1.0 TITLE PAGE

Forest Research Institute
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STUDY NO. SCT-MD-32

Title: A Double-Blind, Flexible-Dose Study of Escitalopram in Pediatric Patients With Major Depressive Disorder

Name of Study Drug: Escitalopram

Study Phase: IIIb

Initiation Date: April 1, 2005

Completion Date: May 31, 2007

The study was carried out in compliance with ICH-E6 Good Clinical Practice.

Report Date: **March 11, 2008**

9.0 INVESTIGATIONAL PLAN

The study protocol and amendments are provided in Appendix 16.1.1.

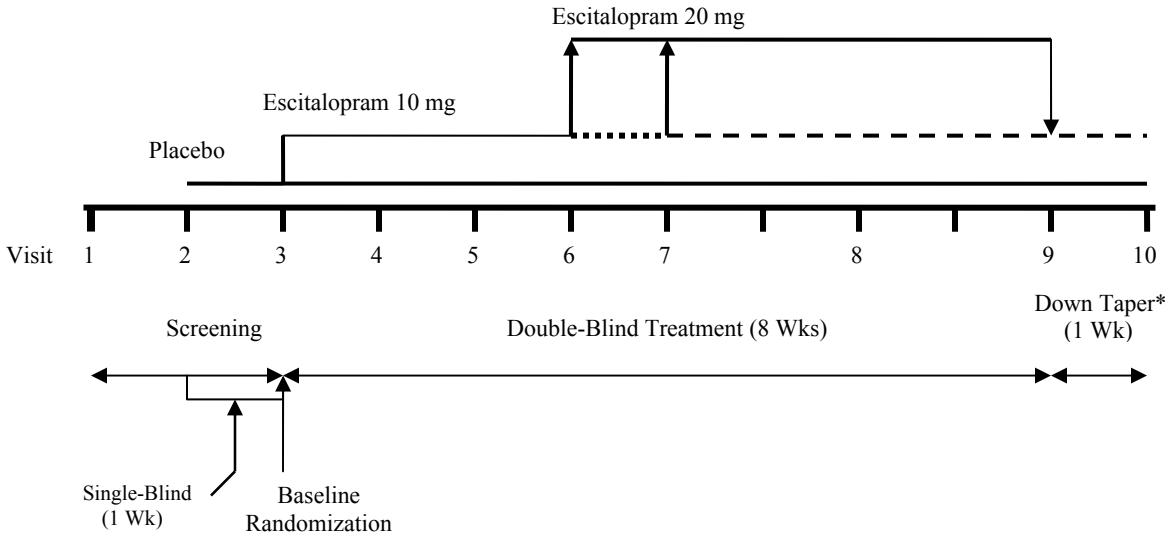
9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study. As shown in Figure 9.1–1, the study consisted of a 2-week screening period, including single-blind placebo lead-in during the second week, followed by 8 weeks of double-blind treatment. At the end of the single-blind period, patients meeting the entry criteria for this study were randomized 1:1 to one of two double-blind treatment groups (escitalopram or placebo). The escitalopram dosage was 10 mg/d for the first three weeks of double-blind treatment. The dosage could be increased to 20 mg/d by the Investigator at the end of Treatment Week 3 (Visit 6) or Treatment Week 4 (Visit 7).

Patients who completed the 8-week double-blind treatment period were eligible to enter a 1-week double-blind down-taper period or to continue in an extension study (Study SCT MD-32A). Patients who prematurely discontinued during Study SCT-MD-32 were also eligible to enter a 1-week double-blind down-taper period.

Detailed descriptions of each study visit are in the study protocol (Appendix 16.1.1). A sample eCRF is provided in Appendix 16.1.2.

Figure 9.1–1. Study Design



* Optional for patients not continuing into the extension study

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

The double-blind, placebo-control design was chosen for demonstration of efficacy, and the flexible dosing allowed the PI to titrate to efficacy in individual patients. The study design, population, and dosages used were chosen on the basis of previous pediatric and adult studies with citalopram and escitalopram, as discussed in Section 7.0.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

In order to be eligible to participate in the study, patients must have met the following criteria:

1. Provided assent to participation, and their parent or legal guardian provided written informed consent before the conduct of any study-specific procedures

2. Outpatients, male or female, between 12 and 17 years of age inclusively at Visit 1

3. Met *Diagnostic and Statistical Manual, Fourth Edition* (DSM-IV) diagnostic criteria for MDD. The duration of the current major depressive episode must have been at least 12 weeks at Visit 1

4. A parent or caregiver who was capable of providing information about the patient's condition and agreed to accompany the patient to all clinic visits

5. A family that was sufficiently organized and stable to guarantee to adequate safety monitoring

6. A score of 45 or greater on the CDRS-R at Visits 1 and 3

7. A CGI-S score of 4 or greater at Visit 3

8. A general intellectual functioning IQ score of 80 or higher on the Kaufman Brief Intelligence Test at Visit 1

9. Normal physical examination, laboratory tests, and ECG results at screening Visit 1 (or Visit 2), or if abnormal, the results must have been deemed not clinically significant by the Investigator and documented in the case report form

10. Female patients of childbearing potential had a negative β-human chorionic gonadotropin pregnancy test at screening Visit 1 (or Visit 2)

The Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime (K-SADS-PL) was used to confirm the diagnosis of MDD and to document the patient's psychiatric history (Kaufman, 1997). The K-SADS-PL is a semi-structured diagnostic interview that assesses the major diagnostic criteria relevant to psychiatric disorders in children and adolescents, including depression, through separate interviews of the patient and the parent/caregiver. It evaluates both past and current episodes.

In addition to the inclusion criteria for the patient, primary caregivers providing health economic information had to provide written informed consent at Visit 3 before undergoing any health economic assessment.

9.3.2 Exclusion Criteria

Patients who met any of the following criteria were to be excluded from the study:

1. Patients who had a principal diagnosis meeting DSM-IV criteria for any Axis I disorder other than MDD

2. Patients who met DSM-IV criteria for:

    a. attention deficit-hyperactivity disorder

    b. obsessive-compulsive disorder

    c. posttraumatic stress disorder

    d. bipolar disorder

    e. pervasive developmental disorder

    f. mental retardation

    g. conduct disorder

    h. oppositional defiant disorder

3. Patients with a history of a manic or a hypomanic episode

4. Patients with a first-degree relative with bipolar disorder

5. Patients with any psychotic features or with a history of any psychotic disorder, as defined by DSM-IV

6. Patients who were considered to be a suicide risk (active suicidal ideation), who had made a suicide attempt, or who had ever been hospitalized because of a suicide attempt

7. Patients with any personality disorder of sufficient severity to interfere with participation in the study

8. Patients with history of substance abuse or dependence, including alcohol, within the past year

9. Patients who tested positive for alcohol or any other prohibited medication on the urine drug screen at screening Visit 1 (or Visit 2)

10. Patients who had a history of anorexia nervosa or bulimia within the past year

11. Females who were pregnant or breast feeding

12. Females of childbearing potential who were not practicing, or were not willing to practice, a reliable method of birth control

13. Patients with a concurrent medical condition that might have interfered with the conduct of the study, confounded interpretation of the study results, or endangered the patient's well-being. Patients with evidence or history of malignancy (other than excised basal cell carcinoma) or any significant hematologic, endocrine, cardiovascular (including any rhythm disorder), neurologic, respiratory, renal, hepatic, or gastrointestinal disease. (If there was a history of such disease but the condition had been stable for more than 1 year and was judged by the Investigator not likely to interfere with the patient's participation in the study, the patient may have been included with the documented approval of the Study Director)

