CLINICAL REVIEW

Application Type /Submission #:	NDA 21-323/S-30 (tablets) [redacted] (b) (4) (oral solution)
Submission Code	SE5
Letter Date	5/22/08
Stamp Date	5/23/08
PDUFA Goal Date	3/23/09
Reviewer Name	Roberta Glass, M.D.
Review Completion Date	1/29/09
Established Name	Escitalopram
Trade Name	Lexapro
Therapeutic Class	Selective Serotonin Reuptake Inhibitor (SSRI)
Applicant	Forest Laboratories, Inc.
Priority Designation	S
Formulation	Tablets (5 mg, 10 mg, and 20 mg) and Oral Solution (5 mg/mL)
Dosing Regimen	10 to 20 mg/day
Indication	Major depressive disorder (MDD)
Intended Population	Adolescents (12-17 years old)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that escitalopram be approved for the indication of MDD in the adolescent population at an initial dose of 10 mg qd; this dose may be sufficient for clinical improvement. Some patients may benefit from a dose increase to 20 mg qd, but this upward titration should occur only after a sufficient trial at the lower dose of 10 mg. The labeling may state that safety and efficacy of doses 10 mg and 20 mg escitalopram are demonstrated in the adolescent population.

Because escitalopram has been shown to be effective in the acute treatment of adolescent MDD, current policy allows for the extrapolation of the adult MDD maintenance claim/data to support a maintenance claim in the adolescent population.

It is recommended that any pediatric claim be restricted to adolescents (12-17) and not include children (6-11), because the escitalopram pivotal study includes adolescents only. Even though the pivotal citalopram study supporting this efficacy claim includes children (7-11), the efficacy results strongly suggest that the adolescent group demonstrates a greater benefit of treatment for MDD than the younger aged children. The negative study in escitalopram, which includes both children and adolescents, also demonstrates a greater response in adolescents than children.

Finally, it is recommended that the labeling include language that encourages clinicians to focus on a comprehensive treatment plan of which drug treatment is only one aspect of the effective treatment of MDD in adolescents.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

It is important that the sponsor continue to monitor treatment emergent suicidality in this very vulnerable population of adolescents suffering with major depressive disorder.

1.2.2 Required Phase 4 Commitments

Because escitalopram will obtain labeling for the adolescent population with MDD, it is likely that clinicians will increase their use in younger children off-label. It would be helpful if the sponsor would power a study to assess the efficacy of escitalopram in this younger population.

It is curious that a subgroup analysis revealed that patients categorized as African American did not demonstrate an improvement in MDD symptoms with escitalopram treatment. This observation and the fact that the escitalopram data base was composed primarily of Caucasians (>70%) would suggest that studying adolescents in varied racial background would offer clinicians better guidance for treatment decisions for individual patients.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Escitalopram, the S-enantiomer of the racemic citalopram, is a selective serotonin reuptake inhibitor (SSRI) marketed in the United States since 2002. Escitalopram is labeled for two indications: 1) the acute and long term treatment of patients with **major depressive disorder (MDD),** and 2) **generalized anxiety disorder (GAD)**; both indications are limited to the **adult** population. This current application proposes to expand the labeling to include **adolescents** for the indication of **MDD.**

To fulfill the requirement of two placebo-controlled studies to support efficacy of pediatric MDD for escitalopram, FDA agrees to accept one positive pivotal study in citalopram (Study 18) and one positive study in escitalopram (Study 32). Because Study 32 is in adolescents only, and the positive efficacy results of Study 18 are primarily in the adolescent treatment group, the recommended pediatric claim is limited to treating MDD in adolescents. Current FDA policy allows for long term pediatric claims based on adult MDD maintenance claim data once acute pediatric treatment is established as efficacious; therefore, the labeling may be eligible for an adolescent MDD maintenance claim based on the extrapolation of adult data.

Study 32 is an 8 week, double-blind, placebo-controlled, adolescent (12-17), flexible dose (10-20 mg/d escitalopram) study. **Study 18** is an 8 week, double-blind, placebo-controlled, flexible dose (citalopram 20-40 mg/d) study in children (7-11) and adolescents (12-17). The following two studies included in this current submission can't be used to support efficacy claims, but did contribute to the escitalopram adolescent safety data base: 1) **Study 15**, an 8 week, placebo-controlled study in children and adolescents has negative results, and 2) **Study 32A,** a 16-24 week extension study has uninterpretable results due to design flaws.

In the **escitalopram** adolescent safety data base (Studies 15 and 32; Study 32A is an extension study of 32), there are 135 females (or 57.7%), and 99 males (42.3%) with a mean age of 14.6 years (± 1.6) exposed to escitalopram. A total of 210 patients (181 adolescents) received **escitalopram** for at least 8 weeks, and 53 patients (all adolescents) received **escitalopram** for at least 24 weeks.

In the **citalopram** pediatric safety data base, 211 patients (154 adolescents) received **c**italopram for at least 8 weeks, and 66 patients (30 adolescents) received **citalopram** for at least 24 weeks. The sponsor concludes that the **escitalopram/citalopram** safety data base includes 83

adolescents (of 119 pediatric patients) who were exposed for up to 24 weeks of **escitalopram** or **citalopram**.

1.3.2 Efficacy

For the primary efficacy variable, the Children's Depression Rating Scale-Revised (CDRS-R), the sponsor demonstrates a statistically significant difference in change from baseline when comparing escitalopram treatment with placebo using the ANCOVA model for both Study 32 (escitalopram: p=0.022) and Study 18 (citalopram: p=0.038).

The key secondary efficacy variable established is the CGI-I, a clinician-rated instrument used to rate the total improvement or worsening in a patient's mental illness, based on the Investigator's clinical opinion. Study 32 (escitalopram) demonstrates statistically significant difference in change from baseline when comparing escitalopram treatment with placebo using the ANCOVA model for the CGI-I (p=0.008); however, Study 18 (citalopram) doesn't demonstrate statistical significance for this efficacy variable.

There are less than 25% of non-Caucasians in the data base; a subgroup analysis conducted by FDA statistician suggests that patients categorized as African American don't demonstrate an improvement in CDRS-R scores with escitalopram treatment.

1.3.3 Safety

The safety data base for this review is primarily limited to the escitalopram in the placebo-controlled studies in adolescents with MDD. Overall, the safety profile in this supplement was consistent with current labeling. Many of the safety concerns that arose with this supplement NDA data base are discussed in the marketed adult labeling for escitalopram.

Of continuing concern is the higher incidence of treatment emergent suicidal gestures/events in the treatment group compared to placebo; this phenomenon is recognized for all anti-depressant use in the pediatric population, and has resulted in a black box warning of suicide in all anti-depressants labeling.

Another phenomenon observed in this safety data base, already recognized in the adult labeling, is a QTc prolongation of 3-4 msec.

1.3.4 Dosing Regimen and Administration

Escitalopram (Lexapro®) is currently labeled for the indication of major depressive disorder and generalized anxiety disorder; both indications are currently **limited to the adult population.**

For **major depressive disorder**, the recommended dose is 10 mg daily at morning or night with or without food; this dose can be titrated up to 20 mg daily after a one week trial of the lower dose. It is noted that in clinical studies, the treatment using 20 mg daily did not show a more significant improvement in treatment than the 10 mg daily use. The labeling supports longer term use of 10 or 20 mg/day for maintenance treatment of major depression, with supporting data of up to 36 weeks treatment exposure.

For **generalized anxiety disorder (GAD)**, the recommended starting dose is 10 mg daily. If the dose is to be increased to 20 mg daily, this should occur after one week at the lower dose. Longer term maintenance treatment for GAD is not supported by the current label.

In the proposed labeling for this submission, the sponsor adds the indication of **major depressive disorder (MDD) in adolescents** aged 12 to 17. The proposed labeling states that the recommended starting dose for escitalopram in adolescents is 10 mg once daily. It recommends that clinical treatment at this lower dose continue for a minimum of 3 weeks prior to titrating upward to 20 mg daily.

1.3.5 Drug-Drug Interactions

The concomitant use of escitalopram with MAOIs is contraindicated. As an SSRI, escitalopram should be used with caution with drugs that affect hemostasis (e.g. NSAIDs, aspirin, warfarin), and other serotonergic drug (e.g. triptans, linezoilid, lithium, tramadol, St. John's Wort, other SSRIs, SNRIs, and typtophan). Caution is also recommended when co-administering escitalopram with any CNS drug or alcohol.

1.3.6 Special Populations

For the special populations of elderly and hepatically impaired patients, the recommended escitalopram dose is 10 mg daily. As with other SSRIs or SNRIs, use of escitalopram in pregnant women during the third trimester may cause neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding; this information has warranted a **Precaution** to use only if the benefits out weigh the risks.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Escitalopram is a selective serotonin reuptake inhibitor (SSRI), and has been marketed in the United States since 2002. It is the S-enantiomer (single isomer) of the racemic derivative citalopram (marketed by Forest as Celexa®). Escitalopram is labeled for two indications: 1) the acute and long term treatment of patients with **major depressive disorder (MDD),** and 2) **generalized anxiety disorder (GAD)**; both indications are limited to the **adult** population. This current application proposes to expand the labeling to include **adolescents** for the indication of **MDD.**

This submission includes two short-term, placebo controlled MDD pediatric studies with the study drug escitalopram; only one of these studies has positive results. The sponsor also presents two short-term, placebo controlled, pediatric studies using the racemic derivative, citalopram, as the study drug. As with escitalopram short-term pediatric studies, only one of the citalopram studies has positive results. (b) (4)

citalopram is not labeled for use in children or adolescents. Because they had conducted the two pediatric studies in the racemic citalopram in response to an FDA issued Written Request, the sponsor received pediatric exclusivity for citalopram and escitalopram in 2002. The sponsor reached an agreement with FDA that a pediatric claim for escitalopram, an isomeric version of citalopram, could be obtained with the support of one positive pediatric study in escitalopram in addition to the one positive study in citalopram. (please see regulatory history Section 2.5 for further details).

In this submission, the sponsor submits longer term escitalopram MDD study in adolescents to support a maintenance claim in this population (Study 32A); however, there are several flaws with this longer term study, deeming the results uninterpretable. More recent regulatory policy allows for a pediatric maintenance claim to be extrapolated from adult data if the following two conditions are met: 1) short term pediatric efficacy is demonstrated in two acute placebo controlled studies, and 2) efficacy has been established for adult longer term treatment.

2.2 Currently Available Treatment for Indications

Currently there is only one drug, fluoxetine (Prozac®), able to demonstrate efficacy in two placebo-controlled studies in the pediatric (children and adolescent) population for the indication of MDD. Fluoxetine is currently the only drug labeled in the U.S. for the treatment of pediatric MDD. There are many anti-depressants marketed in the U.S. that are used off-label to treat MDD in the pediatric population.

2.3 Availability of Proposed Active Ingredient in the United States

Escitalopram (Lexapro®) has been marketed in the United States since 2002. It is currently available in tablet and oral solution formulations.

2.4 Important Issues With Pharmacologically Related Products

Escitalopram shares class label warnings with the SSRIs, SNRIs, and general warnings of anti-depressants. (please refer to the current labeling for more details).

2.5 Pre-submission Regulatory Activity

On April 18, 2002, Forest submitted two pediatric studies assessing the safety and efficacy of citalopram in the use of pediatric MDD in response to an FDA Written Request dated 4/28/99. (b) (4) on July 12, 2002, pediatric exclusivity was awarded to both citalopram (Celexa®) and it's isomer, escitalopram (Lexapro®).

As summarized in the meeting minutes of 10/30/07 (Grewal/Laughren: 11/6/07), a letter from FDA Division of Psychiatric Products (DPP) to Forest Laboratories dated September 23, 2002, confirms that Study CIT-MD-18, a pediatric MDD study with citalopram, is considered positive. In addition, a letter from DPP to Forest Laboratories dated January 31, 2003, confirms that one positive study with racemate citalopram (Study CIT-MD-18) and one positive study with the enantiomer escitalopram (Study SCT-MD- 15) in pediatric patients is sufficient to support a claim for escitalopram use in pediatric patients with MDD.

Study SCT-MD-15 has negative results, and can't be used to support a pediatric MDD claim. In a letter (August 2, 2004), Forest Laboratories requests DPP's input and agreement on potential designs of a proposed new study to support escitalopram use to treat adolescent patients (12-17 years) with MDD. On November 16, 2004, the Division confirms that one additional positive acute treatment study with escitalopram in adolescents, in addition to Study CIT-MD-18, is adequate evidence to support a labeling claim that escitalopram is an effective acute treatment of MDD in adolescents. Thus, Study SCT-MD-32 in adolescent patients was initiated in February 2005.

Also in the meeting minutes of 10/30/07, DPP expresses concern that the protocol design of extension Study 32A can't support a long term claim in pediatric MDD, because patients aren't re-randomized at the beginning of Study 32A (after the completion of Study 32).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No new information was submitted in this NDA.

3.2 Animal Pharmacology/Toxicology

No animal studies were submitted with this NDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of data in this review are the clinical trials submitted by the sponsor (original submission: 5/22/08 and Safety Update: 9/1/08). For other submissions during this review period, please refer to the following EDR link:

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Also considered were the following FDA reviews:

Statistical Review and Evaluation of Escitalopram for MDD; NDA 21-323/ S-030, S-031; 21-365/ S-021, S-022. by George Kordzakhia, Ph.D. (1/28/09).

