI-I) and for Severity (CGI-S)
- Hamilton Anxiety Rating Scale (HAMA)
- HAMD 17-item
- Others (refer to submission)

Safety assessments:

- Recording of adverse events
- Vital signs (including body weight)
- Physical examination
- 12-lead ECG
- Laboratory parameters:
  - Hematology, blood chemistry screen (includes measures of renal function, electrolytes, glucose, liver function tests, among others)
  - Urinalysis
  - Serum beta-HCG in women of childbearing potential at screening only
  - Thyroid Function Test (TSH) at screening only
  - Urine drug screen at screening only

In addition to the safety assessments conducted at screening and baseline visits, as above, a psychiatric evaluation was conducted at screening, that included a Mini International Neuropsychiatric Interview (MINI).

Monitoring of Drug and Metabolite Plasma Levels. Blood samples were collected between 8 and 14 hours after the previous dose, if possible at the end of the week 8 visit or upon early termination to determine plasma concentrations of escitalopram and its metabolites.

6. Fixed Dose Study SCT-MD-01: Analysis Plan

Dataset Analyzed. The ITT Efficacy dataset was analyzed (data from Ss who had at least one dose of double blind study drug and at least one post-baseline MADRS assessment). The last observation carried forward (LCOF) dataset was used for the primary analysis, but the observed cases (OC) dataset was also analyzed.

The primary efficacy variable was as follows:

- The mean change from baseline to treatment endpoint (week 8) on the MADRS.

The secondary efficacy variables are listed below.

a. Mean change from baseline to treatment endpoint (week 8) on the following scores:
   - HAMD (24 item)
   - CGI-S
   - CGI-I
   - HAMA
   - HAMD 17-item

b. Responders on the MADRS defined as a ≥50% decrease from baseline to week 8 in the MADRS score.

Statistical Tests Employed. For continuous variables, treatment and center main effects and interaction effects analysis of covariance (ANCOVA) model was employed covarying for the baseline measure. Since the CGI-I is a score on improvement relative to baseline (a baseline measure is not applicable), this secondary efficacy variable was analyzed using a treatment by site analysis of variance (ANOVA) model. For each analysis, the treatment by site interaction term was dropped from the model if it was not significant at a level of p equal or greater than 0.10. If a significant treatment main effect ($p<0.05$) was found, then pair-wise treatment group comparisons were conducted between each SCT group and the placebo group. Results are provided as values obtained from a SAS Type III analysis, calculating the difference between two treatment groups using the least square means. The Cohchran-Mantel-Haenszel (CMH) chi-squared test was used for the responder analysis (responders on the MADRS with centers as strata).

7. Fixed Dose Study SCT-MD-01: Patient Disposition

The number of screened Ss could not be found in the submission. A total of 506 Ss were randomized to the double-blind treatment phase of the study Ss as follows:

- 124 Ss in LD SCT group
- 128 Ss in HD SCT group
- 127 Ss in CT group
- 127 Ss in the placebo group

Among the randomized Ss a total of 21 Ss (placebo: 8Ss, LD SCT group: 6 Ss, HD SCT group: 5 Ss, CT group: 2 Ss) did not meet criteria for being included in the ITT Efficacy population (Ss who had at least one dose of study drug and at least one post-baseline MADRS assessment).

Tables VI.B.6-7 in the appendix (as provided in the submission) summarize the enumeration and disposition of the ITT Safety population (Ss who had at least one dose of double blind study drug). In summary the treatment groups were similar in various reasons for discontinuation except for withdraw due to lack of efficacy or due to an adverse event (AE) in which a significant treatment group effect was observed ($p=0.02$ and $p=0.03$, respectively). The incidence of dropouts due to AEs appeared to increase from placebo to increasing dose groups of SCT, while the incidence in the CT group (40 mg/day) appeared similar to that of the HD SCT (20 mg/day) group. The incidence of dropouts due to lack of efficacy also appeared to show a dose dependent effect that was inversely related to SCT dose, while the CT group and HD SCT groups appeared to show similar incidence rates.

8. Fixed Dose Study SCT-MD-01: Baseline Demographics/Medical/Psychiatric Comorbidity and Baseline Efficacy Measures

Baseline Demographics. Treatment groups (ITT Safety Population) 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 (59 to 71%/group) with slightly more women in each SCT group (67 or 70%/group) than in the placebo and CT groups (59% and 62%, respectively), but these small differences were not significant. The majority of

Ss were Caucasian (81 to 87%/group). The mean age of the Ss was approximately 40 ±12 years in which only 6% (30 Ss) were 60 years old or older. The mean weight of the study cohort was approximately 176 pounds. The table VI.B.8 in the appendix (as provided by the sponsor) summarizes the demographic results of each treatment group.

Medical and Psychiatric Comorbidity. Treatment groups (ITT Safety population) were reported to be similar in their history of psychiatric, suicide, medical and psychotropic drug treatment. Incidence tables for various medical and psychiatric disorders were provided by the sponsor upon request. The sponsor provided incidence rates by treatment groups for abnormal medical history categorized by major body systems. Treatment groups were generally similar in these incidence rates. Upon request the sponsor provided incidence rates of ongoing psychiatric disorders in which treatment groups were generally similar in distribution of Ss with various conditions. The approximate incidence rates (% of Ss/treatment group) of the following concomitant disorders are noted:

- Anxiety disorder (a general category encompassing DSMIV anxiety disorders) in 10% of Ss. Incidence rates of some of the key subcategories under the main category of Anxiety disorder were as follows:
    - Generalized Anxiety disorder in 5% of Ss
    - Panic Disorder in 2%
    - Social Phobia in 2%
- Dysthymic disorder in 6%
- Substance Related disorders in 3%
- Other psychiatric disorders in < 1%

Treatment groups (Safety Population) were similar on various demographic features regarding their MDD, such as the duration of the disorder (approximately 11 years), the age of onset (approximately 29 years), and the duration of the episode (16 to 25months/group). The duration of the current episode was at least 1 to 6 months in 44% of Ss and over 6 months to 2 years in 35% of Ss. 49% of Ss had not received antidepressant treatment prior to study entry. Among the remainder of Ss (51%) who did have previous antidepressant treatment a subgroup of them had no change or a "poor" response to a previous antidepressant treatment (30%) or were intolerant of treatment (13%).

The table VI.B.9 in the appendix shows the mean baseline scores for various efficacy measures (the MADRS, HAMD and the CGI-S) for the ITT Efficacy Population (Ss with at least one dose of assigned study drug and at least one post-baseline efficacy assessment on the MADRS). Significant but small group differences on the mean baseline MADRS, HAMD and HAMA scores, as described in the submission. Nevertheless, the magnitude of these differences were not considered clinically relevant.

Concomitant Medications.

Treatment groups were similar in the percentage of subjects taking concomitant medications during the double-blind treatment phase of the study (approximately 82 to 84%/group). Treatment groups were generally similar in the distribution of Ss across various medication categories. Common (≥10% in any of the groups) concomitant medications were the following (approximate percentage of users/group):

- Analgesics: 39 to 46%/group

- Antacids, drugs for treatment for peptic ulcer disease and flatulence: 11-16%/group
- Systemic Anti-bacterials: 7 to 17%
- Systemic Anti-histamines: 9 to 10%/group
- Anti-inflammatory and anti-rheumatic products: 26 to 43%/group
- Endocrine therapy (does not include thyroid therapy): 6 to 11%/group
- Nasal preparations: 6 to 11%
- Sex hormones and modulators of the genital system: 8 to 14%
- Vitamins: 22 to 30%

9. Fixed Dose Study SCT-MD-01: Efficacy Results

Results on the Primary Efficacy Variable: the mean change from baseline to treatment endpoint (week 8) on the MADRS.

See the Table VI.B.10 in the appendix (as provided in the submission) which shows the results on the primary efficacy variable. As previously described, significant treatment group differences in the mean MADRS score were observed (p=0.036 for a treatment group effect) at baseline. However, the magnitude of these group differences was small (mean differences of 1 to 1.5 score units with group means ranging from 28.0 ±5.o to 29.5±4.6). When conducting a treatment and study site effects and interaction effects ANCOVA (covarying for the baseline MADRS score) a significant treatment group effect (p>0.0001) was revealed. Pair-wise comparisons between treatment groups showed that each SCT group had a significantly greater improvement (p<0.001 for each comparison) than that of placebo. The CT group also showed a significantly greater improvement than placebo (p<0.05). No comparisons were made between the CT group and each SCT group.