14. Patients with a history of seizures

15. Patients who had been treated with any antidepressant or anxiolytic medication within the 2 weeks before Visit 3 (4 weeks for fluoxetine)

16. Patients who had been treated with any neuroleptic or stimulant (eg, methylphenidate) within the 6 months before Visit 1

17. Patients who required concomitant treatment with any psychotropic drug (except zolpidem or zaleplon for sleep) or any drug with a psychotropic component (see Appendix 16.1.1 for Appendix II of Protocol)

18. Patients who required concomitant treatment with any prescription or over-the-counter medications that were not allowed by the protocol (see Appendix 16.1.1 for Appendix II of Protocol)

19. Patients who had been in a previous investigational study of citalopram or escitalopram

20. Patients with a history of hypersensitivity reaction to escitalopram or citalopram or other SSRIs

21. Patients who had previously failed to respond to an adequate trial of escitalopram or citalopram or to adequate trials of two other SRIs

22. Patients who had received treatment with any investigational drug within the 30 days or 5 half-lives (whichever was longer) before study entry

23. Patients who had initiated psychotherapy or behavioral therapy within the 3 months before the screening visit or who planned to initiate or change such therapies during the course of the study

24. Patients or patients whose parents or primary caregivers were unable to speak, read, or understand English to allow completion of all study assessments

25. Patients judged by the Investigator to be unable or unlikely to follow the study protocol

26. Patients who were employees or relatives of employees of the investigational site

9.3.3 Removal of Patients from Therapy or Assessment

A discontinuation occurred when a randomized patient ceased participation in the study, regardless of circumstances, before completion of the study. Drug treatment could be terminated the following reasons, one of which was to be identified as the primary reason for discontinuation in the eCRF:

- Adverse event
- Insufficient therapeutic response
- Protocol violation, including lack of compliance
- Withdrawal of consent
- Patient lost to follow-up
- Other reasons, such as administrative reasons or pregnancy

All patients who prematurely discontinued were to be seen for a final evaluation. Final evaluation was defined as completion of the evaluations scheduled for Visit 9. Patients who discontinued after randomization were not replaced.

9.4 TREATMENTS

9.4.1 Treatments Administered

Throughout the study, patients were instructed to take one tablet of study drug daily in the evening, starting on the day the study drug was dispensed. Dosing could be switched to mornings if the patient preferred.

9.4.1.1 Single-Blind Lead-In

Patients who met the eligibility criteria at Visit 2 were given 10 placebo tablets.

9.4.1.2 Double-Blind Treatment

Patients who met all eligibility criteria at baseline (Visit 3) were assigned a randomization number, and all subsequent dispensations of double-blind study drug were in accordance with the assigned treatment groups. At Visits 3 through 5, patients were given 10 tablets of either placebo or 10 mg escitalopram.

The dosage could be increased at Visit 6 or 7. At Visit 6, if the Investigator decided to not increase the dosage, patients were given 10 tablets of either 10-mg escitalopram or placebo. Alternatively, if the Investigator decided to increase the dosage, patients were given 10 tablets of either 20-mg escitalopram or placebo. At Visit 7, a patient's daily dosage could be increased if this had not occurred at Visit 6. Starting at Visit 7 and continuing to the end of double-blind treatment, visits occurred biweekly. Accordingly, at Visits 7 and 8, patients were given bottles containing 20 tablets of either 10-mg escitalopram, 20-mg escitalopram, or placebo. At Visit 8 patients were given the same daily dosage received at Visit 7.

9.4.1.3 Double-Blind Down-Taper

Patients who completed the study but who did not enter the extension study (Study SCT-MD-32A) and patients who prematurely discontinued from the study could enter an optional 1-week double-blind down-taper period. Patients who entered the double-blind down-taper period received 10 tablets of either escitalopram 10 mg or placebo, in accordance with their assigned treatment group.

9.4.2 Identity of Investigational Products

All study drug was supplied by Forest Laboratories, Inc., as film-coated tablets of identical appearance. For the double-blind treatment period, identically appearing tablets contained 10-mg escitalopram, 20-mg escitalopram, or placebo. Drug was supplied in bottles containing 10 or 20 tablets. Bottles designated "Bottle A" contained either escitalopram 10-mg tablets or placebo tablets. Bottles designated "Bottle B" contained either escitalopram 20-mg tablets or placebo tablets.

All study-drug bottles were labeled with the study number, visit number, storage and warning information, and instructions to take the tablets as directed. For double-blind study drug, the label also contained the patient randomization number. Immediately before dispensation, the patient initials, study center number, and date were to be written on the label.

The lot numbers for the study drug tablets used in this study are shown in Table 9.4.2–1.

Table 9.4.2–1. Lot Numbers of Study Drugs

Study Drug	*Lot Numbers*
Placebo tablets, single-blind lead-in phase	BN0001671
	L0000346/02008C
Placebo tablets, double-blind treatment phase	BN0001671
	L0000346/02008C
Escitalopram, 10-mg tablets	BN0001798
	L0000403/04030C
Escitalopram, 20-mg tablets	BN0001786
	L0000409/04053D

9.4.3 Method of Assigning Patients to Treatment Groups

At Visit 1, each patient was assigned a unique 7-digit patient identification number consisting of the 3-digit study center number followed by a 4-digit screening number assigned sequentially by each study center, beginning with 3201 (eg, 0013201, 0013202).

Patients who met all of the eligibility criteria at baseline (Visit 3) were randomized 1:1 to placebo or escitalopram in accordance with a randomization list generated by Statistical Programming at Forest Research Institute. A hard copy of the randomization list was retained by Drug Safety Surveillance at Forest Research Institute. Each study center was provided with double-blind study drug supplies corresponding to a sequence of patient randomization numbers. At each study center, the first patient to be randomized was to be assigned the first (lowest) available number in the sequence, and each subsequent patient entered was to be assigned the next number in the sequence. Treatment codes were unblinded at the termination of the study after the databases for both the lead-in and the extension studies (SCT-MD-32 and SCT-MD-32A) were locked.

Listing 16.1.7 provides the randomization scheme and codes.

9.4.4 Selection of Doses in the Study

The dosages of escitalopram used in this study (10 or 20 mg/d) were chosen on the basis of previous studies of the efficacy and pharmacokinetics of escitalopram and citalopram in both adults and adolescents.

For adults, three double-blind, placebo-controlled studies showed that escitalopram at a daily dose of 10 or 20 mg produced significantly greater improvement than placebo in patients' depressive symptomatology. In pediatric and adolescent patients, post hoc OC analyses of Study SCT-MD-15, an 8-week, double-blind study in patients 6-17 years of age with MDD, showed that a daily dose of escitalopram 10 or 20 mg produced significantly greater improvement than placebo in patients' depressive symptomatology. Furthermore, in both the overall pediatric population and in the adolescent subgroup of Study CIT-MD-18, a daily dose of citalopram 20 or 40 mg produced significantly greater improvement than placebo in patients' depressive symptomatology.

Three pharmacokinetic studies in pediatric or adolescent subjects (SCT-PK-10, CIT-PK-07, CIT-PK-13) have also shown that there are no clinically relevant differences relative to adults in the systemic exposure that results from a single 10-mg dose of escitalopram or after a single 20-mg dose or multiple 40-mg doses of citalopram.