Pregnancy and Nursing Mothers labeling Lexapro (escitalopram oxylate), NDAs 21-323/S-030,031 and 21-365/S-021,022. by Jeanine Best, MSN, RN, PNP (draft: January, 2009).

Statistical Review and Evaluation for IND 58,380 (escitalopram) of Trial SCT-MD-32A by Yeh-Fong Chen, PhD (10/19/07).

Memorandum: Consult: Suicidality in pediatric clinical trial with paroxetine and other antidepressant drugs by Andrew D. Mosholder, M.D., M.P.H. (9/4/03).

(b) (4)

Review and Evaluation: NDA 20822 (Celexa) by Earl D. Hearst, MD (9/12/02).

4.2 Tables of Clinical Studies

Please refer to the Table 4.2 below for a summary of all studies submitted in this current application.

Study 32 is the only study reviewed for efficacy in this review. Study 18 (review by Dr. Hearst: 9/12/02) supports the escitalopram efficacy claims for the acute treatment MDD in adolescents. The sponsor proposes that Study 32A can support the efficacy claims of maintenance treatment of MDD in the adolescent population; however, due to design flaws, Study 32A is limited to support the safety of escitalopram only. Please refer to the Table 4.2 below for a summary of all studies in the sponsor's current submission.

Table 4.2 Summary table of all studies submitted in current application

STUDY	DESIGN	POPULATION	RESULTS
ESCITALOPRAM PEDIATRIC STUDIES—SHORT TERM PLACEBO CONTROLLED			
Study SCT-MD-32 40 US Centers	8 week double-blind, pbo-controlled, flex dose (10-20 mg/d) escitalopram 1° efficacy variable: CDRS Δ from baseline to 8th week; (CDRS: Children's Depression Rating Scale – Revised). 2° efficacy variable: CGS-S, CGI-I, CGAS, K-SADS.	Adolescents (12-17) with MDD Pbo: n=*155/126* Escit: n=*157/133* (*entered/ completed*) Mean age: 14.5	1° efficacy variable *Pbo:* -18.4± 1.1 *Cit:* -22.4 ± 1.1 **p=0.022** 2° efficacy variable: CGI-I: **p=0.008**
Study SCT-MD-15 25 US Centers	8 week, double blind, pbo controlled, flexible dose, escitaloprm 10-20 mg/d 1° efficacy variable: CDRS Δ from baseline to 8th week;	Children/adoles. (6-17) with MDD All Patients: Pbo: n=*133/115* Escital: n=*131/102* Subset of Adolescents: Pbo: n=81 Escital: n=79 Mean age: 12.3	**NEGATIVE** study results Pbo: -20.3±1.3 Escital: -20.9±1.3 **Greatest improvement in 12-17 y.o.**
LEXAPRO PEDIATRIC STUDIES—LONGER TERM PLACEBO CONTROLLED			
SCT-MD-32A 35 US Centers	fixed dose (10 or 20 mg/d) extension study of Study 32 Adolescent patients with MDD. Originally a 24 week open label study, several amendments later, it changed to a 16 week pbo controlled study .	Open label: n=*37/22* (escital: n=19; pbo: n=18) Double blind n=165	Results **uninterpretable** -Patients not re-randomized at beginning of study.

STUDY	DESIGN	POPULATION	RESULTS
	1° efficacy variable: Originally, time to premature discontinuation. Amended to CDRS Δ from baseline (visit 3 of Study 32) to 24th week (visit 9 of Study32A) 2° efficacy variable: Originally, Family Interaction (estimated with the McMaster Family Functioning Subscale) Amended to CGI-I score at Treatment Week 24.	(escital: n=*83/37*; pbo: n=*82/40*) Mean age =14.6	-design changed during study -high withdrawal rate
CITALOPRAM PEDIATRIC STUDIES—SHORT TERM PLACEBO CONTROLLED			
Study CIT-MD-18 (Originally submitted: 4/18/02) 21 US Centers	8 week double-blind, pbo-controlled, flexible dose citalopram (20-40 mg/d) study. 1° efficacy variable: CDRS Δ from baseline to 8th week; 2° efficacy variable: CGS-S, CGI-I, CGAS, K-SADS.	Children/adolescents (7-17) with MDD. Pbo group: n=38 (7-11yo) n= 47 (12-17) Cit group n=*45/36* (7-11) **n=***44/35* **(**12-17) Mean age = 12 years	1° efficacy variable *Pbo:* -16.5 ± 1.6 *Cit:* -21.7 ± 1.6 **p=0.038** **Greatest improvement in 12-17 y.o.**
Study 94404 Originally submitted: 4/18/02) 31 International sites	12 week double-blind, placebo controlled, flexible dose (10-40 mg/d) 1° efficacy variable: Kiddie-SADS-P Δ from baseline to 8th week;	Adolescents with MDD	**Negative study:** Improvement in both placebo and citalopram groups.

4.3 Review Strategy

There is only one study, Study 32, reviewed to evaluate efficacy data supporting the sponsor's escitalopram efficacy claim for the acute treatment of Major Depressive Disorder in the adolescent population. The other study, Study 18, (b) (4) was previously reviewed (Hearst: 9/12/02), and summary results are presented.

The safety data base for escitalopram in adolescents with MDD consists of two acute placebo controlled studies, Studies 32 and 15, in addition to the longer term extension Study 32A.

4.4 Data Quality and Integrity

According to internal FDA communications with DSI, there have been two inspection sites investigated. Both sites are determined to be acceptable to be considered for efficacy data. The formal DSI report is pending at the time of this review.

4.5 Compliance with Good Clinical Practices

According to internal FDA communications with DSI, the DSI report investigating two study sites find no violations that would compromise the efficacy findings of the pivotal study reviewed in this submission. The formal DSI report is pending at the time of this review.

4.6 Financial Disclosures

Executive Vice President and CMO of Forest Laboratories, Inc signed the Form 3454 testifying that, to his knowledge, there were no financial arrangements made with investigators that could affect the outcome of the studies as defined in 21 CFR 54.2 (a), and that no listed investigator (attached to the form) was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f) for the listing of investigators attached to each 3454.

The sponsor reports the following three investigators as having relevant financial disclosures:

1. (b) (4), investigator for Study (b) (4) This investigator owned 1,000 shares of Forest Laboratories stocks on November 18, 2002 with shares valued at $106.10 per share ($106,100);

2. (b) (4) sub-investigator, (b) (4) for (b) (4) received $37,515.00 to conduct an investigator initiated trial on the relationship between immune function and depression;

3. (b) (4), sub-investigator for (b) (4) received a total of $20,200.00, honoraria for speaking on behalf of Forest Laboratories Inc.

Although (b) (4) is the investigator for one of the larger sites for (b) (4), this is one of (b) (4) other sites in this placebo-controlled study. Because (b) (4) is double-blind placebo-

controlled, multi-centered with multiple investigators at each site, and that the sponsor analyzed each site's effect on the overall efficacy results, the sponsor has concluded that none of the financial disclosures above affected the study outcome results.

Studies 15 and 32A weren't used to support labeling claims; therefore, the financial disclosures listed for these studies need not be addressed for purposes of this review.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Escitalopram has a mean terminal half-life of about 27-32 hours with mainly hepatic biotransformation and renal clearance. In vitro studies using human liver microsomes indicate that CYP3A4 and CYP2C19 are the primary isozymes involved in the demethylation of escitalopram. The single and multiple dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10-30 mg/day. With once-daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of escitalopram in young healthy subjects was 2.2-2.5 times the plasma concentration observed after a single dose. Absorption of escitalopram is not affected by food.

5.2 Pharmacodynamics

Escitalopram is the S-enantiomer of racemic citalopram. In vitro and in vivo studies in animals suggest that escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake. Escitalopram is thought to be more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Escitalopram has no or very low affinity for serotonergic or other receptors including alpha- and beta-adrenergic, dopamine, histamine, muscarinic, and benzodiazepine receptors.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication for this supplement NDA is major depressive disorder (MDD) in the adolescent population. The current labeling for escitalopram includes the treatment of MDD in adults. DSM IV defines a major depressive episode as a relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes as least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor

agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

To date, the DSM IV doesn't make a diagnostic distinction between adult and adolescent symptomatology for MDD.

6.1.1 Methods

For the purposes of determining the efficacy of escitalopram for the treatment of MDD in adolescents, the following two positive studies are considered the pivotal studies supporting the proposed indication:

1. **Study 32** – an 8 week, double-blind, placebo-controlled, **adolescent** (12-17), flexible dose (10-20 mg/d escitalopram) study:
   Entered: n=312;
   Completed: n=259: pbo: n=126 (81%)
   escitalopram: n=133 (85%)

2. **Study 18**- an 8 week double-blind, placebo-controlled, flexible dose (citalopram 20-40 mg/d) study in children (7-11) and adolescents (12-17):
   Children:
   Entered: n=83
   Completed: n=66: pbo: n=30 (78.9%)
   citalopram: n=36 (80%)
   Adolescents:
   Entered: n=91
   Completed: n=72: pbo: n=37 (78.7%)
   citalopram: n=35 (79.5%)

The other studies submitted in this escitalopram application can't be used to support efficacy in the proposed labeling. They include **Study 15** and **Study 32A**. Study 15 has negative results showing a statistically insignificant difference between placebo and study drug. The results of Study 32A are uninterpretable due to the following flaws in the study design: a) patients are not randomized at the beginning of this extension study (after completing the acute term Study 32), and b) the study design changes during the study from being open label to placebo controlled.

Because Study 15 and Study 32A can't be used to support labeling claims, they aren't reviewed for efficacy. However, they are included in the escitalopram safety data base for the adolescent population.

6.1.2 General Discussion of Endpoints

The primary efficacy variable of Study 32 is the Children's Depression Rating Scale-Revised (CDRS-R). The CDRS-R is a semi-structured, clinician-rated instrument designed for use with children and adolescents between the ages of 6-17 years. It contains 17 ordinally scaled items used to evaluate the presence and severity of symptoms commonly associated with depression in childhood. According to the protocol, the CDRS-R is administered separately to the patient and to the identified parent or caregiver.

The key secondary efficacy variable of Study 32 is the CGI-I. The CGI-I is a clinician-rated instrument used to rate the total improvement or worsening in a patient's mental illness, based on the Investigator's clinical opinion. The score ranges from 1 to 7, with 1 being very much improved and 7 being very much worse, relative to baseline. Scoring is independent of whether the Investigator considers any changes due to treatment with the study drug.

6.1.3 Study Design

6.1.3.1 Study **32**

Investigators/Location

This study is conducted in 40 study centers in the United States of which 38 centers randomized patients.

Objective(s)/Rationale

The objective of the study is to assess the safety and efficacy of escitalopram in the treatment of major depressive disorder in the adolescent population.

Population

Included in the study are physically healthy, adolescent outpatients (12-17 y.o.) with a diagnosis of a current major depressive episode for at least 12 weeks. Patients are required to have a CDRS-R score of ≥ 45, CGI score of ≥ 4, and IQ score ≥ 80 at the beginning of the double blind portion of the study. Female patients must have a negative serum pregnancy test, and, if sexually active, are required to use a reliable method of birth control.

Excluded from the study are patients who have any concomitant psychiatric diagnosis, psychotic symptoms, are a suicide risk, or have a history of the following: substance abuse/dependence with in the past year, positive urine drug screen, first degree relative with bipolar disorder, seizures.

No antidepressant or anxiolytic medications are allowed for 2 weeks prior to the study. Fluoxetine must be terminated 4 week prior to the study, and patients may not be treated with any neuroleptic or stimulant for 6 months prior to the study.

Neither psychotherapy nor behavioral therapy are allowed to be started within 3 months prior to the study, and no changes in talking therapy may be done during the study.

Design

This is a double blind, randomized, placebo-controlled, flexible dose (10-20 mg escitalopram), 8 week study. The study is preceded by a 2 week screening period, which includes a single-blind placebo lead-in during the second week. The study ends with a one week double blind tapering schedule.

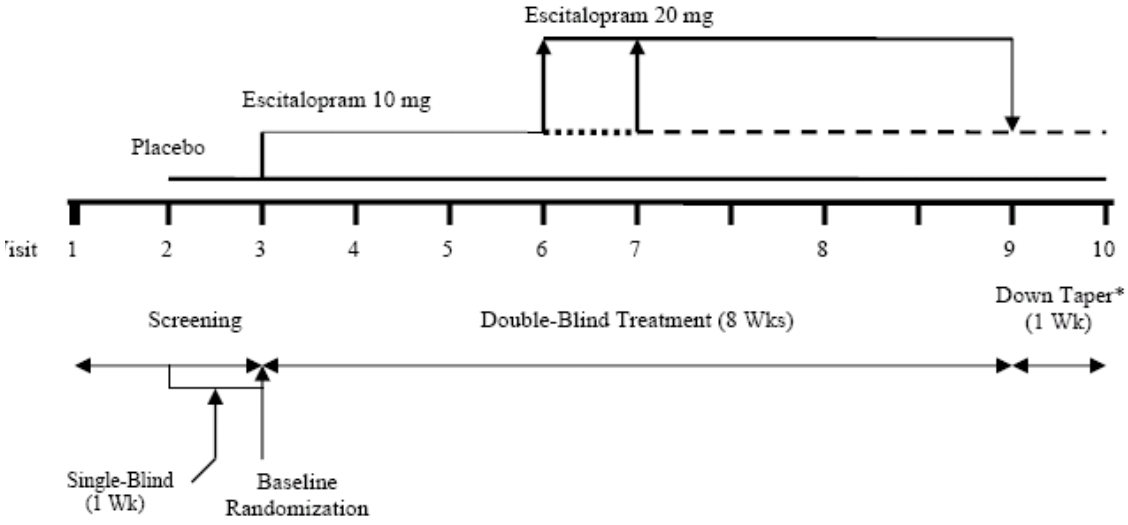
It is unclear if a psychiatric interview was conducted to make the diagnosis of MDD. In the protocol, it states that psychiatric history was collected, and that two different clinicians must be in agreement regarding the findings from two structured interview questionnaires (the K-SADS-PL and the KBIT). However, it appears that the diagnosis was not made during a clinical interview.