Table VI.B.11 in the appendix (as provided by the sponsor) shows results of the primary efficacy variable by study visit for each treatment group. Some preliminary results are described in the submission and shown in this table that are based on preliminary statistical analyses without correction for multiple tests/comparisons. The table shows that an overall significant treatment group effect was revealed by ANCOVA (conducted at each time-point) starting at visit week 2 (p<0.05) which continued throughout the remaining visits (weeks 4, 6, and 8 with p≤0.02, 0.001 and 0.0001, respectively). Pair-wise comparisons of each SCT or CT group to placebo showed a significantly greater improvement than placebo for each SCT group (LD and HD groups) starting at week 2 (P<0.03 for each comparison) and continuing through weeks 4 (p<0.02 for each comparison), 6 (p<0.001 for each comparison) and 8 (p<0.001 for each comparison). The CT group failed to show a significantly greater improvement compared to placebo until week 8 (p<0.05) with a trend for greater improvement on week 6 (p=0.067).

Pair-wise comparisons between active treatment groups LD to HD SCT groups or between CT to each SCT group were either not described or not found in the submission. Inspection of the results in Table VI.B.11 shows that the LD and HD SCT groups show a similar magnitude of improvement at most time-points (weeks 1, 2, 4, 6 and 8) during treatment. The magnitude of improvement in each SCT group appears to be similar to or less than that of the CT group on most time-points. However, these observations are considered preliminary. See a section below on "Results on Monitoring Plasma Concentrations" regarding results on correlating efficacy with plasma concentrations of SCT.

A few additional preliminary observations on the time of a peak response are noted in this paragraph. These observations are based solely on inspection of results in Table VI.B.11 (in the appendix). It appears that a placebo response for improvement on the primary efficacy

variable occurred and peaked at week 4 or 6. Improvement in the SCT and CT groups appears to peak on week 6, week 8 or possibly later (no observations past 8 weeks, given that the trial was for 8 weeks). These observations are based on an LOCF dataset and assume that all Ss completed the trial, whereas not all Ss were in fact completers but nevertheless, were in the majority (75 to 80% completers/group).

The above results were those of the LOCF dataset. When analyzing the OC dataset, similar results were revealed for both mean change from baseline to treatment endpoint and when examining treatment group effects at each time-point (at each visit).

Secondary Efficacy Variables.

The table below summarizes results of the change from baseline to treatment endpoint on various secondary efficacy measures for the LOCF dataset which are also summarized in this paragraph. The results are consistent with that reported for the primary efficacy variables for those secondary measures designed for assessing depressive symptoms (HAMD measures) or for assessing overall clinical improvement (CGI-I and CGI-S measures). However, measures designed to reflect anxiety symptoms (the HAMA score and HAMD anxiety subscale) failed to show significantly greater improvement from baseline to treatment endpoint in each pair-wise comparison between each SCT group and placebo, as shown below. However these anxiety variables showed trends for greater improvement in each SCT group compared to placebo.

Summary of Results of Treatment Group Effects on Secondary Efficacy Variables				
Efficacy Variable	**P for Overall Treatment Group Effect***	**The Least Square Mean Difference between Each SCT† group and Placebo on the Change from Baseline and Treatment Endpoint Scores****		**P Value for Each Pairwise Comparison*****
		10 mg SCT Group	**20 mg SCT Group**	
HAMD (24 items)	<0.02	-2.6	-3.0	<0.02
HAMD (17 items)	<0.05	-1.8	-2.0	<0.05
HAMD depressed mood item	<0.01	-0.4	-0.4	<0.02
HAMD Melancholia subscale	<0.001	-1.4	-1.6	<0.01
CGI-I	<0.001	-0.5	-0.6	<0.001
CGI-S	<0.0001	-0.5	-0.6	<0.001
HAMA	0.09	-0.08	-1.5	0.36 and 0.10, respectively
HAMD Anxiety subscale	<0.05	-0.2	-0.6	0.50 and 0.054, respectively

*Based on an ANCOVA (Treatment group, Center and Treatment group by Center Effects) covarying for baseline score (LOCF dataset).
** The least square mean difference from baseline to treatment endpoint (Week 8) scores except for CGI measures. CGI-I and CGI-S is least square mean at endpoint.
*** Based on a pair-wise comparison between each SCT group and placebo
† SCT = escitalopram

Results of the CT group compared to placebo on various efficacy measures were also described in the submission. In summary the CT group showed results similar to those of the SCT groups (shown in the above table) but the magnitude of the effect (the difference between CT and placebo) appeared to be more comparable to that observed for the 10 mg group. However, given the multiple comparisons employed and the small magnitude effect for all active treatment groups, these results are considered preliminary.

Results of an analysis of change in mean scores on various efficacy variables at each time-point (each visit) were generally consistent with results of the analysis of change from

baseline to treatment endpoint analyses, as above. At least trends for greater improvement in each SCT group was observed for measures of depression (HAMD measures) and overall improvement (CGI measures) were observed visit weeks 2 or 4.

The number (%) of responders (defined as a ≥50% decrease from baseline to week 8 in the MADRS score) for each group was as follows in which each SCT or CT group had at least a trend for a greater rate than that of the placebo group ($p<0.01$ not correcting for multiple comparisons on various secondary efficacy variables):

- **Placebo group** (N=118): n=33 (28%)
- **10 mg SCT group** (N=118): n=51 (50%)
- **20 mg SCT group** (N=123): n=63 (51%)
- **CT group** (N=125): n=57 (46%)

Gender Subgroup Analysis

Upon request, the sponsor conducted gender subgroup analysis on the primary efficacy variable (mean change from baseline to treatment endpoint on the MADRS score) of the LOCF dataset using the ANCOVA model for a treatment group and gender group main effects and a treatment by group interaction effect with the baseline MADRS score as a covariate. The results were provided in 8/13/01 (BM) submission under this NDA and are summarized in Table VI.B.12 in the appendix of this review (as provided by the sponsor). This analysis revealed no significant gender ($p=0.28$) or treatment group by gender interaction ($p=0.09$) effects. However, the sample size of males is only approximately 40 Ss in each treatment group compared to a sample size of approximately 80 female Ss per group. A numerical trend for a greater treatment group effect (on the mean change from baseline to treatment endpoint on the MADRS) in males compared to females did appear to exist as follows:

- 10 mg SCT group: a mean change of -6.1 and –1.6 in males and females, respectively.
- 20 mg SCT group: -7.9 and –2.3 in males and females, respectively.

However, this observation may be reflecting a numerical trend for a greater placebo effect in females (-11.2 compared to –6.8 in males).

Results on Plasma Concentration Monitoring.

Results showed that trough plasma concentrations of SCT obtained at treatment endpoint (end of week 8 or upon early termination) were not significantly correlated ($r= -0.04$) with the primary efficacy measures (change from baseline to treatment endpoint on the MADRS). These results are based on an analysis of data collected from 77 LD SCT Ss and 78 HD SCT Ss (Pearson Product correlation was employed). The data from these Ss were selected for this analysis because they met the following criteria:

- blood sample was obtained within 27 hours after the final dose
- detectable levels (≥1 ng/ml) of SCT could be obtained from the sample
- the MADRS score and blood sample were obtained on the same visit

10. Fixed Dose Study SCT-MD-01: Conclusions

According to the results described in the submission, Study MD-01 (an 8-week trial) which examined outpatients with MDD showed a significantly greater improvement in each SCT group (the 10 mg and the 20 mg groups) than the placebo group. Improvement was demonstrated with the primary efficacy measure (the change form baseline to treatment endpoint on the MADRS), as well as with other secondary measures designed for assessing depression or for overall clinical

improvement (pending confirmation by the Biometric Reviewer). The significant treatment group effects on the primary efficacy variable were revealed while controlling for baseline scores on this measure. Therefore, this study supports the claim that daily doses of 10 mg or 20 mg of SCT are effective in treating MDD outpatients. Furthermore, the treatment group effect on the primary efficacy variable was not found to be significantly influenced by gender, based on a gender subgroup analysis. However, the sample size of males may be insufficient to yield a significant gender group effect.

A comparison between the 10 mg and 20 mg groups could not be found in the submission. However, upon inspection of the results provided, the two groups appeared to show a similar magnitude of effect when comparing each group to placebo for most time-points (visits) during the treatment phase of the study. Despite these apparent similarities on efficacy, the lower dose appears to be better tolerated based on the safety analysis, as described in a later section of this review (refer to section VII H). Consequently, the sponsor recommends a starting daily dose of 10 mg SCT and that the daily dose may be increased in nonresponders to 20 mg after a minimum period of one week on the lower dose.

Some potential caveats to the overall conclusion of Study MD-01 demonstrating efficacy in MDD outpatients exist and are provided below. However, these caveats are not substantial or of great enough concern to refute the overall conclusion regarding this study, for reasons as described below.