9.4.5 Selection and Timing of Dose for Each Patient

Patients who met all eligibility criteria at baseline (Visit 3) were assigned a randomization number and given their corresponding double-blind study drug, either escitalopram or placebo. This was a flexible-dose study in which patients randomized to escitalopram received 10 mg/d through either Visit 6 or 7, with an option for the Investigator to increase the dosage to 20 mg/d at Visit 6 or 7. The dosage increase was based on the Investigator's evaluation of the patient and the absence of dose-limiting AEs. After Visit 8, patients were continued at the same daily dosage they received at Visit 7. However, if a patient whose dosage had been increased to 20 mg/d was unable to tolerate the study drug, the dosage could be decreased to 10 mg/d at any time.

Throughout the study, patients were instructed to take one tablet of study drug daily in the evening, starting on the day the study drug was dispensed. Dosing could be switched to mornings if the patient preferred.

9.4.6 Blinding

Bottles of double-blind study drug had two-part, three-panel labels. When the bottle was dispensed to the patient, the first panel remained on the bottle, and the second and third panels were torn off at the perforation and placed in the patient's file. If opened because of safety reasons, the third panel revealed the treatment corresponding to the patient randomization number. Breaking the blind at the study center would immediately disqualify the patient from further participation in the study. If the blind was broken for any reason Forest Research Institute was to be notified immediately, and a full written explanation was to be provided.

No randomization code was unblinded during the conduct of Study SCT-MD-32.

9.4.7 Prior and Concomitant Therapy

A complete list of drugs that were allowed or not allowed as concomitant medications is provided in the study protocol (see Appendix 16.1.1). No concomitant psychotropic medication or medication with a psychotropic component was permitted during the study except zolpidem or zaleplon as a sleep aid, at a maximum dosage of 10 mg/d up to three times per week. Medication history, including psychotropic medication use during the previous 5 years and use of any other medication during the previous 3 months, was to be recorded during screening. Thereafter, any changes in concomitant medication or new medications added were to be recorded in the eCRF.

9.4.8 Treatment Compliance

Study drug compliance was evaluated based on the number of tablets instructed to be taken (one per day) and the number actually taken. At the discretion of the Investigator and the Sponsor, patients could be discontinued for a lack of compliance (protocol violation).

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy and Safety Measurements Assessed

The schedule of study procedures and assessments is displayed by visit in Table 9.5.1–1. Patients were to be seen by a physician at each visit, and all evaluations were to be documented. Assessments were not to be administered if the patient was not accompanied by the parent or caregiver identified at Visit 1.

Table 9.5.1–1. Schedule of Evaluations

	Screening		***Baseline***	***Double-Blind Treatment Period***						***Double-Blind Down Taper***
End of Week	*–2*	*–1*	*0*	*1*	*2*	*3*	*4*	*6*	*8*	*9*
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[a]**	**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[b]								x	
Clinical laboratory determinations	x[b]							x[c]		
Serum pregnancy test	x[b]							x[c]		
Thyroid function test	x[b]									
Urine drug screen	x[b]							x[c]		
Electrocardiogram	x[b]			x				x[c]		
Plasma sample								x[c]		
Vital signs	x[b,d]		x[e]	x[e]	x	x	x	x[c,e]	x[d]	
KBIT	x									
K-SADS-PL	x	x								
CDRS-R	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
Adverse events		x	x	x	x	x	x	x	x[f]	x[f]
Concomitant medications	x	x	x	x	x	x	x	x	x	x
Drug dispensing		x	x	x	x	x	x	x	x[g]	
Drug return			x	x	x	x	x	x	x	x
Final evaluation									x[h]	x[h]

Table 9.5.1–1. Schedule of Evaluations

	Screening		*Baseline*	*Double-Blind Treatment Period*						*Double-Blind Down Taper*
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)[i]							x		x	

a All Visit 9 assessments were to be completed for patients who discontinued before Week 8.

b Could be performed at the Investigator's discretion at Visit 2.

c To be performed as part of Early Termination Visit for patients who discontinued before Visit 8.

d Height was to be recorded at Visit 1 and Visit 9 (or Early Termination Visit) only.

e Standing blood pressure and heart rate were to be recorded 1 minute after the patient stood.

f Clinical findings upon termination were to be followed until the condition returned to prestudy status or could be explained as unrelated to study drug. If necessary, a follow-up visit was to be scheduled within 28 days of termination. Applicable for patients not entering the extension study.

g For patients entering double-blind down taper.

h For patients completing double-blind down taper, otherwise to be completed at Visit 9.

i To be completed by caregivers of patients who discontinued before Visit 9.

CDRS-R = Children's Depression Rating Scale–Revised; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impressions–Improvement; CGI-S = Clinical Global Impressions–Severity; KBIT = Kaufman Brief Intelligence Test; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime; MC-SSRS = Modified Columbia–Suicide Severity Rating Scale; SIQ-JR = Suicidal Ideation Questionnaire–Junior High School Version.

9.5.2 Efficacy Measurements

Efficacy measurements included the CDRS-R, the CGI-I, the CGI-S, and the CGAS. All efficacy scales were evaluated by a clinician.

9.5.2.1 Primary Efficacy Assessment

The CDRS-R is a semistructured, clinician-rated instrument designed for use with children and adolescents between the ages of 6 and 17 years (Poznanski and Mokros, 1996). It contains 17 ordinally scaled items that evaluate the presence and severity of symptoms commonly associated with depression in childhood. The CDRS-R was administered at Visits 1, 3, 5, 7, 8, and 9, including early termination. At each visit, it was administered separately to the patient and to the parent or caregiver. The clinician was then to use the child-based scores and the parent-based scores to derive a best description of the child.

9.5.2.2 Secondary Efficacy Assessment

The CGI-I is a clinician-rated instrument to rate the total improvement or worsening in the patient's mental illness, based on the Investigator's clinical opinion (Guy, 1976). The score ranges from 1 to 7, with 1 being very much improved and 7 being very much worse, relative to baseline (Visit 3). Scoring is to be independent of whether the Investigator considers any changes to be due to treatment with the study drug. The CGI-I was performed at Visits 4 through 9, including early termination.

9.5.2.3 Additional Efficacy Assessments

The additional efficacy assessments used in this study were the CGI-S and CGAS.

The CGI-S, a clinician-rated instrument, was used to rate the severity of the patient's MDD on a scale from 1 to 7, with 1 being normal and 7 being a patient who was among the most extremely ill based on the Investigator's opinion and clinical experience. The CGI-S was administered at Visits 3 through 9, including early termination.

The CGAS, a clinician-rated instrument, was used to rate patients on a scale of 1 to 100 on the basis of their general level of overall functioning for the previous 14 days (Shaffer et al, 1983). The CGAS was administered at Visits 3, 7, and 9, including early termination.

9.5.3 Safety Measurements

Safety measurements included recording of AEs, clinical laboratory tests, vital signs, ECGs, physical examinations, the Suicidal Ideation Questionnaire–Junior High School Version (SIQ-JR), and the Modified Columbia–Suicide Severity Rating Scale (MC-SSRS). All safety assessments were conducted by a physician.

9.5.3.1 Adverse Events

At each visit, starting with Visit 2, patients were queried regarding any AEs since the last visit. Study center personnel recorded all pertinent information in the eCRF. Patients were asked nonleading questions to elicit them to volunteer information concerning AEs (eg "How do you feel?"). AEs were collected at Visit 2 and all subsequent visits, including early termination.

An AE was any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not considered related to study drug. Adverse events included:

- Changes in the general condition of the patient
- Subjective symptoms offered by or elicited from the patient
- Objective signs observed by the Investigator or study personnel
- All concurrent diseases that occurred after the start of the study, including any change in severity or frequency of pre-existing diseases
- All clinically relevant laboratory abnormalities or physical findings that occurred during the study

At each study visit (and during any contact with a patient or patient representative occurring outside of a defined study visit, including any contact up to 30 days after study completion), all AEs reported by the patient or patient representative or observed or otherwise identified by the Investigator or other study personnel were documented.