After the one week placebo lead in, patients are then randomized to either escitalopram or placebo group. All patients in the escitalopram group are given 10 mg escitalopram for the first 3 weeks, and then at Week 3 or 4, and upon investigator evaluation of each patient for dose limited adverse events, the dose of escitalopram could be increased to 20 mg daily. The dose given at Week 4 (i.e. 10 or 20 mg) is continued for the remainder of the study; if adverse events occur, patients may return to the 10 mg dose.

An optional "down taper" week is available for patients who chose to not enter the extension study or who terminate the study prematurely. During this period, patients are given either 10 mg escitalopram or placebo, depending on their randomized assignment group at the beginning of the study.

All medication are administered as one tablet daily at evening, but can be switched to morning time.

Figure 6.1.3.1a Sponsor's schematic of the study design for Study 32



* Optional for patients not continuing into the extension study

Analysis Plan

The primary efficacy variable is the change from baseline to week 8 of the CDRS-R total score. The primary analysis is performed using the LOCF approach. Comparison between escitalopram and placebo is performed by a two way ANCOVA model with treatment group and study center as factors and baseline CDRS-R as a covariate. The secondary efficacy variable is the CGI-I at Week 8.

A history and physical is conducted at screening. At screening and termination, the following evaluations are done: routine lab, serum pregnancy tests, thyroid function test, UDS, and ECG. Vitals are assessed weekly throughout the study. Please see Appendix 1 for the sponsor's Schedule of Events.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 584 patients screened for the study, 316 patients are randomized into double-blind treatment. Reasons given for ineligibility include the following: entry criteria not met (n=201), adverse event (n=1), protocol violation (n=5), lost to follow-up (n=17), withdrew consent (n=37), and "other" (n=7). Of the 316 patients in the intent-to-treat population, there are 4 patients who withdrew before the first dose, and aren't considered part of the efficacy or safety population. Therefore, 312 patients are in the efficacy/safety population; however, there are 311 patients in the ITT with at least one post-baseline CDRS-R assessment. Of the 157 patients

randomized to placebo, 133 (85%) completed the study; of the 155 patients randomized to escitalopram treatment, 126 (80%) completed the study. Table 6.1.3.1b (below) summarizes the reasons for early withdrawal.

As can be seen from Table 6.1.3.1b, discontinuations due to adverse events are more prevalent in the escitalopram group compared to the placebo group. Otherwise, there are no statistically significant difference between the escitalopram and the placebo groups with regard to reasons for early withdrawal.

Table 6.1.3.1b Reasons for early withdrawal for Study 32
(sponsor table from Study 32 study report)

	Placebo (N = 157) n (%)	*Escitalopram (N = 155) n (%)*	*Total (N = 312) n (%)*
Prematurely discontinued	24 (15.3)	29 (18.7)	53 (17.0)
Reason for discontinuation			
Adverse event	1 (0.6)	4 (2.6)	5 (1.6)
Insufficient therapeutic response	5 (3.2)	5 (3.2)	10 (3.2)
Protocol violation, including lack of compliance	0	3 (1.9)	3 (1.0)
Withdrawal of consent	9 (5.7)	8 (5.2)	17 (5.4)
Lost to follow-up	6 (3.8)	8 (5.2)	14 (4.5)
Other	3 (1.9)[a]	1 (0.6)[b]	4 (1.3)

Demographics /Group Comparability

The majority of the patients in this study are Caucasian females with a mean age of 14.6 years old (range of 13 to16). The population consists of 184 females (59%) and 128 (41%) males of which there are 236 (75.6%) Caucasians, 54 (17.3%) African-Americans, 3 (1 %) Asian, and 19 (6.1%) "other." The sponsor reports that there are no statistically significant differences between the treatment groups with respect to demographics.

Concomitant Medications

Concomitant medications used most frequently include the sponsor's general categories of "analgesics" and "anti-inflammatory and anti-rheumatic products" (the sponsor does not provide the specific medications within these categories); both these categories appear to be used comparably in both the placebo and escitalopram group. It is noted that "drugs for acid related disorder" and "sex hormones and modulator of the genital systems" are used by more patients in the escitalopram group than in the placebo group; however, this trend is also observed at baseline (see 6.1.3.1c below). It is unclear what the sponsor is referring to as "psycholeptics" which were used by 5.2 % (n=8) of escitalopram patients and 4.5 % (n= 7) of placebo patients.

Table 6.1.3.1c Notable differences in concomitant medications:

MEDICATION GROUP	BASELINE		DURING STUDY	
	Escitalopram (n=155)	Placebo (n=157)	Escitalopram (n=155)	Placebo (n=157)
Drugs for acid related disorders	10 (6.5%)	2 (1.3)	14 (9.0)	7 (4.5)
Sex hormones and modulators of the genital system	15 (9.7)	8 (5.1)	15 (9.7)	9 (5.7)

Efficacy Results

The sponsor reports a statistically significant difference (p-0.022) comparing the escitalopram and placebo groups in change from baseline to Week 8 of the primary efficacy instrument, the CDRS-R total score. The sponsor also reports a statistically significant difference comparing the two treatment groups in the change from baseline to Week 8 in the CGI-I score, the key secondary variable (p=0.008). These findings are verified and supported by the FDA statistical reviewer, Dr. George Kordzakhia (1/28/09). Dr. Kordzakhia also confirms the sponsor's analysis for the primary efficacy variable using the mixed-effects model for repeated measures (MMRM); his findings again support the primary analysis results.

Of the 154 intent-to-treat patients treated by escitalopram, 54 had 10mg on their last visit, and 100 patients received 20mg on their last visit.

In a subgroup analysis, Dr. Kordzakhia notes that patients categorized as African American did not demonstrate an improvement in the primary efficacy variable with escitalopram treatment (see Table 6.1.3.1d).

Table 6.1.3.1d Subgroup Analysis: CDRS-RS Total score mean change from baseline with missing values imputed by LOCF method (adapted from Statistical Review and Evaluation by George Kordzakhia, Ph.D., draft: 1/28/09)

Subgroup	**Placebo**		**Escitalopram**		**Treatment Difference: Escitalopram - Placebo**	
	N	LS Mean (SE)	N	LS Mean (SE)	LS Mean (SE)	95% CI
Gender						
Male	65	-18.75 (1.70)	62	-21.84 (1.74)	-3.09 (2.45)	(-7.93, 1.75)
Female	92	-18.81 (1.36)	92	-22.25 (1.36)	-3.44 (1.93)	(-7.24, 0.37)
Race						
White	123	-17.90 (1.19)	112	-22.73 (1.25)	-4.83 ((1.72)	(-8.23, -1.43)
African American	24	-24.74 (2.39)	30	-18.38 (2.13)	6.36 (3.26)	(-0.17, 12.90)
Other	10	-18.22 (5.29)	12	-22.90 (4.83)	-4.67 (7.17)	(-19.67, 10.32)

Conclusions for Study 32

The statistical results of this study support the sponsor's claim that escitalopram is effective in the treatment of major depressive disorder (as defined in this protocol) in the adolescent population.

One possible flaw in this study is that it is unclear if a psychiatric interview was conducted to make the diagnosis of MDD. In the protocol, it states that psychiatric history was collected, and that two different clinicians must be in agreement regarding the findings from two structured interview questionnaires (the K-SADS-PL and the KBIT). However, it appears that the diagnosis was not made by a clinical interview with a trained clinician.

6.1.3.2 **Study 32A**

Study 32A is presented by the sponsor to support the labeling for a longer term use of escitalopram to treat MDD in the adolescent population.

Because of major flaws in the design of Study 32A, it can't be used to support efficacy labeling claims. Study 32A was originally designed as a 24 week open-label, flexible-dose, extension study. After the study began and patient data was collected, the protocol was amended several times to evolve into a 16 week, double blind, placebo controlled, extension study.

Most importantly, the study design doesn't re-randomized patient assignment at the beginning of Study 32A after completing Study 32. As Dr. Chen points out in her SAP review (10/10/07), when the data of the acute phase (Study 32) is combined with the long-term phase (Study 32A), coupled with a high drop out rate, the maintenance effect would be confounded with the acute effect. Study 32A has an almost 75% drop out rate for both treatment groups (Kordzakhia, 1/28/09).

Because of the high drop out rate, and that patients are not re-randomized prior to beginning Study 32A, the data for this study is considered uninterpretable.

6.1.3.3 **Study 15**

Study 15 is a double-blind, placebo-controlled, flexible dose (10-20 mg/d **escitalopram**), 8 week study in children and adolescents (aged 6-17) diagnosed with MDD. There are 263 participants in this study (129 on escitalopram), with a mean age of 12.3 years. This study doesn't demonstrate a statistical significance (p=0.084) when comparing the treatment groups' change from baseline to eight weeks of the primary efficacy variable (CDRS-R). Therefore, this is considered a negative study and isn't reviewed for efficacy. Study 15 is included in the safety

data base. It's noted that the sponsor's post-hoc analysis by age revealed that the adolescent (12-17) group demonstrates a greater improvement in the primary efficacy variable than patients under 12 y.o.

6.1.3.4 **Study 18**

In April, 2002, Study 18 (b) (4) **citalopram**, the racemic mixture which includes escitalopram. Dr. Earl Hearst, FDA clinical reviewer, reviewed this positive study, in addition to the negative Study 94404 (9/12/02). (b) (4) Later it was determined that Study 18 could used as one of the two positive studies required to support pediatric labeling for escitalopram (an isomer of citalopram) in the treatment of MDD (DPP letter of 11/16/04).

Study 18 is an 8 week, randomized, double-blind, placebo-controlled, flexible dose citalopram (20-40 mg/d) study conducted in 160 pediatric patients (aged 7-17) diagnosed with MDD. The treatment groups are stratified for age group (children: 7-11 and adolescents: 12-17). The primary efficacy variable is the change from baseline to 8 weeks comparing the placebo and citalopram groups on the Children's Depression Rating Scale-Revised (CDRS-R). As discussed in Dr. Hearst's review (9/12/02), the placebo group included 38 patients aged 7-11 y.o. and 47 patients 12-17 y.o. The mean age in both treatment groups is 12 y.o. with the majority of patient being female (53% for citalopram and 54 % for placebo) and Caucasian (81% and 73%, respectively). The following is a further breakdown of the patient population by age:

Children (7-11):
Entered: n=83
Completed: n=66: pbo: n=30 (78.9%)
citalopram: n=36 (80%)

Adolescents (12-17):
Entered: n=91
Completed: n=72: pbo: n=37 (78.7%)
citalopram: n=35 (79.5%)

The study is positive for the primary efficacy variable of change from baseline of the CDRS-R total Score (p=0.038). As can be seen from Table 6.1.3.4, there is a greater improvement for the adolescent group than the children group when comparing the differences to placebo. As Dr. Laughren notes in his memo of 9/16/02, "…it appears that the positive results for this trial are coming largely from the adolescent subgroup."

Table 6.1.3.4 Summary of primary efficacy variable for Study 18 by age subgroups
(extracted from Memorandum by Laughren: 9/16/02).

Efficacy Results (Children) on CDRS-R Total Score for Study CIT-MD-18 (LOCF)

	Mean Baseline CDRS-R	Mean O baseline CDRS-R
Citalopram	**60.0**	**-20.9**
Placebo	**56.8**	**-17.1**

Efficacy Results (Adolescents) on CDRS-R Total Score for Study CIT-MD-18 (LOCF)

	Mean Baseline CDRS-R	Mean O baseline CDRS-R
Citalopram	**57.5**	**-22.6**
Placebo	**58.6**	**-15.4**

6.1.4 Efficacy Conclusions

Study 32 has positive results supporting the labeling claim that escitalopram is an effective acute treatment for adolescents diagnosed with major depressive disorder (MDD). It is noted that the other acute escitalopram study (Study 15) has negative results.

There are several medications effective in treating adults with MDD that haven't been able to prove effective in the pediatric population in the required placebo-controlled design. Because of the paucity of positive pediatric studies in MDD, DPP requires two positive studies in the pediatric population to support a labeling claim for MDD in children and adolescents.

It is agreed between the sponsor and FDA that the one positive citalopram, placebo-controlled, study in the pediatric population diagnosed with MDD can be used to support labeling claims for escitalopram. The rationale behind this agreement rests in the concept that escitalopram in the S-isomer of the racemic compound citalopram.