Some Potential Caveats to Consider

Pseudospecificity is one possible caveat regarding the treatment group effects, particularly regarding potential anxiolytic effects given that several SSRIs are approved for various anxiety disorders and anxiety disorders such as generalized anxiety disorder commonly coexist with MDD. However, in the case of Study MD-01 pseudospecificity does not appear to account for the results observed for various reasons, some of which are described in the following. The study protocol involved exclusion of Ss with specific DSM-IV Axis I disorders listed in the exclusion criteria of the protocol (also listed in section 3 above). The protocol also required exclusion of Ss with other Axis I disorders not included in this list (other than MDD), if the disorder was their primary diagnosis. Consistent with these eligibility criteria, the baseline mean HAMÅ°scores of each treatment group was only approximately 15 to 17 in contrast to the mean baseline MADRS and HAMD scores. Furthermore, the majority of the study population failed to have ongoing or active anxiety disorder(s) at screening. Finally, a significant treatment group effect was generally absent for those secondary efficacy variables that were designed to examine anxiety symptoms, whereas a treatment group effect was present on the depressed mood item of the HAMD, as well as the melancholia subscale of the HAMD. Positive results on the mood item and melancholia subscale of the HAMD are consistent with a specific effect of SCT on MDD symptoms rather than on anxiety symptoms. Therefore, a pseudospecific anxiolytic effect of SCT on subjects of Study MD-01 does not appear to account for the treatment group effects revealed on the primary efficacy variable and on secondary variables assessing symptoms of MDD.

Premenstrual Dysphoric disorder (PMDD) is another disorder for which some SSRIs are approved as therapeutic agents. However, given the cyclical nature of symptomatology of PMDD and severity of symptoms relative to the menstrual cycle, as defined by DMS-IV criteria, it is unlikely that female Ss with PMDD were inadvertently included in Study MD-01. Ss on MD-01 were required to have symptoms of MDD for a period of at least 4 weeks at the baseline

visit and by DSM-IV criteria symptoms must be present for most days over a period of 2 weeks. In addition to meeting these criteria, Ss were followed for one week during a placebo run-in phase during which placebo "responders" were subsequently excluded, as previously described. These measures were likely to decrease the chance of inadvertently including female Ss with undiagnosed PMDD. Furthermore, the effects on SCT on the primary efficacy variable compared to placebo did not appear to be significantly influenced by gender, based on results of a gender subgroup analysis. Consequently, pseudospecific effects on possible undiagnosed and underlying PMDD in female Ss of Study MD-01, does not appear to exist and in turn, does not appear to account for the positive results on primary and secondary variables in this study.

C. Study SCT-MD-02, Flexible Dose Comparison of the Safety and Efficacy of Lu 26-054 (Escitalopram), Citalopram, and Placebo in the Treatment of Major Depressive Disorder
This multi-center, double-blind, placebo controlled, randomized flexible dose, parallel group study employed almost identical methods as Study MD-01, except that a flexible dose regimen, rather than a fixed dose design was used in Study SCT-MD-02 (MD-02). This study is almost identical in methodology to that of MD-01 and is briefly described in this section. Because Study MD-02 failed to show a significant treatment group effect on the primary efficacy measure, while Study MD-01 was positive, any key differences between studies MD-01 and MD-02 are also noted.

1. **Study SCT-MD-02 Investigators and Sites:** See Table VI.B.2 in the appendix (as provided by the sponsor) for a listing of 22 investigative centers in the United States.

2. Study SCT-MD-02 Objective.
The primary objective of this study was to compare SCT to placebo treatment on efficacy and safety in outpatients with MDD.

2. **Study SCT-MD-02 Population:** The study population consisted of 386 randomized generally healthy 18 to 80 year old male and female outpatients with DSM-IV MDD. 368 of the 386 randomized Ss were included in the ITT Efficacy population (125 placebo Ss, 124 SCT Ss, and 119 CT Ss). See Table IV.B.1 (in section IV B, above) for a further breakdown of Safety and Efficacy populations. The disposition of the Ss is described in section C5 below. Inclusion and exclusion criteria were similar those employed for study MD-01, with one key exception. Older Ss (maximum age cut-off of 80 years old) were included in study MD-02 (maximum age cut-off in MD-01 was 65 years old).

4. Study SCT-MD-02 Design, Assessments and Statistical Analysis Plan.
The study design, assessments and statistical analysis plan were similar to that of Study MD-01 except Ss were randomized (1:1) to the following treatment groups (flexible oral daily doses):

- 10-20 mg SCT group
- 20-40 mg CT group
- Placebo

The 8-week double blind treatment phase of the study followed a 1 week single blind placebo run-in phase. Ss were started on one daily capsule (10 mg SCT, 20 mg CT or placebo in each group, respectively) which was continued during Weeks 1-3 of the treatment phase. The daily dose could be increased to two capsules in each group (2 X 10 mg SCT, 2 X 20 mg CT, or 2 X

placebo, respectively) as early as Week 3 or on subsequent weeks (if not previously increased). This increment in dose occurred only when dose-limiting AE(s) were absent and if the investigator judged the response to treatment as unsatisfactory. The dose could also be decreased at any time for AEs, although a minimum dose of 1 capsule (10 mg SCT, 20 mg CT or placebo in each respective group) was employed.

Blood samples for plasma concentrations of parent compound and metabolites were not collected. Primary and secondary efficacy variables and methods of the statistical analysis of the results were similar to those employed for Study MD-01.

5. Study SCT-MD-02 Patient Disposition and Baseline Demographic Features.

Table VI.C.1 in the appendix (as provided in the submission) shows the results on the disposition of the Ss which is similar to that observed in Study MD-01 except that no significant treatment group effects were revealed for any categories by reason for discontinuation. However, a trend for a treatment group effect for incidence of adverse dropouts did appear to exist in which 9% of SCT Ss were adverse dropouts compared to 4% and 3% of CT and placebo Ss, respectively.

Regarding demographic features treatment groups (ITT Safety population) showed no significant differences in mean age, mean weight, distribution by gender or race. The majority of Ss were female (49 to 58%/group) and Caucasian (82-86%/group). Despite the inclusion of Ss over 65 years old (maximum cut-off of 80 years) in contrast to Study MD-01 (maximum cut-off of 65 years old), the mean age of Ss and proportion of Ss 60 years and older was similar in both studies. In Study MD-02 Ss were approximately 42±12 years with 9% of them ≥60 years old, compared to a mean age of approximately 40±12 years and 6% of Ss ≥60 years old in Study MD-01. The median weight was approximately 174 to 178 lbs in each group. The treatment groups were reported to be similar in suicide, psychiatric, medical, psychotropic and nonpsychotropic medication histories which is described in more detail below.

Regarding baseline efficacy parameters the treatment groups showed similar mean baseline scores on the MADRS, HAMD, and CGI-S (mean scores of approximately 28±5 score points, 25±5 points, and 4.3±0.6 points respectively) that are comparable in severity to that observed in the study population in Study MD-01.

Concomitant Illness and Medications

Treatment groups were generally similar in incidence of medical conditions (by body system categories) and ongoing psychiatric disorders in which the following approximate incidence rates (% Ss/treatment group) were reported by the sponsor upon request:

- Dysthymic disorder in 3%
- Social Phobia in 2%
- Other psychiatric disorders or categories of disorders < 1% in each category

The majority of Ss (73%) were taking concomitant medications during the double-blind treatment phase of the study. Results of concomitant medication use were similar to those observed in Ss of Study MD-01.

6. Study SCT-MD-02 Efficacy Results.

Results on the Primary Efficacy Variable. The LOCF dataset failed to show a significant treatment group effect on improvement from baseline to treatment endpoint (week 8) on the mean total MADRS score based on an treatment by center ANCOVA covarying for the baseline MADRS score. The treatment by site interaction was not significant (p=0.106). Significant group differences between placebo and each active drug group (SCT or CT) could not be

revealed upon pair-wise comparisons at any of the time-points (Weeks 1, 2, 3, 4, 6 and 8). See Table VI.C.2 in the appendix for primary efficacy results by visit and endpoint, as provided in the submission.

The OC dataset did show at least a trend for a treatment group effect ($p \leq 0.05$) on the mean change from baseline to treatment endpoint on the MADRS, based on an ANCOVA analysis. Significant group differences between placebo and each active drug group (SCT or CT) could not be revealed upon pair-wise comparisons for weeks 1, 2, 3 and 4. However, significantly greater improvement was observed in the SCT group than that of placebo on week 6 ($p<0.01$) and at least a trend for greater improvement in the SCT group on week 8 ($p<0.05$). The CT group showed trends for greater improvement than placebo on these same weeks (week 6, $p=0.06$ on week 6 and $p=0.05$ on week 8). These results are without correction for multiple comparisons.

7. Study SCT-MD-02 Treatment Exposure (flexible dose study)

Since this was a flexible dose study that failed to observe significant treatment group effects on the primary efficacy LOCF dataset the extent of exposure of Ss to SCT is provided in this section. The mean dose exposure in the SCT group of ITT Safety population was 13.7 mg/day and among the completers (78% of Ss were completers) was 17.6 mg/day (exposure results of the ITT Efficacy population could not be found but the majority of ITT Safety Ss were also in the ITT efficacy population).