For each AE, the Investigator provided an assessment of the severity, timing, causal relationship to study drug, seriousness of the event, and whether the event was considered suggestive of self-harm. All actions taken with regard to study drug and any other treatment measures taken were documented. The Investigator or other study personnel was to inform Forest Laboratories, Inc., immediately (within 24 hours) of any AE considered serious, as defined in Section 9.5.3.2. Reporting was not to be delayed pending resolution or outcome of the event. If an outcome for an AE was not available at the time of the initial report, follow-up information was provided until such time as an outcome was known.

9.5.3.1.1 Causality Assessment

The Investigator provided an assessment of causal relationship to study drug for all AEs. The causality assessment was recorded on the appropriate AE reporting page of the patient's eCRF. Causal relationship was assessed according to the following scale:

Related: There was a reasonable temporal relation to study drug administration which could not be reasonably explained by other factors (such as the patient's clinical state, concomitant therapy, and/or other interventions), or there was an application/injection site reaction.

Possibly Related: The relationship to study drug could not be ruled out.

Not Related: Data were available to clearly identify an alternative cause for the event (eg, viral antigen in a case of suspected drug-induced hepatitis, hemorrhage due to mechanical injury).

9.5.3.1.2 Severity Assessment

The Investigator provided an assessment of the severity of each adverse event by recording a severity rating on the appropriate AE reporting page of the patient's eCRF. Severity was assessed according to the following scale:

Mild: The adverse event was an annoyance to the patient, but did not further hinder baseline functioning; the adverse event may have been intermittent or continuous.

Moderate: The AE caused the patient to experience some discomfort or some interference with normal activities, but was not hazardous to health; prescription drug therapy may have been employed to treat the AE.

Severe: The AE caused the patient to experience severe discomfort or severely limited or prevented normal activities, and represented a definite hazard to health; prescription drug therapy and/or hospitalization may have been employed to treat the AE.

9.5.3.1.3 Self-Harm Assessment

The Investigator's assessment of whether each AE was considered suggestive of self-harm was recorded on the AE reporting page of the patient's eCRF. All AEs considered by the Investigator to be suggestive of self-harm were then further categorized by the Investigator as suicide attempt, suicidal ideation, self-injurious behavior (nonsuicidal), accidental overdose, or other.

9.5.3.2 Serious Adverse Events

The Investigator or other study personnel was to immediately (within 24 hours) inform Forest Research Institute of all SAEs that occurred in study patients. An SAE was one that:

- Resulted in death
- Was an immediate threat to life
- Required hospitalization, or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital abnormality or birth defect
- In addition to the above, important medical events that did not result in death, were not life-threatening, or did not require hospitalization were considered SAEs when, based upon appropriate medical judgment, they were considered to have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed above

Although not an SAE in itself, any pregnancy during the study—even if no AE was produced in the mother—was to be reported within 24 hours, and the pregnancy followed to outcome.

9.5.3.3 Clinical Laboratory Tests

Blood and urine specimens for clinical laboratory determinations were collected during screening (at the Investigator's discretion at either Visit 1 or Visit 2) and at Visit 8 (or upon early termination if before Visit 8). The following parameters were measured:

Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count and differential, and platelet count.

Chemistry: alkaline phosphatase, albumin, blood urea nitrogen, calcium, cholesterol, chloride, creatinine, glucose, potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, total bilirubin, total protein, and uric acid.

Urinalysis: specific gravity, pH, glucose, white blood cells/high-power field, red blood cells/high-power field, casts/low-power field, protein, and ketones.

Other: Serum β-human chorionic gonadotropin pregnancy test for all female patients; thyroid-stimulating hormone test; and a urine drug screen.

At screening, the PI assessed the clinical significance of any values outside their respective reference ranges. Patients who had abnormalities judged to be clinically significant were excluded from the study. All reference ranges are presented in Listing 16.2.8.1. Positive results on the urine drug screen or pregnancy test excluded patients from participating in the study. Potentially clinically significant (PCS) clinical laboratory values were identified according to the criteria presented in Section 9.2 of the SAP, Appendix 16.1.9.1.

9.5.3.4 Vital Signs

Systolic and diastolic blood pressure and pulse rate (measured after the patient had been sitting for 5 minutes) and body weight were recorded at Visit 1 (or 2) and Visits 3 through 9 (or upon early termination). At Visit 3, Visit 4, and Visit 8 (or upon early termination if before Visit 8), the blood pressure and pulse rate were also measured 1 minute after the patient stood. Whenever possible, the patient's weight was measured at the same time of day. Patients were to wear their usual indoor clothing but take off their jacket and shoes. Only a well-calibrated balance beam scale was used. Height was recorded at Visit 1 (or Visit 2) and Visit 9 (or upon early termination). PCS vital sign values were identified according to the criteria presented in Section 9.3 of the SAP, Appendix 16.1.9.1.

9.5.3.5 Electrocardiograms

A complete standardized 12-lead ECG was performed during screening (at the Investigator's discretion at either Visit 1 or Visit 2) and at Visits 4 and 8 (or upon early termination if before Visit 8*).* The interpretation of the ECG was the responsibility of the Investigator. PCS ECG values were identified according to the criteria presented in Section 9.4 of the SAP, Appendix 16.1.9.1.

9.5.3.6 Physical Examination

A complete physical examination was performed during screening (at the Investigator's discretion at either Visit 1 or Visit 2) and at Visit 9 (or upon early termination). The physical examination was performed by a physician or by a health care professional listed on the form FDA 1572 and licensed to perform physical examinations.

9.5.3.7 Other Observations Related to Safety

9.5.3.7.1 Suicidal Ideation Questionnaire–Junior High School Version

The SIQ-JR was completed at Visits 1, 3, 4, 7, and 9 (or upon early termination). The SIQ-JR is a patient-rated questionnaire that identifies thoughts and cognitions about taking one's life (Reynolds, 1987). It consists of 15 items that the patient rates on a 7-point scale (0 = never had this thought; 1= had this thought before but not in the past month; 2 = about once a month; 3 = couple of times a month; 4 = about once a week; 5 = couple of times a week; 6 = almost every day). The total score range is 0 to 90. Patients should be considered for further evaluation if their total score is over 31 or, irrespective of total score, if the patient has two or more individual item scores of 5 or 6 on Questions 2, 3, 4, 7, 8, and 9.

9.5.3.7.2 Modified Columbia–Suicide Severity Rating Scale

Following Protocol Amendment #2, the MC-SSRS was administered at each visit, except Visit 2. The MC-SSRS is a clinician-rated instrument that reports the severity of both suicidal behavior and ideation (see Appendix III of Protocol in Appendix 16.1.1). Suicidal behavior is classified on a 6-item scale: 0 (nonsuicidal), 1 (preparatory acts or behavior communicating ideation), 2 (aborted attempt), 3 (interrupted attempt), 4 (actual attempt), and 5 (multiple attempts). More than one classification can be selected provided they represent separate episodes. Suicidal ideation is classified on a 6 item scale: 0 (nonsuicidal), 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with associated thoughts of methods without intent), 4 (active suicidal ideation with some intent to act on suicidal thoughts without clear plan), and 5 (active suicidal ideation with plan and intent). The MC-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability/intrusiveness, definitiveness/certainty, and deterrents and intent.

9.5.4 Health Economic Measurements

Health economic measurements were administered to the patient's caregiver at Visits 3, 7, and 9, including early termination. Participation of caregivers in the health economic assessments was voluntary.