Study 32A, submitted by the sponsor to support a maintenance claim for adolescents, has uninterpretable results due to design flaws. However, a long term claim in the adolescent population can be extrapolated from adult data, because the following conditions have been met: 1) short term pediatric efficacy is demonstrated in two acute placebo controlled studies, and 2) efficacy has been established for adult longer term treatment.

In conclusion, given the positive results of the escitalopram Study 32, and the citalopram Study 18, the sponsor has fulfilled FDA requirements to support the claim that escitalopram is effective in the treatment of acute treatment of MDD in the adolescent population. Longer term maintenance claim in for the adolescent population is supported by extrapolation from adult data.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This safety review focuses on the sponsor's escitalopram (Lexapro®) safety data base for pediatric patients diagnosed with major depressive disorder (MDD). In their current application, the sponsor includes data from the racemic compound, citalopram (Celexa®). The safety data base from the pediatric citalopram placebo-controlled and pharmacokinetic studies were previously reviewed in depth by FDA (see Hearst: 9/12/02) and has a safety profile consistent with the label for the adult MDD indication. This review will include only significant findings in the pediatric citalopram longer term open label extension Studies 18 and 19, and make mention of any significant findings in the pediatric citalopram studies previously reviewed.

The cut-off date for this safety data base is December 31, 2007. All the escitalopram and citalopram studies considered for this pediatric claim have completion dates prior to this submission. The safety update covers the period of January to May, 2008, and includes pediatric data from post-marketing spontaneous reports (see Section 7.2.9 below).

7.1.1 Deaths

There are no deaths reported in this pediatric safety data base.

7.1.2 Other Serious Adverse Events (SAE)

Table 7.1.2a, below, summarizes the incidence of serious adverse events in the pediatric MDD population exposed to escitalopram (Celexa®). As can be seen from this table, there doesn't appear to be any significant findings when comparing escitalopram and placebo groups.

In the citalopram safety data base, the most common SAE for the citalopram placebo controlled study 944404 was suicide attempt (citolopram: n= 13 pbo: n=4). In addition to these cases, the sponsor reports one placebo and one citalopram patient with suicidal ideation or tendency. In the citalopram extended long term study 20, there is one ECG abnormality noted (no details provided in ISS).

Please see Table 7.1.2b, below, for the sponsor's summary table of SAEs in the escitalopram safety data base. Narratives of these cases reveal 4 escitalopram SAEs attributed to suicidal gestures or attempts, and 1 patient hospitalized for increased irritability; 5 placebo patients have SAE of suicidal gestures/attempts and 1 SAE of increased depression

Table 7.1.2a Incidence of Adverse Events in the pediatric escitalopram clinical studies
(extracted from the Sponsor's ISS)

Age Range, y; Event	*No. (%) of Patients*				
	Short-term Studies		*All Studies*		
	SCT-MD-15 and SCT-MD-32		*SCT-MD-15, SCT-MD-32, and SCT-MD-32A*		
	Placebo	**Escitalopram**	**Placebo**	**Escitalopram**	**Open-Label Escitalopram**
Adolescents (12-17)					
N	238	234	238	234	37
Death	0	0	0	0	0
SAE	5 (2.1)	4 (1.7)	7 (2.9)	6 (2.6)	2 (5.4)
AE discontinuation	3 (1.3)	6 (2.6)	3 (1.3)	10 (4.3)	2 (5.4)
TEAE	174 (73.1)	177 (75.6)	181 (76.1)	184 (78.6)	32 (86.5)
Children (6-11)—Study SCT-MD-15 only					
N	52	52	52	52	—
Death	0	0	0	0	—
SAE	0	2 (3.8)	0	2 (3.8)	—
AE discontinuation	0	0	0	0	—
TEAE	34 (65.4)	34 (65.4)	34 (65.4)	34 (65.4)	—
All ages (6-17)					
N	290	286	290	286	37
Death	0	0	0	0	0
SAE	5 (1.7)	6 (2.1)	7 (2.4)	8 (2.8)	2 (5.4)
AE discontinuation	3 (1.0)	6 (2.1)	3 (1.0)	10 (3.5)	2 (5.4)
TEAE	208 (71.7)	211 (73.8)	215 (74.1)	218 (76.2)	32 (86.5)

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Cross-reference: After-Text Tables 5.1.1, 5.1.2, 5.1.3, 5.4.1A, 5.4.1B, 5.4.3A, and 5.4.3B; Study SCT-MD-32/32A, Tables 14.5.1.1A and 14.5.1.1C.

Table 7.1.2b Adolescent patients with serious adverse events (SAEs) in the escitalopram safety data base (extracted from Sponsor's ISS table 5.1.4.1-1)

Study	*Patient ID*	*Age, y/ Sex*	*Days on Study Drug*[a]	*SAE Start Day*[b]	*Preferred Term*	*Investigator Term*
Before first dose of study drug (not randomized)						
SCT-MD-32	0243207	13/F	—	—	Suicidal tendency	Suicidal ideation
				—	Depression aggravated	Severity of depressive symptoms
Placebo						
SCT-MD-15	0071506	13/M	56	72	Allergic reaction	Allergic response to a virus
SCT-MD-15	0081514	17/M	52	51	Manic reaction	Manic episode[c,d]
SCT-MD-15	0261508	14/M	7	22	Depression	Hospitalization for depression
SCT-MD-32	0323202	13/F	45	55	Suicidal tendency	Intensified suicidal ideation[d,e]
SCT-MD-32	0353212	14/F	5	5	Depression aggravated	Worsening depression[c,d]
SCT-MD-32A	0343202	17/F	228	149	Suicidal tendency	Threatening to cut herself
SCT-MD-32A	0383225	16/M	174	197	Suicide attempt	Suicide attempt[f]
Escitalopram						
SCT-MD-32	0243210	17/F	57	53	Inflicted injury	Sexual assault upon patient
SCT-MD-32	0283210	16/M	33	44	Suicidal tendency	Intensified suicidal ideation requiring psychiatric hospitalization
SCT-MD-32	0443209	14/M	10	14	Irritability	Exacerbation of increased irritability[d]
SCT-MD-32	0453202	16/F	49	50	Inflicted injury	Self-injurious behavior with no suicidal intent[c]
SCT-MD-32A	0213204	12/M	104	99	Failure to thrive	Failure to thrive[c]
SCT-MD-32A	0373212	14/M	75	95	Suicidal tendency	Self-harm gesture
Open-label escitalopram						
SCT-MD-32A	0033206	15/F	80	80	Non-accidental overdose	Intentional overdose of study medication[c]
SCT-MD-32A	0103201	12/M	153	130	Pleuritis	Viral pleurodynia

7.1.3 Dropouts and Other Significant Adverse Events

The incidence of premature withdrawal is significantly greater in the escitalopram groups compared to the placebo group (4.3% vs. 1.3%). The most common AE associated with withdrawal in the escitalopram group is insomnia; self inflicted injury, fatigue and restlessness are more prevalent in the escitalopram group compared to placebo. Please refer to Table 7.1.3 below for further details. Narratives of early withdrawals describe symptomatology already described in current escitalopram labeling.

Table 7.1.3 Incidence of patients with common AE (n ≥ 2 patients) leading to premature discontinuation in the escitalopram safety data base. (extracted from sponsor's ISS Table 5.1.5-1)

Preferred Term	*No. (%) of Patients*				
	Short-term Studies		*All Studies*		
	SCT-MD-15 and SCT-MD-32		**SCT-MD-15, SCT-MD-32, and SCT-MD-32A**		
	Placebo (N = 238)	*ESC (N = 234)*	*Placebo (N = 238)*	*ESC (N = 234)*	*Open-Label ESC (N = 37)*
Patients with ≥ 1 AE leading to premature discontinuation	3 (1.3)	6 (2.6)	3 (1.3)	10 (4.3)	2 (5.4)
Insomnia	0	2 (0.9)	0	3 (1.3)	0
Fatigue	0	1 (0.4)	0	2 (0.9)	0
Inflicted injury	0	1 (0.4)	0	2 (0.9)	0
Restlessness aggravated	0	2 (0.9)	0	2 (0.9)	0

7.1.4 Other Search Strategies

There were no other search strategies utilized in this review.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

It is unclear from the protocols if adverse events were specifically solicited or if adverse events were noted only when a patient made specific complaints. The protocols merely state that patients are "queried" regarding AEs.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor groups treatment-emergent adverse events by occurrence. It is unclear from this submission what classification system/dictionary is used to classify events.

7.1.5.3 Incidence of common adverse events

Common AEs occurring with greater frequency in the escitalopram group compared to placebo in acute studies include the following: **headache,** abdominal pain, nausea, and insomnia; headache was identified as the most common treatment emergent AE in the adolescent escitalopram data base. In the longer term escitalopram study, diarrhea and urinary tract infections (UTI) are also considered common AEs (note: UTI is reported in ≥ 5 % of escitalopram patients with an incidence of ≥ 2 times observed in placebo patients).

Below, Tables 7.1.5.3a (acute escitalopram studies) and 7.1.5.3b (longer term escitalopram study), summarize the common AEs in the escitalopram adolescent safety data base.

Table 7.1.5.3a Common treatment-emergent AE ≥ 5% in short-term escitalopram studies for adolescent safety data base only. (extracted from sponsor's ISS Table 5.1.2.1.1-1)

Preferred Term	*Placebo, n (%) (N = 238)*	*Escitalopram, n (%) (N = 234)*
Patients with ≥ 1 TEAE	174 (73.1)	177 (75.6)
Headache	56 (23.5)	57 (24.4)
Abdominal pain	14 (5.9)	23 (9.8)
Nausea	17 (7.1)	22 (9.4)
Insomnia	12 (5.0)	21 (9.0)
Menstrual cramps[a]	21 (15.1)	12 (8.9)
Pharyngitis	18 (7.6)	19 (8.1)
Inflicted injury	25 (10.5)	18 (7.7)
Rhinitis	16 (6.7)	16 (6.8)
Fatigue	15 (6.3)	14 (6.0)
Upper respiratory tract infection	18 (7.6)	13 (5.6)
Vomiting	12 (5.0)	13 (5.6)
Influenza-like symptoms	10 (4.2)	12 (5.1)

Studies SCT-MD-32 and SCT-MD-15.
a Female population only: placebo, N = 139; escitalopram, N = 135.
TEAE = treatment-emergent adverse event.

Table 7.1.5.3b Common treatment-emergent AE ≥ 5% in longer term adolescent escitalopram Study 32/32A (extracted from sponsor's ISS Table 5.1.2.1.4-1) ***

Preferred Term	*Placebo, n (%) (N = 157)*	*Escitalopram, n (%) (N = 155)*
Patients with ≥ 1 TEAE	125 (79.6)	128 (82.6)
Headache	44 (28.0)	44 (28.4)
Inflicted injury	32 (20.4)	24 (15.5)
Menstrual cramps[a]	14 (15.2)	12 (13.0)
Nausea	15 (9.6)	18 (11.6)
Insomnia	11 (7.0)	17 (11.0)
Pharyngitis	20 (12.7)	17 (11.0)
Rhinitis	23 (14.6)	15 (9.7)
Abdominal pain	15 (9.6)	14 (9.0)
Upper respiratory tract infection	22 (14.0)	14 (9.0)
Vomiting	9 (5.7)	14 (9.0)
Fatigue	15 (9.6)	13 (8.4)
Influenza-like symptoms	9 (5.7)	13 (8.4)
Diarrhea	6 (3.8)	8 (5.2)
Urinary tract infection	2 (1.3)	8 (5.2)
Coughing	13 (8.3)	6 (3.9)
Appetite decreased	8 (5.1)	4 (2.6)

***REVIEWER'S NOTE: "N" in the 1st line heading under "Placebo" and "Escitalopram" is inflated as this is a pooled table including patients in Study 32. The true "N" for the longer term Study 32A is the following: *Escitalopram:* n=83 entering /37 completing; *Placebo* : n=82 entering/40 completing)**

7.1.5.4 Common adverse event tables

The identified common AEs are consistent with the current adult labeling. Although the sponsor does not present a new common adverse events table in their proposed labeling for this supplement, it is helpful to have specific information regarding the adolescent population in at least the foot notes of the common AE table in labeling.

7.1.6 Suicidality

Please refer to Table 7.1.6a for the incidence treatment-emergent AE potentially associated with suicidal behavior in the escitalopram adolescent safety data base. For self-inflicted injury, it appears that there was a greater treatment-emergent incidence in the escitalopram safety data base compared to the placebo. Table 7.1.6 b summarizes the suicidal gestures/attempts described in the narratives in this safety data base.