8. Study SCT-MD-02 Conclusions.

Significant treatment group effects on the primary efficacy variable were not revealed in Study MD-02 when analyzing the LOCF dataset. Interpretation of results of the OC dataset can only be considered preliminary for several reasons, some of which are described in the following. There were twice as many adverse dropouts in the SCT group, the group of interest, compared to the placebo and CT groups. Furthermore a p of less than or equal to 0.05 is not considered significant, particularly without correcting for multiple comparisons.

Despite the failure to show significant treatment group effects in this study the actual mean values for change from baseline to treatment endpoint and at various time-points throughout treatment phase were generally in the direction in favor of SCT and CT over placebo. However, these results need to be interpreted with caution given that were not designated *a priori* primary comparisons which were conducted in the absence of an overall treatment group effect by ANCOVA and without correction of p values for multiple comparisons. The numerical trends for greater response with SCT and CT treatment compared to placebo, together with failure to show significant treatment group effects between the active comparator group (CT) and placebo, suggests that this study is a failed rather than a negative study. Therefore, while the results of MD-02 do not appear to support the sponsor's claim that SCT is indicated for MDD, they do not appear to refute this claim, particularly given the aforementioned positive results of MD-02 and additionally, the positive results of two European studies (99001 and 99003) summarized below.

The reasons that MD-02 failed to show a significant treatment group effect remains unclear. Demographic factors, baseline comorbidity features, extent of exposure, percentage of completers among other factors do not appear to reveal any explanation for failure to observe significant treatment group effects. However, there did appear to be larger placebo effect in study MD-02 compared to MD-01, while the magnitude of effect on the SCT groups of both

studies were similar. Consistent with this observation is that only 1 placebo Ss (0.08%) in MD-02 withdrew from the study because of an insufficient response to treatment compared to 6 placebo Ss (5%) that dropped out due to lack of efficacy in MD-01. Furthermore, the SCT groups across these two studies were similar on incidence rates of Ss withdrawing in either of these two dropout categories (for at least the 20 mg SCT group of MD-01 compared to the SCT group of MD-01). It is not clear why Study MD-02 appears to show a greater placebo effect that Study MD-01, as the studies were almost identical in methodology.

D. A Summary of European Studies 99001 and 99003.

Studies 99001 and 99003 were similar to studies MD-01 and MD-02, respectively in objectives, design, primary efficacy analyses, study population and treatment regimen. A summary description of each study and their results are provided below.

1. a. Summary Description of Study 99001 (Design, Methods, Study Population). This study is an 8-week, parallel group, fixed dose, multicenter, double blind, randomized, placebo controlled study examining the safety and efficacy of 10 mg SCT (191 randomized Ss) compared to placebo (189 randomized Ss) administered daily (oral) in 18-65 year old outpatients with MDD (by DSM-IV criteria). There were a total of 40 study sites in 5 countries: 3 in Canada, 4 in Estonia, 27 in France, 5 in the Netherlands and 1 in the United Kingdom (see Table VI.B.3 for a listing of sites).

The eligibility criteria of Ss in this study were similar to those of the US studies with some exceptions noted in the following in which Study 99001:

- Employed a maximum cut-off score on the MADRS for exclusion of Ss (Ss with a score > 40 were excluded).
- Did not use a minimum cut-off score on Item 1 of the HAMD for inclusion of Ss into the study.
- Excluded Ss with an eating disorder (this disorder was not specified as being an exclusionary disorder for participation in the studies MD-01 or MD-02).
- Did not specify exclusion of Ss with a personality disorder or Axis I disorder other than MDD (DSM-IV criteria), although the list of specific Axis I disorders that were prohibited in Ss was provided similar to that for Studies MD-01 and MD-02. This list was as follows (but as in the previous item this list also included eating disorders):
  - Bipolar disorder
  - Schizophrenia or any Psychotic disorder
  - Obsessive Compulsive disorder
  - Mental Retardation, Pervasive Developmental disorder, or Cognitive disorder
  - Substance Abuse/Dependence within 12 instead of 6 months of study entry

Serum concentrations of SCT and two major metabolites S-DCT and S-DDCT were obtained in 105 SCT Ss. The primary efficacy variable and statistical methods for Studies 99001 and 99003 were the same as those employed in Studies MD-01 and MD-02. Secondary efficacy variables and statistical methods for these variables were generally the same as those for the US studies (MD-01 and MD-02). However, the HAMD and HAMA scales were not employed. The primary statistical analysis was conducted on the LOCF ITT efficacy dataset (the OC dataset was also analyzed).

Table VI.D.1 in the appendix summarizes the disposition of Ss (as provided by the sponsor). Treatment groups were similar on various demographic features. 76% of Ss were female and 98% were Caucasian. The mean age of Ss was 40±11 years and mean Body Mass Index was 25+6 kg/m^2. Treatment groups were similar on various demographic features. The mean baseline MADRS and CGI-S scores were approximately 29 and 4.4 points, respectively and treatment groups were similar on these baseline efficacy measures. The most common (incidence of >5% in a given group) medical conditions (none of them had an incidence of ≥10%) were as follows:

- Menopause
- Headache
- Low back pain
- Asthma
- Essential hypertension
- Various types of allergies

Concomitant psychiatric conditions were found in approximately 20% of the Ss with the following noted (incidence provided):

- Unspecified anxiety disorders (12% of placebo Ss and 7% of SCT Ss)
- "Nonorganic" insomnia (12%/group)

1. b. Summary of Efficacy Results of Study 99001.

Tables VI.D.2 in the appendix (as provided in the submission) summarizes results of the mean change from baseline to treatment endpoint on the primary efficacy variable. Table VI.D.3 in the appendix (as provided in the submission) provides results of the primary efficacy variable for each time-point (each visit). In summary, the SCT group showed a significantly ($p<0.01$) greater improvement than placebo on mean change from baseline to treatment endpoint (Week 8) on the MADRS total score. The adjusted mean change was -2.7 greater in the SCT group than that of the placebo group (see Table VI.D.2 in the appendix).

A significant baseline MADRS score main effect was observed on the primary efficacy variable in which Ss with higher baseline scores showed greater improvement ($p<0.01$). A baseline MADRS by treatment group interaction effect was also reported as significant ($p=0.075$), using the *a priori* defined 10% level of significance used by the sponsor for interaction effects. This interaction effect was in the direction of greater treatment group effects in favor of SCT over placebo for Ss with lower baseline MADRS scores than for Ss with higher baseline scores. However, a significant treatment group main effect ($p<0.002$) was still observed using a model that adjusted for interaction effects.

Analysis of the secondary efficacy variables generally revealed results consistent with findings on the primary efficacy analysis. Results of the change in the MADRS score from baseline to a given time-point (visit) were similar to those observed for Study MD-01. Regarding the response rate in each treatment group, 42% of the placebo group were responders (defined as ≥50% decrease from baseline to treatment endpoint in MADRS Total Score) compared to 55% in the SCT group ($p<0.05$, Fisher's exact test). At least trends for greater improvement was also revealed in the SCT group compared to placebo on the CGI-I and CGI-S scores at treatment endpoint ($p=0.064$ and 0.01, respectively when employing the CMH test with centers as strata or $p\leq0.05$ for each measure when using ANCOVA).

Upon request the sponsor conducted a subgroup analysis on the basis of gender for the primary efficacy variable, using the LOCF dataset and the ANCOVA model with the baseline

MADRS score as a covariate, which is similar to that previously described for Study MD-01. This analysis failed to reveal significant gender group effect (p=0.18) or treatment group by gender interaction (p=0.48) effects. It should be noted that the sample size of males was only 42 or 50 Ss in the placebo and SCT groups, respectively, in contrast to a sample size of over 140 Ss of females in each treatment group. The difference between placebo and SCT groups within each gender subgroup on the mean change from baseline to treatment endpoint of the MADRS score was a difference of 1.9 for males compared to 3.0 in females with the standard deviations being approximately 7 to 8 units.

2. a. Summary Description of Study 99003 (Design, Methods, Study Population).

This study is an 8-week, parallel group, flexible dose, multicenter, double blind, randomized, placebo controlled study examining the safety and efficacy of 10-20 mg SCT (156 randomized Ss) and 20-40 mg CT (161 randomized Ss) compared to placebo (154 randomized Ss) administered daily (oral) in 18-65 year old outpatients with MDD (by DSM-IV criteria). The 10-20 mg SCT and 20-40 mg CT daily doses are the same as those employed in Study MD-02. The eligibility criteria were identical to those of study 99001. The study was conducted at 69 study sites in 8 countries (3 in Canada, 22 in France, 17 in the United Kingdom, 3 in Belgium, 10 in Finland, 4 in Switzerland, 2 in Sweden and 8 in Norway).

Following the one-week single blind placebo run-in phase Ss were randomly (1:1) assigned to one of the three double blind treatment groups:

- 10-20 mg SCT
- 20-40 mg CT
- Placebo

Ss were started on a single tablet of assigned study drug (10 mg SCT, 20 mg CT or placebo in each respective group). The dose could be increased by an additional tablet which was also the maximum allowed dose (2 of 10 mg SCT tablets p.o., 2 of 20 mg CT tablets p.o. or 2 placebo tablets p.o. in each group, respectively) on Weeks 4 or 6. The dose increase occurred if a S had an "unsatisfactory" response or had an increase in his/her CGI-S core. The dose could be decreased to the lower dose due to AEs.