The assessments included background information of the caregiver and family, the Resource Utilization and Productivity Instrument, the Family Interaction Instrument, the General Health Instrument, and, as needed, the Follow-Up Questionnaire. The Follow-Up Questionnaire was to be administered by telephone to primary caregivers of patients who prematurely discontinued from the study.

A description and analysis of the health economic measurements will be presented in a separate report.

9.5.5 Drug Concentration Measurements

A blood sample for the determination of the plasma concentration of escitalopram and its principle metabolite, S-desmethylcitalopram, was collected at the end of Visit 8 (or upon early termination if before Visit 8). The date and time of all blood draws were recorded in the eCRF, along with the date and time of the previous dose of study drug.

9.6 DATA QUALITY ASSURANCE

Before starting the study, representatives of Forest Research Institute met with the Investigators and their study center staff to familiarize them with the protocol, eCRFs, and procedures for proper source documentation. All eCRFs were reviewed by clinical monitors (field monitors) against source documents at the study center for validity, accuracy, and completeness.

A combination of manual and programmatic edit checks was used to review the eCRF data for completeness, logic, and adherence to study protocol. Any resulting queries were addressed by the study center and returned to Forest Research Institute for review. If necessary, the database was updated to reflect the new or changed information. After the end of the study and once all issues had been resolved, the database was locked and the treatment codes were unblinded.

9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

A complete discussion of the statistical methods and data handling is provided in the Statistical Analysis Plan (SAP) in Appendix 16.1.9.1. The SAP was finalized on May 20, 2005. Amendment 1 of the SAP was finalized on May 9, 2007, and treatment codes were unblinded on November 15, 2007. All statistical analyses were performed using the Statistical Analysis System (SAS) version 9.1.3 under a UNIX operating system.

9.7.1.1 Patient Populations

Four patient populations were defined for the study.

The Screened Population consisted of all patients who signed the informed consent form and were assigned a screen number.

The Randomized Population consisted of all patients in the Screened Population who were randomized to a treatment group.

The Safety Population consisted of all patients in the Randomized Population who took at least one dose of the double-blind study drug.

The Intent-to-Treat (ITT) Population consisted of all patients in the Safety Population who completed at least one postbaseline assessment of the CDRS-R.

9.7.1.2 Patient Disposition

The number of patients included in the Randomized, Safety, and ITT Populations was summarized by treatment group and study center. For the Screened Population, data were summarized by study center.

The number and percentage of patients who prematurely discontinued during the double-blind treatment period are presented for the Safety Population. Screen failures and the associated reasons are tabulated. Reasons for premature discontinuation from the double-blind treatment period as recorded on the termination page of the eCRF were summarized (number and percentage) by treatment group for all patients in the Safety Population.

Overall comparisons of the proportion of patients who prematurely discontinued from the study in each treatment group were performed using Fisher's exact test.

9.7.1.3 Demographics and Other Baseline Characteristics

Demographic parameters (age, sex, race, and ethnicity) and other baseline characteristics (weight and height) were summarized by treatment group for the Safety and ITT Populations.

Psychiatric history (disease course, number of major depressive episodes, duration of MDD, duration of current episode, age at onset, the incidence of ongoing secondary psychiatric disorders, and the combined incidence of previous or ongoing secondary psychiatric disorders) were summarized by treatment group for the Safety Population. The baseline scores of efficacy parameters were summarized by treatment group for the ITT Population.

Descriptive statistics (n, mean, SD, median, minimum, maximum, and SEM for baseline efficacy only) are presented for continuous variables and frequency distributions (count and percent) are presented for categorical variables.

Imbalance between treatment groups was tested using a two-way analysis of variance model with treatment group and study center as factors for continuous variables. The Cochran-Mantel-Haenszel test, controlling for study center, was used for categorical variables.

9.7.1.4 Extent of Exposure and Treatment Compliance

9.7.1.4.1 Study Drug

Exposure to double-blind study drug for the Safety Population was summarized in terms of treatment duration and daily dose.

The treatment duration for the double-blind treatment (excluding double-blind down-taper period) was calculated as the number of days from the date of first dose of double-blind study drug to the date of last dose of double-blind study drug before the start of the down-taper period. The treatment duration for the double-blind down-taper period was calculated as the number of days from the date of first dose of double-blind down-taper drug to the date of last dose of double-blind down-taper drug, inclusively.

The mean daily dose was computed as the total dose (in mg) taken during the interval divided by length of interval (in days). Final daily dose was defined as the last total daily dose taken prior to down-taper period.

Descriptive statistics (n, mean, SD, minimum, median, and maximum) are presented by treatment group for the treatment duration, mean daily dose, and final daily dose for the Safety Population. For mean daily dose, the data was also summarized by week and treatment group. The number of patients with dose increase was also summarized.

Patient-years, defined as total exposure to double-blind study drug (excluding down-taper period) in years, was summarized by treatment group for the Safety Population.

9.7.1.4.2 Prior and Concomitant Medication

The World Health Organization drug dictionary was used to classify prior and concomitant medications by therapeutic class.

For the purpose of summarizing prior and concomitant drug usage, prior medication was defined as any medication taken before the first dose of double-blind study drug. Concomitant medication was defined as any medication taken between the first and last dose of double-blind study drug.

Both prior and concomitant drug usage were summarized by the number and proportion of patients in each treatment group receiving each drug within each therapeutic class. Usage of multiple drugs within the same therapeutic class by a patient was counted only once. Summaries are presented for the double-blind treatment period excluding the down-taper period and for the double-blind down-taper period separately. Any medications started after the last dose of double-blind study drug in the double-blind treatment period excluding down taper or after the double-blind down-taper period are not included in the summary table for that period.

9.7.1.4.3 Measurement of Treatment Compliance

Dosing compliance for a specified period was defined as the total number of tablets actually taken by a patient during that period divided by the number of tablets expected to be taken during the same period multiplied by 100. The number of tablets actually taken was calculated by the number of tablets dispensed minus the tablets returned. The number of tablets expected to be taken during a specified period is the number of days in that period. Descriptive statistics for study drug compliance are presented by treatment group for each period between two consecutive visits as well as for the whole double-blind period of the study prior to down-taper.

9.7.1.5 Efficacy Analyses

All efficacy analyses were performed on the ITT Population. All primary and secondary efficacy analyses were performed using the LOCF approach. In this approach, missing postbaseline values were replaced with the last non-missing value before the missing value. Baseline values were not carried forward unless there was at least one non-missing postbaseline visit. The OC approach, in which only observed values are used, was used as a sensitivity analysis. Visit 3 assessments were used as the baseline for all efficacy parameters. All statistical tests were two-sided hypothesis tests performed at 5% level of significance. All confidence intervals were two-sided 95% confidence intervals.

9.7.1.5.1 Primary Efficacy Parameter

The primary efficacy parameter was the change from baseline to Week 8 in CDRS-R total score. The primary analysis used the LOCF approach. The between–treatment group comparison was performed using a two-way analysis of covariance (ANCOVA) model with treatment group and study center as factors and the baseline score as a covariate.

A sensitivity analysis for the primary efficacy parameter was performed using the mixed-effects model for repeated measures (MMRM) methodology based on the observed postbaseline longitudinal data. The model included study center, treatment group, visit, and treatment group-by-visit interaction as factors and baseline value as covariate. An unstructured covariance matrix was used for the repeated measures across visits.

9.7.1.5.2 Secondary Efficacy Parameter

The secondary efficacy parameter was the CGI-I score at Week 8.