Table 7.1.6a Incidence of patients with treatment-emergent AE potentially associated with suicidal behavior in the escitalopram adolescent safety data base.
(Table extracted from ISS Table 5.1.6.1.1.1-1)

Preferred Term	*No. (%) of Patients*				
	Short-term Studies		*All Studies*		
	SCT-MD-15 and SCT-MD-32		**SCT-MD-15, SCT-MD-32, and SCT-MD-32A**		
	***Placebo* (N = 238)**	***ESC* (N = 234)**	***Placebo* (N = 238)**	***ESC* (N = 234)**	***Open-Label ESC* (N = 37)**
Suicide attempt[a]	0	0	1 (0.4)[b]	0	0
Suicidal tendency[c]	3 (1.3)	1 (0.4)	4 (1.7)	2 (0.9)	1 (2.7)
Non-accidental overdose	2 (0.8)	0	2 (0.8)	0	1 (2.7)
Accidental overdose	0	0	0	0	1 (2.7)
Inflicted injury[d]	25 (10.5)	18 (7.7)	36 (15.1)	28 (12.0)	7 (18.9)
Self-inflicted injury[e,f]	4 (1.7)	7 (3.0)	7 (2.9)	11 (4.7)	1 (2.7)

c Suicidal tendency was also reported in Study SCT-MD-32 for Patient 0243207, who failed screening and did not receive study drug.

d Inflicted injury (sore shoulder due to fall) was also reported in Study SCT-MD-32 for Patient 0073212, who failed screening and did not receive study drug.

e Treatment-emergent adverse events coded to inflicted injury that were specifically indicated by the Investigator in Studies SCT-MD-32 and SCT-MD-32A as suggestive of self-harm or that were indicated as self-inflicted in the Investigator's description of the events. Two escitalopram patients (0033213 and 0383211) had self-injurious events in both Studies SCT-MD-32 and SCT-MD-32A.

f One additional patient (0033214) in Study SCT-MD-32 reported inflicted injury that was considered by the Investigator to be self-injurious, non-suicidal. The event occurred before the start of study medication; the patient subsequently received double-blind escitalopram.

Table 7.1.6b Patient summaries of treatment-emergent self harm/self-inflicted injuries in escitalopram adolescent data base. (extracted from sponsor's ISS Table 5.1.6.1.1.1-2)

Study	*Patient ID*	*Age, y/ Sex*	*Days on Study Drug*[a]	*TEAE Start Day*[b]	*Investigator Term*
Placebo					
SCT-MD-32	0103205	14/F	45	28	Superficial cutting
SCT-MD-32	0193205	14/F	134	4	Superficial scratches left arm[c]
SCT-MD-32	0323202	13/F	45	58	Self-injurious cuts on left arm and thighs[c,d]
SCT-MD-32	0443210	14/F	56	5	Self-mutilation
				39	Contusion left lower leg, accident, no suicidal ideation[i]
SCT-MD-32A	0033211	15/F	229	109	Superficial abrasion left arm
				230	Injury right hand with mild aching pain, diagnosed broken
SCT-MD-32A	0343202	17/F	228	147	Superficial cutting[e]
SCT-MD-32A	0383225	16/M	174	103	Superficial cutting to left thigh[f]
				144	Self-inflicted cutting to left thigh[f]
Escitalopram					
SCT-MD-15	0331509	16/M	14	10	Self-inflicted laceration to right wrist
SCT-MD-32	0193219	13/F	96	29	Contusion (left elbow; after accidentally fall)[i]
				54	Non-suicidal self-injurious behavior[c]
SCT-MD-32	0343201	12/F	106	38	Superficial cutting

Study	*Patient ID*	*Age, y/ Sex*	*Days on Study Drug*[a]	*TEAE Start Day*[b]	*Investigator Term*
SCT-MD-32	0453202	16/F	49	50	Self-injurious behavior with no suicidal intent[g,h]
SCT-MD-32	0493209	12/F	131	56	Superficial right wrist cuts
SCT-MD-32A	0203206	16/F	83	74	Abrasions on both forearms[i]
				79	Laceration left inguinal region[c]
SCT-MD-32A	0333206	16/F	141	135	Laceration to left wrist
SCT-MD-32A	0353214	16/F	73	66	Superficial cutting on arm[c,g]
SCT-MD-32A	0383202	13/F	227	86	Abrasions to left foot, arm, elbow and left lower quadrant of abdomen[i]
				173	Self-inflicted cutting to right lower leg
SCT-MD-32/32A	0033213	16/M	224	33	Injured fist after hitting the wall following an argument with Dad[c]
				143	Possible concussion, no LOC[i]
				156	Contusion left hand[i]
SCT-MD-32/32A	0383211	16/F	102	1	Self-inflicted scratches on forearm
				35	Cutting—shallow lacerations
				66	Poking finger tips with pin
Open-label escitalopram					
SCT-MD-32A	0113201	14/F	174	10	Cut on self

The sponsor also uses the following two instruments to assess improvement in suicidality: 1) the Modified Columbia-Suicide Severity Rating Scale (**MC-SSRS**) and, 2) the Suicidal Ideation Questionnaire-Junior High School Version (**SIQ-JR**).

For Study 32 (acute, placebo-controlled, adolescent escitalopram positive study), it appears that numerically, the placebo group actually demonstrates a greater improvement in the **SIQ-JR** than the escitalopram group. The mean changes from baseline of the SIQ-JR scores (mean ± SD) are –5.8 ± 12.8 for placebo patients and –3.0 ± 11.7 for escitalopram patients. As the sponsor points out, it is difficult to make conclusions based on these results as the study is not powered to detect this difference.

MC-SSRS scores from Studies 32 and 32A (the acute and longer term, placebo-controlled, adolescent escitalopram studies) demonstrate an increase from baseline in MC-SSRS scores for all treatment groups, suggesting a more severe level of suicidality (see Table 7.1.6c). The

implication of these scores is that suicidal ideation has a greater incidence in escitalopram patients compared to the placebo group in the longer term data base of Study 32A, and that escitalopram patients tended to have more severe levels of suicidal ideation than placebo patients.

Table 7.1.6c Number and percentage of adolescent patient with an increase from baseline in the MC-SSRS Scores (extracted from sponsor ISS Table 5.1.6.1.1.3-1)

	Study SCT-MD-32		*Studies SCT-MD-32 and SCT-MD-32A*	
	Placebo, n (%) (N = 128)	*Escitalopram, n (%) (N = 131)*	*Placebo, n (%) (N = 128)*	*Escitalopram, n (%) (N = 131)*
Any suicidal behavior and/or ideation	13 (10.2)	12 (9.2)	14 (10.9)	19 (14.5)
Suicidal behavior	3 (2.3)	2 (1.5)	3 (2.3)	4 (3.1)
Suicidal ideation	12 (9.4)	12 (9.2)	13 (10.2)	19 (14.5)
Modal (most common)	10 (7.8)	6 (4.6)	11 (8.6)	9 (6.9)
Most severe	10 (7.8)	12 (9.2)	11 (8.6)	19 (14.5)

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory tests are performed at baseline and Week 8 (or early withdrawal) for the acute study and again at week 24 for the longer term study.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This review discusses the two short term pediatric MDD placebo-controlled escitalopram studies, Studies 15 and 32, and the longer term escitalopram study, Study 32A.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

When comparing the mean change from baseline of all laboratory values in the escitalopram adolescent MDD safety data base, there is no apparent significant difference between the escitalopram and placebo groups. It is noted that the mean increase for AST is higher in the

escitalopram group than in the placebo group. Please see Table 7.1.7.3.1, below, for a summary of mean change from baseline to endpoint of select clinical laboratory parameters.

Table 7.1.7.3.1 Mean change from baseline to end point in select clinical laboratory parameters in short term adolescent MDD escitalopram clinical studies. (extracted from ISS Table 6.3.1-2)

Parameter (Units)	*Placebo*			*Escitalopram*		
	n	*Baseline, Mean ± SD*	*Change, Mean ± SD*	*n*	*Baseline, Mean ± SD*	*Change, Mean ± SD*
Hematology						
Eosinophils (%)	215	2.4 ± 1.9	–0.0 ± 1.4	209	2.5 ± 2.0	–0.1 ± 1.5
Hemoglobin (mmol/L)	216	8.7 ± 0.7	–0.1 ± 0.4	209	8.6 ± 0.8	–0.2 ± 0.4
Chemistry						
ALT (U/L)	220	17.8 ± 8.9	–0.3 ± 8.7	212	18.5 ± 9.9	0.0 ± 7.6
AST (U/L)	220	20.7 ± 5.5	–0.1 ± 8.6	212	21.4 ± 6.4	0.9 ± 7.0
Bilirubin, total (µmol/L)	220	7.6 ± 5.5	–0.5 ± 3.5	212	7.3 ± 5.7	–0.1 ± 3.4
Potassium (mmol/L)	220	4.3 ± 0.4	–0.0 ± 0.5	213	4.3 ± 0.4	–0.1 ± 0.4

Note: Studies SCT-MD-32 and SCT-MD-15.
End point = last available postbaseline assessment.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; n = number of patients with a screening assessment and at least one postbaseline assessment.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

There are no early withdrawals due to laboratory value abnormalities (however, note that laboratory values are generally not obtained until completion of the study). Table 7.1.7.3.2 lists the incidence of PCS (potentially clinically significant) laboratory values in each treatment group in the adolescent escitalopram MDD safety data base.

Please see Appendix Table 2 for further details of patients presenting with potentially clinically significant post-baseline values in LFT.

Table 7.1.7.3.2 Incidence of patients with potentially clinically significant post-baseline laboratory parameters in escitalopram adolescent MDD patient population
(extracted from ISS Table 6.3.1-1)

Parameter	*PCS Criteria (Units)*	*Short-Term Studies*		*All Studies*		
		SCT-MD-15 and SCT-MD-32		*SCT-MD-15, SCT-MD-32, and SCT-MD-32A*		
		Placebo, n/N (%)	**ESC, n/N (%)**	**Placebo, n/N (%)**	**ESC, n/N (%)**	**Open-Label ESC, n**
Hematology						
Eosinophils	≥ 10%	2/214 (0.9)	1/207 (0.5)	5/215 (2.3)	1/208 (0.5)	1
Hemoglobin	≤ 0.9 × LLN (mmol/L)	0/216	1/209 (0.5)	0/217	1/210 (0.5)	0
Chemistry						
ALT	≥ 3 × ULN (U/L)	1/220 (0.5)	0/212	1/221 (0.5)	0/212	0
AST	≥ 3 × ULN (U/L)	1/220 (0.5)	1/212 (0.5)	1/221 (0.5)	1/212 (0.5)	1
Bilirubin, total	≥ 34.2 µmol/L	0/219	1/211 (0.5)	1/220 (0.5)	1/211 (0.5)	0
Potassium	≥ 5.5 mmol/L	1/218 (0.5)	0/209	2/219 (0.9)	0/209	0
Urinalysis						
Glucose	≥ 2+	3/216 (1.4)	0/210	3/217 (1.4)	0/210	0
Protein	≥ 2+	4/214 (1.9)	4/209 (1.9)	5/215 (2.3)	4/209 (1.9)	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ESC = escitalopram; LLN = lower limit of normal; n = number of patients with a non-PCS baseline value who met criterion at least once during double-blind treatment; N = number of patients with a non-PCS baseline assessment and at least one postbaseline assessment; PCS = potentially clinically significant; ULN = upper limit of normal.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In the short term studies (15 and 32), vital signs monitored weekly include sitting pulse, blood pressure, and weight. Height is recorded at baseline and at study end or early termination. In the longer term study (32A), sitting pulse, blood pressure and weight are measured weekly for the first 5 weeks and then monthly. Orthostasis is assessed in Studies 32 and 32A at baseline and the end of Weeks 1,6,10,12, and 24.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The safety data base includes the two pediatric placebo-controlled escitalopram MDD studies (15 and 32), and the longer term escitalopram adolescent study (32A).

7.1.8.3 Standard analyses and explorations of pulse and blood pressure

The mean change from baseline in diastolic blood pressure is greater in the escitalopram group compared to placebo. Otherwise, there are no notable differences in blood pressure and pulse comparing the placebo and escitalopram groups (please refer to Table 7.1.8.3). Orthostasis is

observed to be greater in the escitalopram group than in the placebo group when assessed in Studies 32 and 32A; however, this mean change doesn't appear to be clinically significant as no patient had more than one episode of orthostasis, and only one patient reported accompanying lightheadedness.

Table7.1.8.3 Mean change from baseline in pulse and blood pressure for escitalopram adolescent safety data base (extracted from ISS Table 7.1.2.1.1-1)

Time Point		*Placebo*		*Escitalopram*	
		n	*Mean ± SD*	*n*	*Mean ± SD*
Sitting systolic blood pressure, mm Hg					
Baseline		236	111.1 ± 10.7	231	111.9 ± 12.5
Change	Week 8	203	1.0 ± 11.4	189	–0.9 ± 10.7
	Week 24	40	0.6 ± 9.7	39	2.2 ± 12.2
	End point[a]	236	0.4 ± 11.5	231	–0.8 ± 11.5
Sitting diastolic blood pressure, mm Hg					
Baseline		236	68.4 ± 8.6	231	68.5 ± 8.8
Change	Week 8	203	–0.3 ± 9.2	189	–0.5 ± 8.1
	Week 24	40	0.9 ± 9.9	39	0.3 ± 10.2
	End point[a]	236	–0.1 ± 9.5	231	–0.3 ± 9.2
Sitting pulse rate, bpm					
Baseline		236	75.8 ± 10.3	231	76.3 ± 11.0
Change	Week 8	203	0.4 ± 10.4	189	–1.0 ± 11.8
	Week 24	40	–2.0 ± 10.4	39	–4.1 ± 13.4
	End point[a]	236	–0.6 ± 10.5	231	–1.1 ± 12.2

7.1.8.4 Height /Weight

Growth assessment in the pediatric population can be determined by use of a z-score, defined by the number of standard deviations from the population mean for a specific subject's weight or height given their age and sex. No change in mean z-score would indication that subjects are growing as predicted by CDC growth charts from age adjusted peers. Decreases in z-score would indicate that subjects are lagging behind in growth.