Table VI.D.4 in the appendix shows the disposition of Ss. Demographically, the treatment groups were similar on various features. Similar to that observed in the other studies 72% of Ss were female and the mean age of the Ss was 43±11 years. The mean Body Mass Index was 26±6 kg/m^2. This study population was demographically similar to that of Study 99001 and the two US studies (MD-01 and MD-02) on most features except for the percentage of Caucasians (versus non-Caucasians). In Study 99003, 99% were Caucasian, similar to that observed in Study 99001. However, approximately 81 to 87% Ss in each treatment group were Caucasians in the US studies, MD-01 and MD-02.

The mean baseline MADRS and CGI-S scores were approximately 29 and 4.3 points, respectively and treatment groups were similar on these baseline efficacy measures. The most common (incidence of >5% in a given group) medical conditions (none of them had an incidence of >12%) were as follows:

Menopause	Various types of allergies
Headache	Diaphragmatic hernia
Low back pain and cervicalgia	Hypercholesterolemia
Asthma	Irritable bowel syndrome
Essential hypertension	Spondylosis and arthrosis (unspecified)

Concomitant psychiatric conditions were found in approximately 10-13% of the Ss in each group with unspecified anxiety disorders in 6% of CT Ss, 3% of placebo Ss and 1% of SCT Ss.

Primary and secondary variables and statistical analyses were similar to those employed in Study 99001 with mean change from baseline to treatment endpoint on the MADRS total score as the primary efficacy variable.

2. b. Summary of Efficacy Results of Study 99003.

Results on the primary efficacy variable are shown in Tables VI.D.5-6 in the appendix (as provided by the sponsor). A significant treatment group effect was reported on the primary efficacy variable with the SCT group showing greater improvement than placebo at treatment endpoint ($p<0.01$) by an adjusted mean margin of approximately -2.9. However, the CT group only showed a numerical trend for greater improvement by a margin of –1.5 compared to placebo ($p=0.11$). As in Study 99001, the baseline MADRS score was positively correlated to the magnitude of improvement among Ss ($p<0.001$). However, this analysis did not reveal a significant treatment group by baseline MADRS score interaction effect ($p>0.10$). The results of the MADRS scores over time was also consistent with at least trends for greater improvement from at least visit 4 and onward for both the SCT ($p<0.02$ to <0.01 among visits) and CT (p ranged from 0.1 to 0.3 among visits) groups. A small numerical trend for the greatest improvement appeared to exist in the SCT group upon inspection of the descriptive results for each treatment group. Secondary efficacy results were generally consistent with the results on the primary efficacy variable.

Gender subgroup analysis on the primary efficacy variable, similar to that previously described for studies MD-01 and 99001, again failed to reveal a significant gender group ($p=0.09$) or gender by treatment interaction effect ($p=0.67$) on the primary efficacy variable. As for previously describes studies the majority of Ss were female, whereby a sample size effect may be playing a role in failure to reveal gender group effects or interaction effects. Inspection of the results does appear to show a numerical trend for a gender by treatment interaction effect in that the difference between placebo and SCT mean change in MADRS scores for each gender subgroup was 1.6 in the males compared to 3.1 in females.

3. Studies 99001 and 99003 Conclusions.

The two European studies (99001 and 99003) appear to show results supporting the sponsor's overall efficacy claim. Given that Study 99003, a flexible dose study was methodologically similar to Study MD-02, it is not clear why Study 99003 was a positive study regarding SCT effects compared to placebo, while Study MD-02 was failed. Minor differences in demographic features existed but do not appear to account for differences observed in the results of these studies. Interestingly, the CT group of Study 99003 failed to show a significant treatment group effect compared to placebo, but only showed a numerical trend for superiority over placebo, which was also observed in Study MD-02 regarding the CT group results.

Upon request the sponsor conducted a subgroup analysis on the basis of gender for the primary efficacy variable, using the LOCF dataset and the ANCOVA model with the baseline MADRS score as a covariate, which is similar to that previously described for Study MD-01. This analysis failed to reveal significant gender group effect ($p=0.09$) or treatment group by gender interaction ($p=0.67$) effects.

E. Results of an Analyses for Potential Treatment Group by Demographic Feature Interaction Effects for the Primary Efficacy Variable.

The submission provides the results of analyses by race, gender, and age when pooling data from Studies MD-01 and MD-02. However, since MD-02 failed to show significant treatment group effects these results are difficult to interpret and are not described in this review. No other pooled or unpooled data subgroup analyses by race, gender or age could be found in the submission. Upon request, the sponsor provided results of a subgroup analysis on the basis of gender for the primary efficacy of each positive study (MD-01, 99001 and 99003). However, the sample sizes of non-Caucasian Ss or elderly Ss (≥65 years old), were insufficient to yield meaningful results from subgroup analyses.

The positive studies did not show significant gender group effects or gender by treatment group effects on the primary efficacy variable (gender subgroups had similar mean baseline scores). However, a sample size effect may account for failure to show significant gender effects. A numerical trend for a greater treatment group effect (an improvement on MADRS) in females compared to males did appear to exist in the two European studies but not in the US study MD-01. The latter study showed a difference between placebo and 10 mg SCT groups on mean change of the MADRS score of 6.1 in males compared to only 1.6 in females and a difference between placebo and the 20 mg SCT group of 7.9 in males compared to 2.3 in females. These results show a numerical trend in the opposite direction observed for the European studies, in which males appeared to show a numerical trend for greater improvement than females in the 10 mg and 20 mg SCT treatment groups compared to placebo. Given these conflicting results and small sample sizes of male Ss, these results appear inconclusive and do not suggest that a treatment group effect is gender dependent.

VII. Integrated Safety Information

A. Background Information

The integrated summary of safety was provided in the 120-Day Safety Update Report dated 7/12/01 for the 4 completed depression trials (MD-01, MD-02, 99001 and 99003). The Update Report provided a description and narratives of deaths and serious adverse events reported in these 4 trials and in other completed and ongoing trials, combined (10 completed PK studies: SCT-PK-01 through SCT-PK-06, 98106, 98107, 98113, and 991166 and 13 ongoing trials), as of the cut-off date of 2/1/01. Refer to Panel 8 on page 219 (also page 38) of volume 2 for a listing of studies in the Update Report. Narratives were also provided for adverse dropouts in the four completed depression trials, 2 of the 13 ongoing trials (both trials were open-label) and for 10 completed PK studies (PK studies did not include placebo Ss).

Incidence rates for adverse events, descriptive statistical results of clinical parameters and incidence rates of outliers on these parameters were provided for the 4 depression trials (combined). This information was generally provided for the 10 PK trials (combined) but there were no placebo Ss for comparison to SCT. Laboratory, vital sign, urinalysis and ECG safety results are described for the 4 depression trials (combined) and were also generally provided for the 10 PK studies. CRFs were provided for serious adverse events, deaths and adverse dropouts for the 4 depression trials and the 10 completed (as of 2/1/01 cut-off date) PK studies. This review primarily focuses on results from the 4 depression trials regarding laboratory, urinalysis, vital sign and ECG data.

duration of 56 days. The exposure of completers could not be found in the submission or the Update Report.

Overall Exposure of Subjects* in the Depression Trials (SCT-MD-01, SCT-MD-02, 99001, 99003)			
	Placebo N=592	Escitalopram N=715	Citalopram N=408
Mean±SD Duration (days)	51±15	51+16	52+15
Median Duration (days)	56	56	56
Range (days)	1-76	1-82	1-71
Mean Patient Years**	83	99	58

*Ss who received at least one dose of study medication
** Patient years = total time of exposure to study drug expressed in years.

85% of Ss received study medication for over 4 weeks. The incidence of Ss (% and number) who received over 56 days of treatment in each group among the four trials combined were as follows:

- 58% of placebo (n=345),
- 57% of SCT (n=409)
- 61% of CT Ss (n=250).

Two of the four trials employed fixed daily doses of 10 mg in Study 99001 and of 10 mg or 20 mg in study MD-01. The other two trials employed flexible daily doses of 10-20 mg in each study (Studies MD-02 and 99003). The overall mean daily dose of the 715 SCT Ss in these four trials was 12.4 mg/day. The incidence of SCT Ss that received a given category of mean daily dose (given as a dose range) among the four trials, was provided in the submission and is summarized below.

- 62% of SCT Ss received 6-10 mg of SCT a day
- 14% of the SCT Ss received 11-15 mg/day
- 24% of the SCT Ss received 16-20 mg/day

Various demographic subgroups (Ss ≥ 60 years old versus < 60 years old, male versus female, Caucasian versus non-Caucasian) were similar in the overall mean daily dose (12 to 13 mg/day per subgroup), as well as in the distribution of Ss across various categories of mean daily dose ranges (dosing categories were the following: >0-5 mg/day, 6-10 mg/day, 11-15 mg/day, 15-20 mg/day and >20 mg).