The between–treatment group analysis was performed using an ANCOVA model with treatment group and study center as factors and the baseline CGI-S score as covariate.

9.7.1.5.3 Additional Efficacy Parameters

The additional efficacy parameters were:

- Change from baseline to Week 8 in CGI-S score
- Change from baseline to Week 8 in CGAS score
- CDRS-R response rate (40% reduction in CDRS-R from baseline)
- CDRS-R remission rate (CDRS-R ≤ 28)
- CGI-I response rate (CGI-I ≤ 2)

For the changes from baseline to Week 8 in the CGI-S and CGAS scores, the between-treatment group comparisons were performed using an ANCOVA model similar to that used for the primary efficacy parameter.

Between–treatment group comparisons for response and remission rates were performed using the logistic regression model (likelihood ratio test) with treatment group and baseline CDRS-R score (CGI-S score for CGI-I response) as explanatory variables.

Additionally, by-visit analyses were carried out for all efficacy parameters using LOCF and OC approaches.

9.7.1.6 Safety Analyses

The safety analyses were performed using the Safety Population. Safety variables included AEs, clinical laboratory parameters, vital signs, ECG parameters, physical examinations, and other safety parameters (SIQ-JR, MC-SSRS). For each safety parameter, the last assessment made before the first dose of double-blind study drug was used as the baseline for all analyses of that safety parameter. The endpoint for each study parameter was the last assessment made before the start of the double-blind down-taper period.

9.7.1.6.1 Adverse Events

All AEs were coded using the World Health Organization Adverse Reaction Terminology Dictionary, version 1998.

An AE that occurred during double-blind treatment, including the down-taper period, was counted as a treatment-emergent adverse event (TEAE) either if it was not present before the first dose of double-blind study drug or if it was present before the first dose of double-blind study drug but increased in severity following the first dose of double-blind study drug. If more than one AE with the same preferred term was reported before the first dose of double-blind study drug, then the AE with the greatest severity was used as the benchmark for comparison to the AEs occurring during the double-blind period under that preferred term. An AE that occurred more than 30 days after the last dose of double-blind study drug was not counted as a TEAE.

The number and percentage of patients who had TEAEs during the double-blind treatment period (before the first dose of down-taper study drug) were tabulated by body system, preferred term, and treatment group; by body system, preferred term, severity, and treatment group; and by body system, preferred term, relationship to study drug, and treatment group. Within a specific category, the patient is counted only once if the patient had more than one event reported.

The number and percentage of SAEs that started on or after the first double-blind study drug dosing date, AEs considered suggestive of self-harm, and AEs leading to discontinuation of double-blind study drug were summarized by body system, preferred term, and treatment group. The incidence of common (incidence $\geq$ 5% in any treatment group) TEAEs was summarized by preferred term and treatment group, sorted in decreasing frequency for the escitalopram treatment group.

Listings are presented for patients with an SAE, patients with AEs leading to premature discontinuation, and patients who died (if any). All patients who had SAEs or who prematurely discontinued, including screen failures, are included in the listings.

Any AE that occurred during the double-blind down-taper period was considered a newly emergent adverse event (NEAE) if it was not present before the first dose of double blind down-taper drug or if it was present before the first dose of the double-blind down-taper drug but increased in severity during the double-blind down-taper period. The NEAEs during the double-blind down-taper period were summarized by body system, preferred term, and treatment group.

9.7.1.6.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) are presented by treatment group at baseline, endpoint, and change from baseline to endpoint for the various parameters. Only patients who had a baseline and at least one postbaseline assessment were included in the summary.

Clinical laboratory test values were considered to be PCS if they met either the low or the high PCS criteria. The number and percentage of patients who had PCS postbaseline values were tabulated by treatment group. The percentages were calculated relative to the number of patients with available non-PCS baseline values and at least one postbaseline assessment. The numerator was the total number of patients with at least one PCS postbaseline value. A supportive listing of patients with PCS postbaseline values is provided including the patient ID, study center, and baseline and postbaseline values. A listing of all AEs for patients with PCS laboratory values is also provided.

9.7.1.6.3 Vital Signs

Vital signs assessed in this study included pulse rate, systolic blood pressure, diastolic blood pressure, body weight, and height. Descriptive statistics are presented for each parameter by visit including the final visit (endpoint). Changes from baseline were also summarized. Only patients who had a baseline assessment and at least one postbaseline assessment were included in the summary.

Vital sign values were considered to be PCS if they met both the observed value criteria and the change from baseline criteria. For each parameter, the number and percentage of patients who had any PCS postbaseline values were tabulated by treatment group, along with supportive listings.

Orthostatic hypotension was defined as a reduction of $\geq$ 20 mm Hg in systolic blood pressure or a reduction of $\geq$ 10 mm Hg in diastolic blood pressure when the patient changed from sitting to standing. The number and percentage of patients who had orthostatic hypotension are provided by treatment group and visit, including the final visit (endpoint) of the double-blind treatment period.

A supportive listing is provided indicating the patient identification number, treatment group, study visit, baseline value, and postbaseline systolic and diastolic blood pressure values (sitting and standing).

9.7.1.6.4 Electrocardiograms

ECG parameters were considered to be PCS if they met PCS criteria. For each parameter, the number and percentage of patients who had PCS postbaseline values were tabulated by treatment group. The percentages were calculated relative to the number of patients who had a non-PCS baseline and at least one postbaseline assessment.

Descriptive summary statistics are presented for each ECG parameter at baseline, Visit 4, Visit 8, and at endpoint (final observation), and for change from baseline to Visit 4 and Visit 8, and at endpoint (final observation) for each treatment group. Only patients who had a screening assessment and at least one postbaseline assessment were included in the summary.

A listing for all patients with PCS postbaseline values is provided including the patient ID, study center, and baseline and postbaseline values.

In addition, a listing of all AEs for patients who had PCS ECG values and a listing of patients who had postbaseline clinically significant ECG abnormalities as reported by the investigators are provided.

9.7.1.6.5 Physical Examinations

For each body system, the number and percentage of patients with transitions from normal or not done at baseline to abnormal postbaseline are presented by treatment group. The percentages were calculated relative to the number of patients having normal or missing assessments at baseline who also had a postbaseline physical examination. A listing of physical examination data for all patients is also provided.

9.7.1.6.6 Other Safety Measurements

9.7.1.6.6.1 Suicidal Ideation Questionnaire – Junior High School Version

Summary statistics are provided for the change from baseline in SIQ-JR total score by treatment group and visit, including the endpoint (final observation). Only patients who had a baseline assessment and at least one postbaseline assessment were included in the summary.

9.7.1.6.6.2 Modified Columbia–Suicide Severity Rating Scale

For the MC-SSRS, the number and percentage of patients who had an increase from baseline (worsening from Visit 3) in the suicidal behavior scores (from 0 to > 0) or suicidal ideation scores (from 0 or 1 to > 1) at any time during the study were tabulated. Only patients who had a baseline assessment and at least one postbaseline assessment were included in the summary. Supportive listings are provided indicating the patient identification number, treatment group, visit number, baseline value, and postbaseline values. Intensity of ideation is also included in these listings. In addition, a list of AEs for patients who had an increase from baseline in the suicidal behavior (from 0 to > 0) or suicidal ideation scores (from 0 or 1 to > 1) at any time during the study is provided.

9.7.2 Pharmacokinetic Analysis

Descriptive statistics are presented for the plasma concentration of escitalopram and its principal metabolite, S-desmethylcitalopram (S-DCT).