The sponsor states that the z-score changes appear to be similar between treatment groups, indicating that escitalopram doesn't have an identifiable effect on height and weight change in the adolescent population. In his review of z-score data, FDA statistician Dr. Kordzakhia confirms the sponsor's findings. Please see Appendix 3a for a summary table of the pooled short term data z-scores for weight from Studies 15, 18, and 32, and Appendix 3b for data regarding the longer term Study 32A (for details, see Statistical Review and Evaluation by George Kordzakhia, PhD:1/28/09).

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program

In the safety data base for adolescent MDD, ECGs are assessed at baseline and at study end/discontinuation of Studies 32 and 15, and at Week 12 during Study 32A. There are no references made to the timing of the ECGs in relation to dosing or food intake.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The safety data base includes the two pediatric placebo-controlled escitalopram MDD studies (15 and 32), and the longer term escitalopram adolescent study (32A).

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

QTc prolongation is noted to be greater in the escitalopram group compared to the placebo group. Even with Bazett's correction (QTcB) and Fredericia's correction (QTcF), QTc prolongation is more prevalent in the escitalopram population (it is questionable if Fredericia's correction is the appropriate correction to use, since there isn't a very significant heart increase observed with escitalopram).

Below, Table 7.1.9.3.1a and Table 7.1.9.3.1b provide summaries of the mean change from baseline of QTc for this safety data base. Because timing of food and drug weren't controlled for during the ECG collections, the interpretation of these findings is limited. These results are consistent with the current label describing an increase in QTc interval of 3.9 msec for Lexapro, compared to placebo.

Table7.1.9.3.1a Mean change from baseline for cardiac parameters for pediatric escitalopram study Studies 32 and 15 (extracted from ISS Table 7.2.2.1.1–1)

Parameter, Units	*Placebo*			*Escitalopram*		
	n	*Baseline, Mean ± SD*	*Change From Baseline to End Point[a], Mean ± SD*	*n*	*Baseline, Mean ± SD*	*Change From Baseline to End Point[a], Mean ± SD*
Ventricular heart rate, bpm	230	71.0 ± 11.0	–0.6 ± 10.8	218	69.6 ± 10.9	0.2 ± 10.9
QRS interval, msec	230	90.2 ± 9.8	–0.3 ± 7.5	218	89.5 ± 9.1	0.8 ± 7.0
PR interval, msec	228	145.3 ± 18.8	1.1 ± 10.5	218	144.7 ± 19.8	1.2 ± 12.2
QT interval, msec	230	376.1 ± 24.9	1.0 ± 22.6	218	378.9 ± 26.9	2.3 ± 22.7
QTcB interval, msec	230	406.4 ± 22.1	–0.7 ± 19.4	218	405.1 ± 21.2	2.9 ± 20.4
QTcF interval, msec	230	395.8 ± 18.2	–0.1 ± 15.4	218	395.9 ± 18.2	2.7 ± 15.5

Table 7.1.9.3.1b Mean change from baseline in weekly mean QTc for adolescent only safety population in Studies 32 and 32A (excerpts from ISS Table 7.2.1.2-1)

Time Point		*Placebo*		*Escitalopram*	
		n	*Mean ± SD*	*n*	*Mean ± SD*
QT interval, msec					
Baseline		156	377.4 ± 24.7	153	377.3 ± 27.0
Change	Week 6	126	1.4 ± 23.7	129	1.9 ± 22.5
	Week 20	40	–2.6 ± 25.4	34	3.6 ± 21.3
	Week 24	22	1.5 ± 26.8	23	7.8 ± 19.2
	End point[a]	156	–2.9 ± 24.0	153	0.4 ± 21.2
QTcB interval, msec					
Baseline		156	405.2 ± 20.5	153	403.9 ± 20.7
Change	Week 6	126	–0.2 ± 16.7	129	3.2 ± 18.7
	Week 20	40	–5.1 ± 18.5	34	0.8 ± 20.3
	Week 24	22	1.0 ± 22.2	23	–3.4 ± 21.4
	End point[a]	156	–1.8 ± 19.6	153	1.7 ± 20.1

Time Point		*Placebo*		*Escitalopram*	
		n	*Mean ± SD*	*n*	*Mean ± SD*
QTcF interval, msec					
Baseline		156	395.5 ± 18.1	153	394.6 ± 17.9
Change	Week 6	126	0.4 ± 14.5	129	2.8 ± 14.7
	Week 20	40	–4.3 ± 16.8	34	1.9 ± 14.4
	Week 24	22	1.0 ± 18.9	23	0.7 ± 17.9
	End point[a]	156	–2.2 ± 16.6	153	1.2 ± 15.2

7.1.9.3.2. Marked outliers and dropouts for ECG abnormalities

There are no dropouts due to ECG abnormalities in this safety data base. 7.1.9.3.2 below summarizes the escitalopram patients with a significant increase in QTc during escitalopram treatment. There are two patients (0091505 and 0303213) with an increased QTc prolongation of > 60 msec; no placebo patients have a clinically significant increase in QTc.

Table 7.1.9.3.2 Summary table of adolescents with significant increase in QTc prolongation during escitalopram treatment for MDD in Studies 32 and 32A.

PATIENT #	AGE/GENDER	BASELINE QT_C (QT_CB/ QT_CF)	QT_C HISTORY DURING STUDY
0323208 (Study 32/32A)	14/M	409/402 msec	Summary: ~ 40 msec ↑QT_C Day 43: 447/441 msec Day 139: 428/431 msec Day 168: 397/398
0091505 (Study 15)	16/F	338/346 msec HR:52 bpm	Summary: ↑QT_C and ↑HR Day 56: 403/382 msec HR: 83 bpm
0303213 (Study 32/32A)	15/F	373/375 msec HR:58	Summary: ↑QT_C and ↑HR Day 42: 440/415 msec HR: 84 bpm Day 98: 413/396 msec HR: 77 bpm

7.1.10 Seizures

A clonic-tonic seizure on Day 47 of Study 32 is reported in one 15 y.o. male escitalopram patient (0383215). This patient completed the study to Day 56, but didn't enroll in the extension study.

7.1.11 Concomitant Medications

For the adolescent safety data base, concomitant medications are used in comparable amounts when comparing the pooled placebo and escitalopram groups. The ISS discusses the higher incidence of abdominal pain, nausea and insomnia reported in the escitalopram compared to placebo, perhaps resulting in the high use of anti-inflammatory and analgesic medications in the escitalopram group. Please see Table 7.1.11 for a summary of concomitant medications in the short term escitalopram studies.

For details regarding the concomitant medications used in Study 32, please refer to the ***Concomitant Medications*** in Section 6.3.1.

Table 7.1.11 Common concomitant medication (≥ 10% of adolescent patients) in short term escitalopram Studies 32 and 15. (extracted from ISS Table 8.3-1)

Preferred Term	*Placebo, n (%) (N = 238)*	*Escitalopram, n (%) (N = 234)*
Patients using ≥ 1 concomitant medication	172 (72.3)	169 (72.2)
Anti-inflammatory and antirheumatic products	79 (33.2)	73 (31.2)
Analgesics	70 (29.4)	69 (29.5)
Antihistamines for systemic use	35 (14.7)	34 (14.5)
Antibacterials for systemic use	32 (13.4)	28 (12.0)
Nasal preparations	26 (10.9)	19 (8.1)

7.1.12 Human Carcinogenicity

No Carcinogenicity studies were submitted with this application

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Studies 32 and 32A both have a down taper period, and the sponsor considers any newly emergent AE during this study period to be a possible withdrawal or rebound effect. The most common newly emergent AE during the taper period for the escitalopram group was irritability (n=2 of 40); for the placebo group, inflicted injury (n=2 of 54) and rhinitis (n=2 of 54) were the most common AE identified.

7.1.14 Human Reproduction and Pregnancy Data

There are no studies on pregnancy in this submission. There are no patients reported to be pregnant while on escitalopram in this escitalopram safety data base.

7.1.15 Assessment of Effect on Growth

Escitalopram doesn't appear to have an identifiable effect on height and weight change in the adolescent population (see Section 7.1.8.4).

7.1.16 Overdose Experience

The following two overdoses reported in the open-label escitalopram Study 32A:

1. An intentional overdose occurred when, on Day 80, a 15 y.o. female ((Patient 0033206) took 40 tablets (a combination of 10 and 20 mg tablets) accumulated throughout the study. The patient was hospitalized for inpatient treatment, and discontinued the study. Other than a moderate headache 1 week after the overdose, no other AEs are reported for this patient.

2. Another overdose termed "accidental" in the ISS describes a 15 y.o. female (Patient 01232040) ingesting six escitalopram 20-mg tablets at one time. At the time of the overdose, the patient reported a moderate headache, thought to be possibly related to study drug. The patient withdrew consent 6 days later, and there is no safety concern reported.

7.1.17 Post-marketing Experience

The sponsor hasn't conducted any post-market pediatric studies beyond those in this submission. According to the sponsor's summary, the post-market adult studies results have been consistent with the current label.

The Medical Dictionary for Regulatory Activities (MedDRA) is used for the escitalopram spontaneous post market reports (or spontaneous adverse events-SAE). Tables 7.1.17a summarizes the incidence of AEs reported, and Table 7.1.17b lists events identified in the pediatric population compared to adults. For the spontaneous pediatric escitalopram reported by the sponsor, the following are of note:

1. Many escitalopram pediatric SAE events may be due to in utero exposure, and, thus, are categorized as congenital anomalies or perinatal complications;
2. The SAE of children (<12 y.o.) exposed to escitalopram, describe overdose and accidental overdose in a higher percentage of total reports than in the adult age group;
3. The SAE of adolescents (12-17 y.o.) suicide attempt, overdose, and intentional overdose comprise a higher percentage of the total reports than in the adult age group.

Table 7.1.17a Total spontaneous reports for escitalopram and citalopram from 10/21/02 to 12/31/07 (extracted from ISS Table 9.2.3-1)

Product	*Child*[a]	*Adolescent*[b]	*Adult*[c]	*Unspecified*	*Total*
Escitalopram	719	1443	26,812	4921	33,895
Citalopram	599	759	21,111	3959	26,428
Total	1318	2202	47,923	8880	60,323

a *Child* defined as aged 0 to 11 years.
b *Adolescent* defined as aged 12 to 17 years.
c *Adult* defined as 18 years and older.

Table 7.1.17b Escitalopram spontaneous AEs in pediatric population compared to adults from 10/21/02 to 12/31/07 (extracted from ISS Table 9.2.4.1-1)

Age Group[a]	*Events Only Seen in Age Group When Compared With Adults and Reported More Than Twice (No. of Reports)*	*Events Seen as a Lower Percentage of Total Reports (> 1% Difference) in Age Group When Compared With Adults (% Difference)*	*Events Seen as a Higher Percentage of Total Reports (> 1% Difference) in Age Group When Compared With Adults (% Difference)*
Child	Premature baby (9)[b] Neonatal jaundice (4)[b] Atrioventricular septal defect (3)[b] Low Apgar score (3)[b]	Nausea (4.3) Insomnia (3.4) Fatigue (2.6) Dizziness (2.5) Headache (2.4) Anxiety (1.8) Diarrhea (1.4) Hyperhidrosis (1.4) Tremor (1.2)	Overdose (42.2) Accidental overdose (5.2)
Adolescent	None	Nausea (3) Insomnia (2.9) Dizziness (1.8) Diarrhea (1.5) Headache (1.4) Fatigue (1.4) Anxiety (1.2) Hyperhidrosis (1)	Suicide attempt (12) Overdose (10) Intentional overdose (6.8) Suicidal ideation (1)

a The age groups were defined as follows: child = 0 to 11 years of age; adolescent = 12 to 17 years of age; adult = 18 years and older.
b These events were reported in newborns who were exposed to escitalopram during pregnancy.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The escitalopram safety data base for treatment of adolescents with MDD includes the following:

1. **Study 32**, a multicenter, 8 week double-blind, placebo-controlled, flexible dose escitalopram (10-20 mg/d) study in adolescents diagnosed with MDD with 2 treatment groups: placebo (n=155) and escitalopram (n=157).

2. **Study 15**, a multicenter, 8 week double-blind, placebo-controlled, flexible dose escitalopram (10-20 mg/d) study in pediatric (6-17 y.o.) patients diagnosed with MDD with 2 treatment groups: placebo (n=133 includes 81 adolescents) and escitalopram (n=131 includes 79 adolescents).

3. **Study 32A,** a multicenter, longer term escitalopram study in adolescents diagnosed with MDD. The following major design changes were implemented after the start of the study: a) primary outcome variable (from time to discontinuation → Δ CDRS from baseline);
   b) 24 weeks open label → 16 weeks placebo-controlled

The sponsor presents their safety data primarily in the adolescent population in the following categories:

1. The **escitalopram** safety data base is comprised of a pooling of data from the two 8 week, placebo controlled studies, Study **32** (ages 12-17) and Study **15** (limited to adolescents within the study population of ages 6-17). Also included in this pooling is the extension Study **32A (**ages 12-17), which began as open label and later evolved into a placebo controlled design.

2. Data from the **citalopram** studies are presented separately and not pooled do to differences in study duration, in patient/out patient status, and imbalance in the number of adolescent patients. The two **citalopram**, placebo controlled studies are Study **18** (outpatient, 8 weeks; ages 7-17) and Study **94404** (in patient and outpatient, 12 weeks; ages 13-18). **Citalopram** open label, longer term extension studies included Study **20** (extension of 18; n=5 adolescents) and Study **19** (extension of 07; n=57 adolescents).