Exposure in Individual Depression Flexible Dose and Fixed Dose Trials (MD-01, MD-02, 99001 and 99003).
The exposure of completers in each of the trials was provided upon request in a 9/27/01 submission, which is shown in Tables 1-3 in Attachment 1 of this review (as provided by the sponsor).

D. Deaths
Two deaths were reported among Ss (approximately 3948 total Ss of which about 2552 Ss received SCT) of all completed and ongoing trials (cut-off date of 2/1/01). In both cases the events were not likely to be drug related, as summarized in this paragraph (see Table VII.D.1 in the appendix for details of each S). One death was a completed suicide in an elderly male in a

depression trial (S 5302), the other death was associated with cerebrovascular accident (CVA) in an elderly S (S 5370) with insulin dependent diabetes mellitus (IDDM) and a positive history of a previous CVA and seizure. This death appeared to be due to underlying disease, given that the patient had this medical history and was elderly. These two deaths occurred in ongoing studies (as of the 2/1/01 cut-off date) such that CRFs were not provided in either the original submission or in the 120 Day Safety Update submission. However, information was provided in narratives.

Two additional deaths were reported in ongoing trials via safety alert, MedWatch reports dated after the 2/1/01 cut-off date. These deaths are described in section M below (Safety Results from Other Sources).

Deaths in 10 Completed PK Studies (Studies SCT-PK-01 through –06, 98106, 98107, 98113 and 99166)

None were reported.

E. Serious Adverse Events (SAEs)

SAEs in 14 Completed Studies (the 4 depression trials and 10 PK studies). A listing of serious adverse events (SAEs) is provided in Table VII.E.1 in the appendix, as provided by the sponsor. A total of 20 Ss were reported to have SAEs out of 1715 Ss. These SAEs were not likely to be related to SCT or CT treatment, with one exception, which was a miscarriage in a CT treated S (see a description of S 3350 below). Regarding this reported miscarriage, CT (Celexa®) is under the pregnancy category C in current labeling.

The distribution of the 20 Ss (out of the 1715 total Ss) with SAEs by treatment group were as follows:

- 8 Ss (0.8%) out of 954 of SCT Ss
- 4 Ss (0.8%) out of 473 CT Ss
- 8 Ss (1.4%) out of 592 placebo Ss.

The following is a brief description of SAEs in the SCT and CT groups. 5 SCT or CT Ss had SAEs were most likely related to underlying MDD and included: non-accidental overdoses, suicide attempts and/or suicidal tendencies. The remaining SAEs that occurred in SCT Ss were also not likely to be drug related and did not result in discontinuation of the study drug. These SAEs are described in Table VII.E.2 of the appendix. SAEs in 2 CT Ss were also not likely to be drug related and are described in Table VII.E.2 of the appendix. However, 1 CT S had a miscarriage and is described below:

- **Miscarriage in CT treated S 3350** who was 19 years old and withdrew from the study after about 25 days of treatment. One month later she became pregnant. Her last menstrual period occurred before study entry. One week after reporting her pregnancy she had a miscarriage. The event could be drug related. Celexa® is in labeling as a Category C drug regarding pregnancy.

SAEs in Ongoing Studies as of 2/1/01 Cut-off Date

Out of the 3948 Ss who received study medication (approximately 2552 of them received SCT) a 158 SAEs were reported among a total of 113 Ss in all completed and ongoing studies (as of

2/1/01). The incidence of SAEs in each treatment group was only 1-2%, with overall exposure for each group provided below:

- **SCT Ss:** 77 SAEs in 57 Ss out of 2552 SCT Ss (2.2%) with an overall exposure of 645 patient years.
- **CT Ss:** 7 SAEs in 5 Ss out of 816 CT Ss (0.6%) with an overall exposure of 65 patient years.
- **Active comparator Ss:** 2 SAEs in 1 Fluoxetine S out of 347 Ss in an active comparator group (0.2%) with an overall exposure of 18 patient years.
- **Placebo Ss:** 8 SAEs in 8 out of 1199 Placebo Ss (0.7%) with an overall exposure of 83 patient years.
- **Blinded Ss:** 64 SAEs in 44 Ss out of 1996 Ss on blinded drug

Treatment groups were similar in the distribution of Ss with SAEs by category (the sponsor did not use dictionary terms (such as MEDRA or COSTART terms) for SAE categories but rather, created a classification system "to facilitate" the classification of SAEs by using "clinically meaningful categories"). These results are shown in Table VII.E.3 in the appendix (as provided by the sponsor).

Selected SAEs occurring in SCT Ss of ongoing trials are described below and include the following SAEs: cardiovascular or cerebrovascular events in 4 Ss, syncope in 1 S and gastrointestinal events in 2 Ss. These SCT Ss had pre-existing conditions and/or risk factors, and/or had a history of similar events. Therefore, the events were likely due to an underlying or pre-existing condition. However, an interaction effect between drug treatment and concurrent or underlying conditions or risk factors for these events cannot be ruled out.

One S (4313 in Study MD-03) on blinded study drug had an SAE that appeared to be temporally related to treatment and is also described below. This S had approximately a 3 to 6 fold increase in liver enzyme levels as described below (baseline and post treatment cessation values were within normal limits). Elevation in liver function tests is described in labeling for Celexa® and other SSRIs.

Descriptions below are based on narratives (no CRFs provided for Ss of ongoing trials).

SAEs of SCT treated Ss (a selected listing):

- **S3263 in Study 99002.** This S is a 55 year old female. On the day after receiving 205 days of daily SCT (she had previously completed a CT study) she had the following AEs: difficulty swallowing, walking and speech with right facial weakness. She was hospitalized with the SAE of **cerebral ischemia** on the next day and was treated with aspirin, dipyridamol, pravastatin with improvement of her condition. This event could be due to an underlying condition, given the patient's age and the likelihood that she was postmenopausal. However, the narrative does not mention any concomitant medication use, current or past medical conditions in this S, suggesting an absence of other risk factors. Consequently, given the information in the narrative, one cannot rule out a possible relationship with the study drug. Yet, she previously received CT, as well as 205 days of SCT, suggesting that the SAE was not likely to be related to exposure to SCT.
- **S7079 in Study 9900.** This was a 46 year old female, smoker with history of thyroid goiter, varicose veins, who had an episode of nausea, vomiting. In addition there was an "up and outwards turning" of the right eye. This SAE was diagnosed as an episode of **cerebral ischemia** "likely due to a small brain stem infarction." The episode occurred on the 49th day of SCT treatment. The events led to cessation of SCT and the S was hospitalized. Head CT,

was hospitalized overnight, with the study drug discontinued (only had one dose on previous day). Upon examination she was "drowsy" but "oriented" with a blood pressure of 140/80 mmHg and a pule rate of 72 bpm. She recovered from the event. Given this patient's underlying cardiac condition along with multiple concomitant medications that are known to affect heart rate and blood pressure, it is likely that this SAE was not related to SCT treatment.

Selected Ss with SAEs on blinded study drug:
S 4313 in Study MD-04. A 25 year old male had an SAE of **increased liver function** tests found on a post-treatment laboratory test on September 8, 2000, 4 days after completing 71 days of treatment. Given the temporal relationship of this event, in which baseline and follow-up values at approximately 2 weeks post treatment were within normal limits, this event appears to be drug-related. Study drug was reported as blinded in this ongoing study, and no other information was provided on this S other than that described in a brief narrative and as follows. This 25 year old male had withdrawn from the study due to difficulties with transportation to the study site upon which he had completed 71 days of treatment of blinded drug with last treatment day occurring on September 4, 2000. On September 8, the S had elevated levels were AST (120 IU/l compared to a baseline value of 22 IU/l) and ALT (73 IU/l compared to 24 IU/l at baseline). These levels returned to baseline levels upon follow-up on September 22, 2000.

S 7334 in Study 99022. This S is a 61 year old, smoker with history of hypertension and hyperlipoproteinemia (receiving valsartan, hydrochlorthiazide, estradiol velerate) who had SAEs of **hypertension, chest pain and dizziness** on the night after Day 1 of treatment with blinded study drug. The hypertension was reported by the S as being sudden and intense and was based on self-measurement. She was hospitalized and the study drug was immediately discontinued. She was found to have a fusiform aneurysm in the left vertebral artery. The S continued to have episodes of dizziness that was believed to be secondary to involvement of the left vestibular nerve due to the aneurysm. She reportedly recovered. Given this S's history and concomitant medications, along with the finding of an aneurysm, it appears that this event was not likely to be related to the study drug.

SAEs in 10 Completed PK Studies (Studies SCT-PK-01 through –06, 98106, 98107, 98113 and 99166)
None were reported.