9.7.3 Determination of Sample Size

The primary efficacy parameter was the change from baseline to Week 8 in CDRS-R total score using the LOCF approach. Assuming an effect size (treatment group difference relative to standard deviation) of 0.325, a sample size of approximately 150 patients in each treatment group was used to provide at least 80% power at a significance level of 0.05 using a two-sided test.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.8.1 Changes in the Conduct of the Study

Subsequent to the study protocol dated December 21, 2004, four amendments were made (March 31, 2005; July 22, 2005; September 30, 2005; April 27, 2007). Each amendment was reviewed and approved by the governing IRBs before implementation at each study center. For the study protocol and each amendment see Appendix 16.1.1.

9.8.1.1 Amendment 1

The primary changes in Amendment 1 (March 31, 2005) were to add an ECG assessment at Visit 4; to add the assessment of standing vital signs (pulse rate and systolic and diastolic blood pressure) at Visits 3, 4, and 8; to add plasma sampling at Visit 8; to change the collection of endpoint clinical laboratory tests from Visit 9 to Visit 8; and to add Zyvox (linezolid) to the list of prohibited concomitant medications.

9.8.1.2 Amendment 2

The primary change in Amendment 2 (July 22, 2005) was to include the MC-SSRS, which was to be completed at each visit except Visit 2.

9.8.1.3 Amendment 3

The primary changes in Amendment 3 (September 30, 2005) were to include health economics assessments to be completed by the patient's primary caregiver and to modify the schedule of CDRS-R assessments so that the CDRS-R was performed at Visits 1, 3, 5, 7, 8, and 9.

9.8.1.4 Amendment 4

The primary change in Amendment 4 (April 27, 2007) was to update the description of the planned statistical analyses, as further described in Section 9.8.2.1.

9.8.2 Changes in the Planned Analyses

Subsequent to the SAP dated May 20, 2005, one amendment was made (May 9, 2007). For the SAP and the amendment see Appendix 16.1.9.1.

9.8.2.1 Amendment 1

Major changes to the analyses specified in the original SAP were as follows:

1. Added analysis of the MC-SSRS, an assessment added by Protocol Amendment #2, dated July 22, 2005

2. Removed the Shapiro-Wilk normality test and the nonparametric ANCOVA based on ranks

3. Added a sensitivity analysis using MMRM methodology to assess the sensitivity of the primary efficacy results to the presence to dropouts

Changes #2 and #3 were based on communications with the FDA (FDA letter dated July 14, 2005, Forest Response dated December 5, 2006). All of the above changes were made before unblinding of the treatment codes.

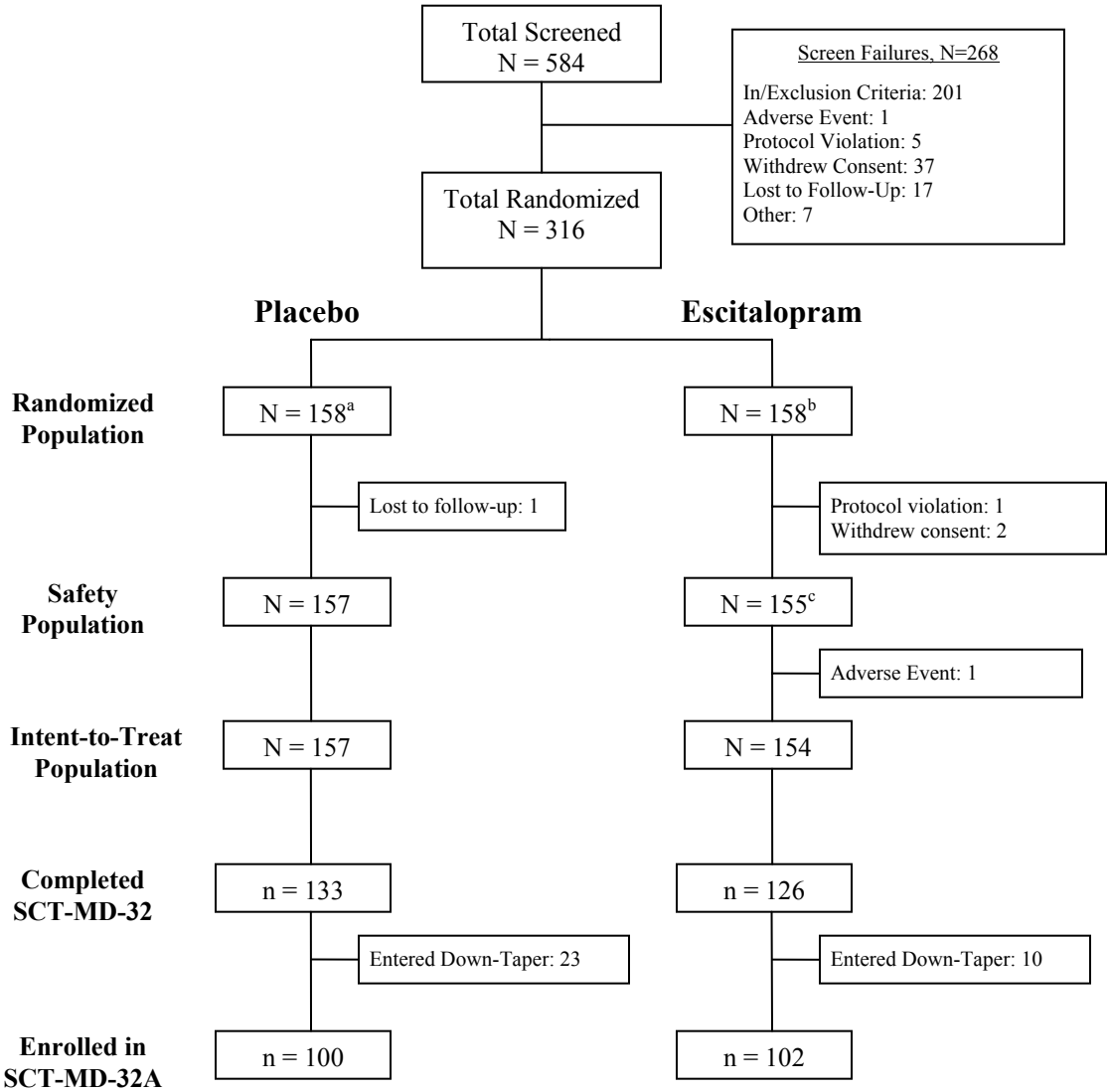
10.0 STUDY PATIENTS

10.1 DATA SETS ANALYZED

Patient populations are illustrated by treatment group in Figure 10.1–1.

A total of 584 patients were screened for eligibility; 316 patients were randomized to receive double-blind study drug; 312 patients received at least one dose of double-blind study drug (Safety Population); and 311 patients had at least one postbaseline CDRS-R assessment (ITT Population).

Figure 10.1–1. Patient Populations



a Patient 0323214 discontinued before taking double-blind placebo.
b Patients 0303210, 0463205, and 0503206 discontinued before taking double-blind escitalopram.
c Patient 0123207 discontinued before having a CDRS-R assessment.
Cross-reference: Tables 14.1.1, 14.1.2, 14.1.3; Appendix 16.2.2.1.

10.2 DISPOSITION OF PATIENTS

The patient disposition for the Safety Population is shown by treatment group in Table 10.2–1. The most frequent reasons for discontinuation from the Safety Population were withdrawal of consent (5.7% placebo, 5.2% escitalopram) and loss to follow-up (3.8% placebo, 5.2% escitalopram). There were no statistically significant differences between the two treatment groups with respect to discontinuation rates.