A total of **988** pediatric patients received ≥1 dose of study drug; of these, **764** patients were between ages 12-17 y.o. and **36** patients aged 18 y.o. (from study 94404). Therefore, the sponsor

counts a total of 800 adolescent patients in the escitalopram/citalopram safety data base with the following breakdown:

placebo: n=387
escitalopram: n=234
citalopram: n=169

7.2.1.2 Demographics

In the escitalopram adolescent safety data base (Studies 15 and 32), there are 135 females (57.7%) and 99 males (42.3%) with a mean age of 14.6years (± 1.6) exposed to escitalopram. The majority of patients exposed to escitalopram are Caucasian (n=162 or 72.2%); other escitalopram exposures include 42 (17.9%) African Americans, 4 (1.7%) of Asian decent, and 19 (8.1%) "other.

7.2.1.3 Extent of exposure (dose/duration)

A total of 210 patients (181 adolescents) received **escitalopram** for at least 8 weeks, and 53 patients (all adolescents) received **escitalopram** for at least 24 weeks; 211 patients (154 adolescents) received **citalopram** for at least 8 weeks, and 66 patients (30 adolescents) received **citalopram** for at least 24 weeks. The sponsor concludes that the **escitalopram/citalopram** safety data base includes 83 adolescents (of 119 pediatric patients) who were exposed for up to 24 weeks of **escitalopram** or **citalopram**.

Doses for escitalopram are either 10 or 20 mg daily. Of the 154 intent-to-treat escitalopram patients in Study 32, 54 patients received 10mg on their last visit, and 100 patients received 20mg on their last visit.

Please see Tables 7.2.1.3a and 7.2.1.3b, below, for sponsor tables summarizing escitalopram exposure.

Table 7.2.1.3a Duration of treatment in escitalopram double-blind clinical Studies 32, 15 and 32A (extracted from ISS Table 4.2.3.1.1-1)

	Adolescents		*All Patients*	
	Placebo (N = 238)	*Escitalopram (N = 234)*	*Placebo (N = 290)*	*Escitalopram (N = 286)*
Overall duration of treatment, d (%)				
1-28	20 (8.4)	32 (13.7)	25 (8.6)	35 (12.2)
29-56	93 (39.1)	77 (32.9)	121 (41.7)	110 (38.5)
57-84	60 (25.2)	61 (26.1)	79 (27.2)	77 (26.9)
> 84	65 (27.3)	64 (27.4)	65 (22.4)	64 (22.4)
Short-term exposure, duration 1 to 56 d				
n	113	109	146	145
Mean ± SD	45.9 ± 15.4	41.8 ± 17.4	46.5 ± 15.3	43.6 ± 16.6
Median (min, max)	55.0 (5, 56)	54.0 (1, 56)	55.0 (2, 56)	54.0 (1, 56)
Overall exposure, d				
n	238	234	290	286
Mean ± SD	83.4 ± 59.5	80.1 ± 57.9	77.9 ± 55.4	75.1 ± 53.7
Median (min, max)	57.0 (5, 235)	57.0 (1, 243)	56.0 (2, 235)	56.0 (1, 243)
Patient-years	54.4	51.3	61.9	58.7

7.2.1.3b Dosing in escitalopram placebo-controlled clinical Studies 32, 32A, and 15 (extracted from ISS Table 4.2.3.1.1-2)

	Adolescents			*All Patients*		
	Placebo (N = 238)	*Escitalopram (N = 234)*		*Placebo (N = 290)*	*Escitalopram (N = 286)*	
	Tablets	**Tablets[a]**	**mg**	**Tablets**	**Tablets[a]**	**mg**
Overall daily dose						
Mean ± SD	1.4 ± 0.4	1.3 ± 0.4	13.3 ± 3.3	1.3 ± 0.4	1.3 ± 0.4	13.0 ± 3.2
Median (min, max)	1.4 (0.7, 2.0)	1.0 (0.6, 2.0)	13.8 (5.9, 19.1)	1.0 (0.7, 2.0)	1.0 (0.6, 2.0)	13.5 (5.9, 19.1)
Distribution of final daily dose, n (%)						
1 Tablet	69 (29.0)	96 (41.0)	—	91 (31.4)	118 (41.3)	—
2 Tablets	169 (71.0)	137 (58.5)	—	199 (68.6)	167 (58.4)	—

Note: 1 tablet=10 mg escitalopram; 2 tablets=20 mg escitalopram

7.2.1.4 Literature

The sponsor conducted a literature search using the electronic databases MEDLINE, BIOSIS, and EMBASE for escitalopram and citalopram in the pediatric population; the credentials of the

person doing the research isn't specified in there submission. The sponsor describes 1870 unique publications discussing some aspect of safety issues related to escitalopram. Unusual events published include emergence of tics (escitalopram), dystonic rabbit syndrome (escitalopram and citalopram), EPS (escitalopram), anaphylaxis with oculogyric dystonia (escitalopram), and enuresis (citalopram). The sponsor summarizes the vast amount of literature regarding suicide in the pediatric population in terms of anti-depressant use; however, the details of this topic are beyond the scope of this review.

7.2.3 Adequacy of Overall Clinical Experience

There are too few non-Caucasians included in the safety data base for escitalopram. Also, most of the safety data base is comprised of adolescents (12-17). There is very little escitalopram data in children 6-12 y.o. Considering the off-label use for younger kids, and that written requests for MDD include the pediatric population aged 6-17, there may be a need to have controlled efficacy and safety data on children aged 6 to 12 y.o.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There are no special animal and/or in vitro testing accompanying this submission.

7.2.5 Adequacy of Routine Clinical Testing

This application focuses on the adolescent population. There is a small number of patients younger than 12 y.o. exposed to escitalopram in a controlled safety data base despite off-label use.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

There are no special studies conducted for the pediatric MDD indication.

7.2.8 Assessment of Quality and Completeness of Data

The sponsor presented an adequate application that summarized data in an organized fashion.

7.2.9 Additional Submissions, Including Safety Update

The safety update dated September 19, 2008, covers the period of January 1 to May 23, 2008. The only studies completed during that period are in the adult population, and findings are consistent with the current label. The spontaneous post-market reporting summary notes many reports of neonates exposed to escitalopram and citalopram in utero. This drug is labeled as a Pregnancy Category C with a note of risks during pregnancy. FDA Maternal Health Team is reviewing and recommending amendments to the Lexapro label to include information from some of these reports.

When comparing adult spontaneous reports to those made of children and adolescents, the pediatric patients are reported to have a higher incidence of overdose and suicidality. Please see Appendix 4, for the sponsor's summary table comparing adult and pediatric spontaneous reports and a listing of events for this safety reporting period. As part of class labeling, escitalopram labeling has a bold warnings regarding pediatric suicide.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Many of the safety concerns reported in this supplemental NDA are addressed in the current escitalopram labeling.

There appears to be a signal (although, not pronounced) of suicidal gesture/attempts in this escitalopram safety data base, in addition to many spontaneously report adverse events identified through the sponsor's search. It is noted that this issue is already recognized by an anti-depressant class label WARNING of increase rates of suicide attempts in children/adolescents/young adults treated with anti-depressants.

Common AEs occurring with greater frequency in the escitalopram group compared to placebo in acute studies include the following: headache, abdominal pain, nausea, and insomnia; headache was identified as the most common treatment emergent AE in the adolescent escitalopram data base. In the longer term escitalopram study, diarrhea and urinary tract infections (UTI) are also considered common AEs (note: UTI was reported in ≥ 5 % of escitalopram patients with an incidence of ≥ 2 times observed in placebo patients).

Events observed in the escitalopram adolescent safety data base already addressed in the adult labeling include: elevated LFTs, orthostasis, and QTc prolongation of 3-4 msec with a couple of outliers with a > 60 msec increase.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

In the proposed labeling, the sponsor recommends 10 mg escitalopram once daily that as the initial dose of Lexapro® to treat adolescents with MDD. After referring to the flexible (10-20 mg daily) dose clinical studies, the labeling states that an increase in dose up to 20 mg should occur after a minimum of 3 weeks at the 10 mg dose.

8.2 Drug-Drug Interactions

There is no new information regarding drug-drug interactions in this supplement. As stated in the marketed labeling, the concomitant use of escitalopram with MAOIs is contraindicated. As an SSRI, escitalopram should be used with caution with drugs that affect hemostasis (e.g. NSAIDs, aspirin, warfarin), and other serotonergic drug (e.g. triptans, linezoilid, lithium, tramadol, St. John's Wort, other SSRIs, SNRIs, and typtophan). Caution is also recommended when co-administering escitalopram with any CNS drug or alcohol.

8.3 Special Populations

There is no new information in this supplement regarding special populations.

For **special populations**, the labeling recommends the dose of 10 mg/day in most elderly patients and patients with hepatic impairment, and that escitalopram should be used with caution in patients with severe renal impairment. There is a precaution that neonates exposed in-utero in the late third trimester may develop complications requiring prolonged hospitalization, respiratory support, and tube feeding.

8.4 Pediatrics

This application is limited to escitalopram treatment of MDD for the adolescent population. There is little safety data in children younger than 12 y.o., and the one study that included this younger age group has negative efficacy results.

8.5 Advisory Committee Meeting

No advisory committee meeting was held to discuss this adolescent MDD claim for escitalopram.

8.6 Literature Review

In the sponsor's literature review, some unusual events reported include emergence of tics (escitalopram), dystonic rabbit syndrome (escitalopram and citalopram), EPS (escitalopram), anaphylaxis with oculogyric dystonia (escitalopram), and enuresis (citalopram).

8.7 Post-marketing Risk Management Plan

The sponsor is encouraged to monitor post-marketing suicidal tendencies/events; especially given that this drug will now be indicated for the high risk group of adolescents.

9 OVERALL ASSESSMENT

9.1 Conclusions

There is one positive escitalopram placebo controlled study, and one positive citalopram study that support the labeling claim that escitalopram is effective in the treatment of MDD in the adolescent population. The escitalopram adolescent safety data base appears to be consistent with the current label for escitalopram, containing no unexpected events.

9.2 Recommendation on Regulatory Action

It is recommended that escitalopram be approved for the indication of MDD in the adolescent population. The dosing of 10 mg and 20mg escitalopram appear to be effect and safe in this population. The sponsor's proposed dosing of beginning at 10mg and, if necessary, titrating to 20 mg after 3 weeks, is consistent with the prudent pediatric dosing concept of "start low and go slow."

When escitalopram receives the labeling claim of acute MDD treatment in adolescents, the label may be eligible to extend this adolescent claim to longer term maintenance MDD treatment by extrapolation of the adult MDD data.

Once escitalopram is labeled for adolescents, it is recommended that the sponsor also include a section entitled **"Need for Comprehensive Treatment Program,"** modeled after this section in the labels for stimulant use in ADHD (an indication that traditionally was solely in pediatrics). This could highlight to clinicians that medication treatment is just one aspect of the effective treatment of adolescents suffering with MDD. Many clinicians (i.e. pediatricians and general practitioners) now prescribing medication to adolescents suffering with MDD, may not be specifically trained to understand the importance that talking therapies, engaging the family and adjusting school programs have in treating psychiatric illnesses in the pediatric population. This need for a "Comprehensive Treatment Program" becomes even more important when considering the elevated suicidality in this vulnerable adolescent population.

9.3 Recommendation on Post-marketing Actions

9.3.1 Risk Management Activity

It is important that the sponsor continue to monitor treatment emergent suicidality in this vulnerable population of adolescents suffering with major depressive disorder.

9.3.2 Required Phase 4 Commitments

Because escitalopram will obtain labeling for the adolescent population with MDD, it is likely that clinicians will increase their use in younger children off-label. It would be helpful if the sponsor would power a study to assess the efficacy of escitalopram in this younger population.

9.3.3 Other Phase 4 Requests

It is curious that a subgroup analysis revealed that patients categorized as African American did not demonstrate an improvement in MDD symptoms with escitalopram treatment. This observation and the fact that the escitalopram data base was composed primarily of Caucasians (>70%) would suggest that studying adolescents in varied racial background would offer clinicians better guidance for treatment decisions for individual patients.

9.4 Labeling Review

The final labeling for this application is the first escitalopram (Lexapro ®) label in the PLR format. Therefore, input is need from all disciplines to ensure continuity of labeling information into the PLR labeling format.

Conceptually, the labeling needs to reflect that most of the pediatric safety data base is in adolescents (12-17) with very little exposure in children (6-12). It also needs to be clear that efficacy for escitalopram is established by one escitalopram adolescent study and one citalopram pediatric study in which the positive results were primarily in the adolescent group.

As discussed in Section 9.2, above, it is recommended that the sponsor add a section entitled "**Need for Comprehensive Treatment Program**." This section can be used to emphasize the need to engage the family and school environment in a complete treatment plan to treat adolescents suffering with MDD, and that medication treatment is just one aspect of effective treatment.

The following are some specific recommendations in response to the sponsor's proposed labeling for this submission:

A. Summary Page:

1. It is unclear how far back the RECENT MAJOR CHANGES should go back. The sponsor's proposed labeling does not include any changes before 2008.
2. In the INDICATIONS AND USAGE section, the listing of "Treatment of Generalized Anxiety Disorder" needs to specify that this is for **adults only**.