F. Dropouts due to Adverse Events

Adverse Dropouts (ADOs) in Four Completed Depression Studies (8-week Depression Trials SCT-MD-01, -MD-02, 99001, and 99003)
The incidence of adverse dropouts (ADOs) in the four completed 8-week depression trials were as follows:

- **SCT Ss:** 5.9% (42 out of 715 Ss)
- **CT Ss:** 5.4% (22 out of 408 Ss)
- **Placebo Ss:** 2.2% (13 out 592 Ss)

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relationship of normal and abnormal ECGs with treatment suggests that the event was drug-related. However, this S had risk factors of cardiac disease (gender and age) and arrhythmias are difficult to detect without multiple ECGs or continuous monitoring, such that the S could have had an underlying, undiagnosed condition.

- A 48 year old female who completed 71 days of SCT who then entered in the open label SCT trial had an **abnormal ECG (moderate junctional rhythm escape)** upon study entry which resolved in a follow-up ECG obtained 4 days post treatment cessation. This temporal relationship of this event and the normal ECG suggests that the event could be drug-related.
- A 45 year old male who had 58 days of CT followed by open-label SCT treatment for 44 days had an **abnormal ECG** resulting in cessation of SCT treatment which showed evidence of **"myocardial infarction or pericardial damage"**. This S had risk factors for cardiac disease, such that the event could be due to an underlying and preexisting condition. However, with the information provided, a possible relationship with study drug cannot be ruled out.
- 24 year old female had **bradycardia** (38 and 47 bpm) during various periods of treatment which lead to cessation of SCT treatment. Prior to treatment cessation the S received a total of 52 days of SCT followed by 18 days of open label SCT. There were no symptoms reported in the narrative and bradycardia is not uncommon in young healthy adults.
- Markedly elevated liver enzymes (increased by 3 to 6 times greater than baseline levels) were reported in a 40 year old S who had normal levels at baseline. This elevation led to cessation of treatment. Upon treatment cessation, this S had received 51 days of CT followed by 58 days of open label SCT treatment. Within 4 days after treatment was discontinued, the elevated levels returned to baseline levels (within normal limits). The elevation in enzyme levels from baseline to Day 51 of open label SCT (after completing 51 days of CT in a previous trial) were as follows:
  - SGOT increased from 23 IU/l at baseline to 74 IU/l.
  - SGPT increased from 26 to 149 IU/l.
  - LDH increased from 163 to 492 IU/l.

G. Specific Search Strategies

Special Populations. There were no PK/safety studies reported in the submission or 120 Update report on special populations (see the subsection of analysis of AE results on the basis of gender, age and race in the next section, Section VII.H of this review). Special population studies, including studies of Ss with hepatic or renal impairment were conducted for the racemate, CT which were submitted under NDA 20-822 and as described in labeling for Celexa® under this approved NDA (also see brief discussion of some studies in the Human PK section, III.A.6 of this review).

The 120-Day Update describes a comparison of incidence rates of common treatment emergent AEs in all SCT treated Ss (N=715) compared to SCT Ss with concomitant cardiovascular (N=158) or with neurological disorders (N=259) for the four depression trials combined (Studies MD-01, MD-02, 99001 and 99003). When examining AEs that had incidence rates of 5% or more in SCT Ss with cardiovascular disease (CVD), impotence was the only AE that showed twice the incidence rate in the diseased group (5.4%) compared to that observed for all Ss (2.7%). Increased sweating (7% of CVD Ss compared to 4.8% for all Ss) and rhinitis (5.7% compared to 4.6%) showed numerical trends for higher incidence rates in the CVD Ss compared to that of all Ss. Comparisons between neurologically diseased Ss and all Ss on AEs

with ≥10 % or ≥5% incidence rates in the former group, failed to reveal differences of clinical significance, as described by the sponsor.

H. Adverse Events in the 8-Week Depression Trials (Studies MD-01, MD-02, 99001 and 99003)

An incidence of 73% (520/715) of SCT Ss, 77% (312/408) of CT and 64% (379/592) placebo Ss had at least one treatment emergent adverse event (AE). Table VII.H.1, in the appendix, shows the incidence rates of common AE's (defined as AE's reported in ≥5% of SCT Ss) reported in each treatment group, as provided by the sponsor. Among these common AE's, AE's with an incidence in SCT Ss that was at least twice that of placebo Ss were the following:

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

Dizziness, diarrhea, and dry mouth are common AEs in the SCT group that appeared to show numerical trends for greater incidences in SCT and CT groups, each compared to placebo, but did not meet the twice that of placebo criterion and were not included in the above list (see Table VII.H.1 in the appendix). It is noted that SCT and CT groups appeared to show similar incidence rates for common AEs.

Dose-Related AEs in the Fixed Dose Depression Trials Combined (SCT-MD-01 and 99001).

The overall incidence rates of Ss with treatment emergent AEs in each group were as follows:

- Placebo Ss: 61%
- 10 mg/day SCT group: 67%
- 20 mg /day SCT group: 86%

The following table shows common AEs (common is defined as ≥5%) that showed an incidence in the high dose group of at least twice that of the low dose group, as well as an incidence of at least twice that of placebo.

Incidence of Common Adverse Events* in Placebo, Low and High Dose Escitalopram Treated Subjects in Fixed-Dose Depression Trials (SCT-MD-01 and 99001)

Common Adverse Event:*	Placebo Subjects (Ss) (N=311)	10 mg/day SCT Ss N=310	20 mg/day SCT Ss N=125
Insomnia	4%	7%	14%
Diarrhea	5%	6%	14%
Dry Mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating Increased	<1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

*Adverse events with an incidence rate of at least 5% in either of the SCT groups that also showed an incidence in the 20 mg/day SCT group of at least twice that of the 10 mg/day SCT group and the placebo group.

Common AEs that showed numerical trends for a dose-related effect but did not meet the criteria to be included in the above table, were as follows:

- **Rhinitis** in 3% of Placebo Ss, 4% of low dose SCT Ss, and 7% in high dose SCT Ss
- **Ejaculation Disorder** in 0% of Placebo Ss, 7% of low dose SCT Ss, and 12% in high dose SCT Ss

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. However, the sponsor describes two completed PK studies (SCT-PK-05 and 99166) comparing young to old Ss and female to male Ss on adverse events. These two PK studies had approximately 31 to 36 Ss fairly evenly distributed among gender and age-groups with the elderly group generally being >65 years old and the young group being adults 45 years or younger (in Study SCT-PK-05 the young age-group was 23-35 years old). There were no SAEs or ADOs reported in either of these two studies and age-groups were similar on the safety profile regarding AEs and on the incidence rates of AEs, with a few exceptions. Diarrhea was the only AE with a higher incidence rate in the elderly group (60%) compared to the young age-group (6%), which was reported for Study 99166, which was not reported in Study SCT-PK-05. It is noted that while age-groups generally failed to show differences in most common AEs, age-group differences were observed on PK parameters in which Cmax, AUC, and T1/2 parameters showed higher mean values in the elderly compared to the young age-groups (see PK section of this review, above).

Despite no gender differences in PK parameters (see PK section of this review) reported in the 2 PK studies (SCT-PK-05, 99166), more women than men appeared to have AEs (67% of women compared to 33% of men in study PK-05 and 94% of women compared to 71% of males in study 99166). In the former study headache was reported in 39% of women compared to 11% of men and in the latter study nausea was reported in 50% of females compared to 24% of males. Study 99166 also showed an incidence of 25% of women reporting fatigue compared to 6% of men. Without a placebo group it is difficult to interpret these results.

The distribution of treatment emergent AEs in male Ss compared to female Ss in each treatment group for the four 8-week depression trials combined were described in the submission. Only two AEs are noted in the following table (taken from Panel 22 in volume 2 of the Update Report), as other AEs did not appear to show gender differences.

Incidence of Selected AEs by Gender and Treatment Group				
	Male		Female	
Preferred Term	Placebo (N=188) n (%)	Escitalopram (N=225) n (%)	Placebo (N=404) n (%)	Escitalopram (N=490) n (%)
Dry Mouth	12 (6.4)	13 (5.8)	15 (3.7)	31 (6.3)
Influenza-Like Symptoms	12 (6.4)	4 (1.8)	12 (3.0)	32 (6.5)

It is difficult to interpret the above results on influenza-like symptoms since gender differences not only existed when comparing placebo groups, but also when comparing placebo to SCT groups within each gender in which the trends appeared in opposite directions (lower incidence in SCT males compared to placebo males and a higher incidence in SCT females compared to placebo females).

I. Laboratory Findings

The sponsor provided an integrated summary of results on laboratory parameters (in the 120 Safety Update) for the four completed 8-week depression trials (SCT-MD-01, SCT-MD-02, 99001 and 99003). The Update Report also included some laboratory safety results for the 10 completed PK studies. This review focuses on the placebo controlled study results from the 4 depression trials.