B. INDICATIONS AND USAGE Section:

1. Under Section 1.1. Major Depressive Disorder, the entire proposed section should be replaced with the following language:

(b) (4)

(b) (4)

2. Under 1.2 Generalized Anxiety Disorder the entire proposed section should be replaced with the following language:

LEXAPRO is indicated for the treatment of Generalized Anxiety in adult patients. *[see Clinical Studies (14.X)]*.

C. In Section 2 DOSAGE AND ADMINISTRATION:

1. Mention of the lower dose in patients with hepatic disorders earlier in this section would be helpful.
2. Under Maintenance Treatment, the sponsor may add that MDD maintenance treatment for adolescents may be extrapolated from adult efficacy data.
3. Generalized Anxiety Disorder heading needs to add "in adults."
4. Special Populations section should be moved to the last listing of this section (b) (4).

D. In Section 5 WARNINGS AND PRECAUTIONS:

1. In Section 5.1 Clinical Worsening and Suicide Risk, the following language should be added to the end of this section:

(b) (4)

E. Section 6.2: Under MDD Pediatrics: In addition to the sponsor's proposal, headache is identified as the most common treatment emergent AE in the adolescent escitalopram data base. UTI is reported in ≥ 5 % of escitalopram patients with an incidence of ≥ 2 times observed in placebo patients.

F. Section 14 CLINICAL STUDIES

1. Study 18, the citalopram 8 week study in children and adolescents needs to be described in this section to explain that this was one of the two required studies used to support the efficacy of escitalopram in the adolescent population.
2. The longer term escitalopram study has several design flaws and the results were uninterpretable; therefore, for the purposed of efficacy, it is inappropriate to include it in labeling. The sponsor may explain that they have obtained a longer term maintenance claim in the adolescent population due to extrapolation of adult efficacy data.

G. In Section 14.2 GAD: specify that this indication is in **adults only**.

10 APPENDICES

Appendix 1

Schedule of Events for Study 32 (sponsor amended version dated 4/27/07)

			End of Double-Blind Treatment Week							*Double-Blind Down Taper*
	Screening		*Baseline*	*1*	*2*	*3*	*4*	*6*	*8*	*9*
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[1]**	**10**
Informed Assent and Consent (Patient)	x									
Informed Consent (Caregiver)			x							
Inclusion / Exclusion (Patient)	x	x	x							
Inclusion Criteria (Caregiver)			x							
Medical History (Patient)	x									
Psychiatric History (Patient)	x									
Background Information of the Caregiver and Family (Caregiver)			x							
Physical Examination	x[2]								x	
Clinical Laboratory Determinations	x[2]							x[3]		
Serum Pregnancy Test	x[2]							x[3]		
Thyroid Function Test	x[2]									
Urine Drug Screen	x[2]							x[3]		
ECG	x[2]			x				x[3]		
Plasma Sample								x[3]		
Vital Signs	x[2,4]		x[5]	x[5]	x	x	x	x[3,5]	x[4]	
KBIT	x									
K-SADS-PL	x	x								
CDRS-R	x		x	x	x	x	x	x	x	
CGI-S			x	x	x	x	x	x	x	
CGI-I				x	x	x	x	x	x	
CGAS			x				x		x	
SIQ-JR	x		x	x			x		x	
MC-SSRS	x		x	x	x	x	x	x	x	x
AEs		x	x	x	x	x	x	x	x[6]	x[6]
Concomitant Medications	x	x	x	x	x	x	x	x	x	x
Drug Dispensing		x	x	x	x	x	x	x	x[7]	
Drug Return			x	x	x	x	x	x	x	x
Final Evaluation									x[8]	x[8]
Resource Utilization and Productivity Instrument (Caregiver)			x				x		x	
Family Interaction Instrument (Caregiver)			x				x		x	
General Health Instrument (Caregiver)			x				x		x	
Follow-Up Questionnaire (Caregiver)[9]							x		x	

			End of Double-Blind Treatment Week							Double-Blind Down Taper
	Screening		Baseline	1	2	3	4	6	8	9
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[1]**	**10**
Informed Assent and Consent	x									
Inclusion / Exclusion	x	x	x							
Medical History	x									
Psychiatric History	x									
Physical Exam	x[2]								x	
Clinical Laboratory Determinations	x[2]							x[3]		
Serum Pregnancy Test	x[2]							x[3]		
Thyroid Function Test	x[2]									
Urine Drug Screen	x[2]							x[3]		
ECG	x[2]			x				x[3]		
Plasma Sample								x[3]		
Vital Signs	x[2,4]		x[5]	x[5]	x	x	x	x[3,5]	x[4]	
KBIT	x									
K-SAD-PL	x	x								
CDRS-R	x		x	x	x	x	x	x	x	
CGI-S			x	x	x	x	x	x	x	
CGI-I				x	x	x	x	x	x	
CGAS			x				x		x	
SIQ-JR	x		x	x			x		x	
AEs		x	x	x	x	x	x	x	x[6]	x[6]
Concomitant Medications	x	x	x	x	x	x	x	x	x	x
Drug Dispensing		x	x	x	x	x	x	x	x[7]	
Drug Return			x	x	x	x	x	x	x	x
Final Evaluations									x[8]	x[8]

1. All Visit 9 assessments to be completed for patients who discontinue prior to Week 8.
2. May be performed at the Investigator's discretion at Visit 2.
3. **To be performed as part of Early Termination Visit for patients who discontinue prior to Visit 8 only.**
4. Height is recorded at Visit 1 and Visit 9 (or Early Termination Visit), only.
5. **Standing blood pressure and heart rate measurements to be recorded in addition to seated measurements.**
6. Clinical findings upon termination must be followed until the condition returns to pre-study status or can be explained as unrelated to study drug. If necessary, a follow-up visit should be scheduled within 28 days of termination. Applicable for patients not entering the extension study.
7. For patients entering double-blind down taper.
8. For patients completing double-blind down taper, otherwise completed at Visit 9.

Appendix 2

Patients with PCS post-baseline values in LFTs in escitalopram safety data base
(extracted from ISS Table 6.3.1-3)

Study	*Patient ID (Age, y/Sex)*	*Parameter (Reference Range)*	*Laboratory Values*				
Placebo							
SCT-MD-32	0153208 (15/M)		*Baseline (11/16/05)*	*End Point (01/04/06)*		*Follow-Up (01/20/06)*	*Follow-Up (01/27/06)*
		Alk Phos (52-171 U/L)[a]	157	136		147	151
		ALT (5-30 U/L)	22	***106***		57	40
		AST (10-38 U/L)	15	***115***		71	38
		Bilirubin, total (0-19 µmol/L)	5	14		7	12
SCT-MD-32A	0303221 (14/M)		***SCT-MD-32***		***SCT-MD-32A***		
			Baseline (02/19/07)	*End Point (04/16/07)*	*Day 141 (07/23/07)*	*Day 155 (08/06/07)*	*End Point (08/20/07)*
		Alk Phos (74-390 U/L)	179	176	162	164	149
		ALT (5-30 U/L)	25	22	21	23	17
		AST (10-38 U/L)	28	27	26	25	22
		Bilirubin, total (0-19 µmol/L)	14	17	***36***	32	26
Escitalopram							
SCT-MD-15	0081501 (13/F)		*Baseline (02/07/03)*	*End Point (04/11/03)*		*Follow-Up (04/16/03)*	*Follow-Up (05/29/03)*
		Alk Phos (50-162 U/L)	184	142		148	180
		ALT (5-20 U/L)	17	44		28	17
		AST (10-31 U/L)	30	***97***		38	29
		Bilirubin, total (0-19 µmol/L)	5	5		5	3

Study	*Patient ID (Age, y/Sex)*	*Parameter (Reference Range)*	*Laboratory Values*					
SCT-MD-15	0231508 (13/F)		*Baseline (05/07/03)*				*End Point (07/10/03)*	
		Alk Phos (50-162 U/L)	147				139	
		ALT (5-20 U/L)	13				12	
		AST (10-31 U/L)	23				19	
		Bilirubin, total (0-19 µmol/L)	29				***38***	
Open-label escitalopram								
SCT-MD-32A	0153206[b] (15/F)		***SCT-MD-32***		***SCT-MD-32A***			
			Baseline (08/03/05)	*End Point (09/21/05)*	*Day 99 (11/16/05)*	*Day 136 (12/23/05)*	*Day 155 (01/11/06)*	*End Point (03/21/06)*
		Alk Phos (47-119 U/L)[c]	99	94	94	99	105	103
		ALT (5-20 U/L)	12	6	11	11	11	15
		AST (10-29 U/L)[c]	15	13	17	***180***	16	17
		Bilirubin, total (0-19 µmol/L)	26	29	29	21	17	19

Appendix 3a

Pooled analysis of weight z-scores for short term placebo-controlled Studies 15, 18, and 32.
(extracted for Statistical Review and Evaluation by George Kordzakhia, PhD: draft, 1/2009).

Pooled	**Placebo**		**Citalopram**		**Escitalopram**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Overall	373		89		282	
Baseline		1.20 (1.09)		1.11 (1.25)		1.13 (1.14)
Change		0.04 (0.125)		0.00 (0.17)		0.03 (0.129)
Male	166		42		124	
Baseline		1.16 (1.13)		1.13 (1.28)		1.04 (1.22)
Change		0.05 (0.14)		0.03 (0.19)		0.04 (0.13)
Female	207		47		158	
Baseline		1.23 (1.06)		1.10 (1.23)		1.21 (1.07)
Change		0.04 (0.11)		-0.04 (0.15)		0.02 (0.13)

Appendix 3b

Mean change from baseline in weight z-scores for Study 32/32A

(extracted for Statistical Review and Evaluation by George Kordzakhia, PhD: draft, 1/2009)

Study 32/32A	**Placebo**		**Escitalopram**	
	N	**Mean (SD)**	**N**	**Mean (SD)**
Overall	82		83	
Baseline		1.37 (1.17)		1.10 (1.20)
Change		0.08 (0.15)		0.09 (0.21)
Male	38		31	
Baseline		1.42 (1.35)		1.52 (1.40)
Change		0.10 (0.18)		0.13 (0.17)
Female	44		52	
Baseline		1.34 (0.99)		0.84 (0.99)
Change		0.06 (0.11)		0.06 (0.23)
	Placebo+Open Label Escitalopram		**Escitalopram+Open Label Escitalopram**	
Baseline	18	1.02 (0.95)	19	1.54 (1.26)
Change	18	-0.01 (0.11)	19	0.04 (0.14)

Appendix 4

Sponsor's Summary Table comparing adult and pediatric patients post-marketing spontaneous adverse event reports (extracted from Safety Update dated 8/19/08)

Table 6.1-1. Total Adverse Events for Escitalopram and Citalopram by Age Group

Product	*Child (0-11 y)*	*Adolescent (12-17 y)*	*Adult (18 y and Older)*	*Unspecified*	*Total*
Escitalopram	753	1494	28,417	5264	35,928
Citalopram	621	776	21,661	4118	27,176
Total	**1374**	**2270**	**50,078**	**9382**	**63,104**

Table 6.1.1-2. Citalopram Adverse Events in Children and Adolescents Compared With Adults

Age Group[a]	*Events Only Seen in Age Group When Compared With Adults and Reported More Than Twice (No. of Reports)*	*Events Seen as a Lower Percentage of the Total Reports (> 1% Difference) in the Age Group When Compared With Adults (% Difference)*	*Events Seen as a Higher Percentage of the Total Reports (> 1% Difference) in the Age Group When Compared With Adults (% Difference)*
Child	Drug withdrawal syndrome neonatal (12)[b] Apgar score low (7)[b] Neonatal respiratory distress syndrome (6)[b] Neonatal disorder (6)[b] Congenital anomaly (5)[b] Infantile apnoeic attack (4)[b] Growth retardation (4)[b] Patent ductus arteriosus (4)[b] Ventricular septal defect (4)[b] Jaundice neonatal (4)[b] Congenital eye disorder (3)[b] Neonatal asphyxia (3)[b] Neonatal aspiration (3)[b] Talipes (3)[b] Neonatal respiratory depression (3)[b] Respiratory disorder neonatal (3)[b] Congenital hand malformation (3)[b] Hyperbilirubinaemia neonatal (3)[b]	Nausea (2.2) Hyponatraemia (1.5) Headache (1.3) Insomnia (1.1) Hyperhidrosis (1.0)	Accidental overdose (1.3) Drug exposure during pregnancy (1.4) Hypertonia (1.1) Hypotonia (1.1) Premature baby (2.4)
Adolescent	None	Diarrhoea (1.1) Nausea (1.1)	Intentional overdose (1.5) Overdose (2.8) Convulsion (2.1) Aggression (1.1) Intentional self-injury (1.1) Suicidal ideation (1.2) Suicide attempt (3.0)

a The age groups were defined as follows: child, 0 to 11 years of age; adolescent, 12 to 17 years of age; adult, 18 years and older.

b Events reported in newborns who were exposed to citalopram during pregnancy.

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/s/

Roberta Glass
1/29/2009 01:19:03 PM
MEDICAL OFFICER

Ni Aye Khin
2/17/2009 09:19:24 AM
MEDICAL OFFICER
I agree with Dr. Glass that this set of NDA supplements should be considered for approval; see memo to file for additional comments.