Treatment groups were generally similar in mean change (from baseline to treatment endpoint) and on incidence rates of Ss meeting criteria for values of potentially clinical significance (PCS) of each laboratory parameter. There were no SAEs in SCT or CT Ss in these four completed trials or in the 10 PK studies that were due to an abnormal laboratory (based on inspection of the Preferred Term line listing of ADOs in these trials).

There were no ADOs in SCT or CT Ss in the 4 depression trials that were due to abnormal laboratory values (based on inspection of the Preferred Term line listing of ADOs in these trials). However, there were ADOs in the 10 PK studies that appeared to be related to abnormal laboratory values, based on an inspection of the Preferred Term line listing as described in the following. As previously described one CT S (S2350) in a PK study had cholestasis intrahepatic with dehydration as an SAE, resulting in cessation of treatment. This SAE and ADO did not appear to be drug-related as the symptoms started during the placebo run-in phase of the study and resulted in hospitalization on Day 1 of CT treatment. An SCT S (S010) as previously described had anemia and dyspnea resulting in cessation of treatment.

While there is no integrated summary of safety results for ongoing trials the SAE Preferred Term S line listing showed a S (4313 in Study MD-04) with an SAE of increased liver function tests (LFTs) as previously described. Elevated LFTs were found on a post-treatment lab test on September 8, 2000, 4 days after completing 71 days of treatment that may have been drug-related. However, the study drug was reported as blinded in this ongoing study, and no other information was provided on this S other than that described in a brief narrative. According to the narrative the S4313 was a 25 year old male had withdrawn from the study due to difficulties with transportation to the study site upon which he had completed 71 days of treatment of blinded drug. The last treatment day occurred on September 4, 2000. The elevated LFTs observed in this S were AST (120 IU/l from baseline of 22 IU/l) and ALT (73 IU/l from baseline of 24 IU/l). Subsequently, these levels returned to baseline levels upon a follow-up assessment conducted on September 22, 2000.

1. Analysis of Central Tendency in Completed 8-Week Depression Trials (SCT-MD-01, -MD-02, 99001 and 99003)

Hematology and Chemistry. Treatment groups were generally similar on mean baseline, mean change and range of change from baseline values of each parameter. The 120 Update submission does not show any results of statistical comparisons between treatment groups but indicates that there were no clinically relevant trends that were observed. Examination of Table 6.4 in this submission (showing descriptive statistical results) confirms the sponsor's interpretation.

2. Analysis of Outliers in Completed 8-Week Depression Trials (SCT-MD-01, -MD-02, 99001 and 99003)

Hematology. Treatment groups demonstrated similar incidences rates of Ss meeting criteria for being potentially clinically significant (PCS) on various hematology parameters, as shown in the table below. The submission does not describe any SAEs or ADOs in the SCT or CT Ss that were due to meeting hematological PCS criteria. One SCT S and 1 placebo S met PCS criteria that were reported to have anemia as a treatment emergent AE. Both Ss had hemoglobin values of 6.7 mmol/l (10 g/dl decreased from approximately 12 g/dl at baseline in the SCT S). PCS criteria were not specified for neutrophils, such that incidence rates for outliers on this parameter were not determined.

Incidence of Subjects Meeting PCS Criteria on Hematology Parameters*				
Hematology Parameter (units)	**PCS Criteria**	**Placebo N=540**	**Escitalopram N=654**	**Citalopram N=363**
Hematocrit (l)	≤0.9 LNL**	1 (0.2)	5 (0.8)	1 (0.3)
Hemoglobin (mmol/l)	≤0.9 LND	8 (1.5)	10 (1.5)	5 (1.4)
Eosinophils (%)	10	5 (0.9)	3 (0.5)	4 (1.1)
Platelet count (g/l)	≤75	3 (0.6)	0	0
White Cell count (g/l)	16	0	1 (0.2)	1 (0.3)
	≤2.8	1 (0.2)	1 (0.2)	0
* This table is similar to Panel 27 in the 120 Update submission. **LNL is lower normal limit of laboratory reference range				

One SCT S (3296 in study 99003) was identified as having a treatment emergent AE of "marrow hyperplasia." However, the Patient Profile that the sponsor provided on this S indicated an elevation of hematocrit (approximately 50 % which appears to be slightly elevated) and hemoglobin at baseline, as well as at treatment endpoint. Her platelet count also increased to 408,000/ul (which appears to be slightly above the upper limit of normal) at treatment endpoint from a count of 277,000/ul at baseline. This S was 58 year old female with chronic obstructive pulmonary disease, whereby she may have a secondary polycythemia (it is not indicated as to whether or not she's a smoker). She also had hyperthyroidism, among other pre-existing medical conditions. There is no indication in the patient profile that a bone marrow biopsy was actually obtained but rather the S was reported as having an AE of elevated blood results. The Preferred Terms selected for this S were "hematology" with "Marrow Hyperplasia". Abnormal hemoglobin and hematocrit at baseline, along with the presence of concomitant medical conditions suggests that this S's abnormal hematology parameters were not drug-related, but rather due to an underlying medical condition.

Chemistry. Overall, treatment groups were generally similar on incidence of Ss meeting PCS criteria. Total billirubin levels appeared to show a numerical trend for higher incidence rates of outliers in the SCT group compared to the placebo group. However, the group difference was small (an incidence of only 1.1% or 7/659 SCT Ss compared to 0.2% or 1/542 of placebo Ss). Furthermore, the CT group showed an incidence (0.3%, 1/364 Ss) similar to that of placebo. Therefore, the clinical relevance or significance of that observed in the SCT group, is unknown. CT or SCT S reported to have SAEs or ADOs due to meeting PCS criteria for chemistry parameters. The following table (similar to that provided in the 120 Safety Update submission)

summarizes incidence rates of chemistry parameters in the four completed 8-week depression trials (SCT-MD-01, SCT-MD-02, 99001 and 99003).

Incidence of Subject Meeting PCS Criteria on Chemistry Parameters				
Chemistry Parameter (units)	**PCS Criteria**	**Placebo N=542**	**Escitalopram N=659**	**Citalopram N=364**
ALT (SGPT) (U/l)	3*UNL	2 (0.4)	2 (0.3)	0
AST (SGOT) (U/l)	3*UNL	2 (0.4)	0	1 (0.3)
Billirubin, Total (umol/l)	34.2	1 (0.2)	7 (1.1)	1 (0.3)
Cholesterol, Total (mmol/l)	7.8	4 (1.8)	7 (2.1)	1 (0.5)
Creatinine (umol/l)	175	0	2 (0.3)	0
Potassium (mmol/L)	5.5	8 (1.5)	10 (1.5)	3 (0.8)
Urea Nitrogen (mmol/l)	10.7	0	1 (0.3)	1 (0.5)
*UNL is upper normal limit of laboratory reference range SCT N=658 for total bilirubin, for total cholesterol, LDH, urea nitrogen, placebo N=222, SCT N=330, CT N=208 (these tests were not conducted in 99001 or 99003), and for sodium SCT N-660. No PCS values were obtained for alkaline phosphatase, LDH, Ca, Na, as described in the submission.				

Urinalysis.

Treatment groups were similar on incidence rates of meeting PCS criteria on glucose and protein urinalysis parameters (an increase in glucose of ≥ 2 was observed in 0.6% of the 327 SCT Ss compared to 0 Ss out of the 221 placebo Ss and 0 Ss out of the 207 CT Ss, elevated protein of ≥2 was observed in 1.5% of SCT Ss compared to 0.5% and 0 of the placebo and CT groups, respectively). There were no SAEs or ADOs due to abnormal urinalysis parameters. Groups were also similar on the mean values for pH and specific gravity parameters.

J. Vital Signs and Body Weight

J.1 Analysis of Central Tendency in Completed 8-Week Depression Trials (SCT-MD-01, -MD-02, 99001 and 99003)

Table VII.J.1, as provided by the sponsor, is in the appendix and shows the mean change from baseline to treatment endpoint of each vital sign parameter and of weight for each treatment group of the four depression trials, combined. Treatment groups were similar on mean baseline and mean change from baseline on the various parameters except for at least, a numerical trend for a small mean decrease in pulse rate when comparing SCT or CT groups to placebo (-1.9 and –2.4 bpm/SCT and CT groups respectively, compared to –0.4 in placebo). Note that the magnitude of this numerical trend was small.

J.2 Analysis of Outliers in Completed 8-Week Depression Trials (SCT-MD-01, -MD-02, 99001 and 99003)

The incidence of outliers on each of the vital sign parameters and on body weight was typically ≤1% or 0% in the SCT or CT groups and similar to that of the placebo group (see Table VII.J.2, as provided by the sponsor in the appendix, which also shows outlier criteria). Incidence of increased body weight reached 2% in the CT group and 1.9% in the SCT group compared to 1.4% in placebo. These group differences are small. There were no Ss in completed trials that had an SAE or ADO due to meeting PCS criteria for abnormal vital signs or weight parameters.