Table 10.2–1. Patient Disposition: Safety Population

	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)
Completed study	133 (84.7)	126 (81.3)	259 (83.0)
Entered Study SCT-MD-32A	100 (75.2)	102 (81.0)	202 (78.0)
Entered down-taper	23 (14.6)	10 (6.5)	33 (10.6)

Percentages are relative to the number of patients in the Safety Population.

a The "other" reasons for discontinuation from the placebo group were "death of mother – subject wishes to go into therapy" for 0033210, "moving out of state" for 0123222, and "positive pregnancy test" for 0503204.

b The "other" reason for discontinuation from the escitalopram group was "subject is moving on short notice to Indiana" for 0323204.

Cross-Reference: Tables 14.1.3, 14.1.4; Listing 16.2.2.1.

A total of 133 (84.7%) placebo patients and 126 (81.3%) escitalopram patients completed 8 weeks of double-blind treatment, and 202 patients (100 placebo, 102 escitalopram) continued into the extension study, SCT-MD-32A. Of the 57 patients who did not continue into the extension study, 33 (23 placebo, 10 escitalopram) entered the double-blind down-taper period. All of these patients, with the exception of placebo Patient 0163201, completed Study SCT-MD-32 before entering down-taper.

The list of patients who prematurely discontinued is provided in Table 14.1.4. The corresponding individual patient data are presented in Listing 16.2.2.1. Patients who discontinued due to AEs are discussed in Section 12.2.3.1.

10.3 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

The demographic characteristics of the Safety Population are presented in Table 10.3–1. The average patient age was approximately 15 years, and approximately three quarters of the patients in each treatment group were Caucasian. Females comprised 59% of the Safety Population. There were no statistically significant differences between the two treatment groups with respect to demographic characteristics. Demographic characteristics of the ITT Population, presented in Table 14.2.2, were similar to those of the Safety Population.

Table 10.3–1. Demographic and Baseline Characteristics: Safety Population

	***Placebo* (N = 157)**	***Escitalopram* (N = 155)**	***Total* (N = 312)**
Age, years, mean ± SD	14.52 ± 1.48	14.74 ± 1.64	14.63 ± 1.56
Sex, n (%)			
Male	65 (41.4)	63 (40.6)	128 (41.0)
Female	92 (58.6)	92 (59.4)	184 (59.0)
Race, n (%)			
Caucasian (White)	123 (78.3)	113 (72.9)	236 (75.6)
Black	24 (15.3)	30 (19.4)	54 (17.3)
Asian	0	3 (1.9)	3 (1.0)
Other	10 (6.4)	9 (5.8)	19 (6.1)
Ethnicity, **non-Hispanic, n (%)**	139 (88.5)	144 (92.9)	283 (90.7)
Weight, lbs, mean ± SD	157.4 ± 47.6	158.9 ± 49.7	158.2 ± 48.6
Height, in, mean ± SD	65.2 ± 3.7	65.1 ± 3.8	65.1 ± 3.7

Cross–reference: Table 14.2.1.

The psychiatric history and incidence of secondary psychiatric disorders in the Safety Population is presented in Table 10.3–2. There were no statistically significant differences between the treatment groups.

Table 10.3–2. Psychiatric History: Safety Population

	Placebo (N = 157)	*Escitalopram (N = 155)*
Major Depression, n (%)		
Single episode	113 (72.0)	109 (70.3)
Recurrent	44 (28.0)	46 (29.7)
Duration of current episode, n (%)		
≤ 1 year	50 (31.8)	53 (34.2)
1-3 years	60 (38.2)	55 (35.5)
3-5 years	29 (18.5)	29 (18.7)
> 5 years	18 (11.5)	17 (11.0)
Age at onset, years, mean ± SD	12.3 ± 2.5	12.4 ± 2.6
Ongoing secondary psychiatric disorder, n (%)	11 (7.0)	8 (5.2)

Cross-Reference: Table 14.2.3; Listing 16.2.3.2.

The baseline efficacy values for the ITT Population are presented in Table 10.3–3. At baseline, there were statistically significant differences in CDRS-R total score and CGI-S between the two treatment groups, with higher depression severity at baseline in the escitalopram group. The two treatment groups did not have different baseline CGAS scores. As established in the SAP (Appendix 16.1.9.1), the ANCOVA models used for the later analysis of all efficacy parameters used the appropriate baseline score as a covariate and thus controlled for any significant differences in the baseline efficacy values.

Table 10.3–3. Baseline Efficacy: ITT Population

	Placebo (N = 157) mean ± SD	*Escitalopram (N = 154) mean ± SD*	*p-value*[a]
CDRS-R total score	56.0 ± 8.3	57.6 ± 8.3	.034
CGI-S	4.4 ± 0.5	4.6 ± 0.6	.007
CGAS	51.9 ± 5.5	51.9 ± 6.3	.851

a p-values are from a two-way analysis of variance model with treatment group and study center as factors.
CDRS-R = Children's Depression Rating Scale–Revised; CGAS = Children's Global Assessment Scale; CGI-S = Clinical Global Impressions–Severity.
Cross-reference: Table 14.2.8.

Summaries by treatment group of demographic characteristics, baseline efficacy and safety variables, and medical and psychiatric history are presented in Tables 14.2.1 through 14.2.9B. The corresponding individual patient data are presented in Appendices 16.2.3.1 through 16.2.3.6.

10.4 PROTOCOL DEVIATIONS

The number and percentage of patients with major protocol deviations are presented in Table 10.4–1. Potential deviations were reviewed and finalized before database lock and unblinding of treatment codes. The proportion of patients with major protocol deviations was similar between treatment groups, with deviations identified in 16 (10%) patients in the placebo group and 13 (8%) patients in the escitalopram group.

Table 10.4–1. Major Protocol Deviations: Safety Population

Deviation	***Placebo (N = 157) n (%)***	***Escitalopram (N = 155) n (%)***
Patients with any deviation[a]	16 (10.2)	13 (8.4)
Inclusion/exclusion criteria deviations		
Age < 12 years	0	1 (0.6)
Duration of current MDD episode < 12 weeks before Visit 1	4 (2.5)	2 (1.3)
Screening CDRS-R total score < 45	1 (0.6)	1 (0.6)
Deviations of study drug dosing		
Incorrect dose of study drug for 2 or more days[b]	0	5 (3.2)
Discontinued study drug for more than 5 consecutive days between study visits	6 (3.8)	5 (3.2)
Prohibited concomitant medication		
Taken ≥ 5 days:		
Pseudoephedrine[c]	3 (1.9)	0
Benadryl	1 (0.6)	0
Taken any time:		
Insulin	1 (0.6)	0
Prednisone	0	2 (1.3)
Sevoflurane	1 (0.6)	0
Propofol	1 (0.6)	0

Percentages are relative to the number of patients in the Safety Population.

a A patient could have more than one deviation. Two patients in the placebo group and three patients in the escitalopram group each had two deviations.

b All patients were to take one tablet per day.

c Pseudoephedrine category includes Dimetapp and Allegra D.

CDRS-R = Children's Depression Rating Scale–Revised; MDD = major depressive disorder.

Cross-reference: Appendix 16.2.

For patient-level information regarding the major deviations identified see Appendix 16.2. There were nine deviations related to the study inclusion/exclusion criteria (5 placebo, 4 escitalopram). One patient (0183210), who was later randomized to escitalopram, was 11.9 years of age at Visit 1. A current episode of MDD that was less than 12 weeks in duration at Visit 1 was found in six patients (4 placebo, 2 escitalopram). In the placebo group, three patients had an MDD duration of 10 weeks, and one patient had an MDD duration of 5 weeks (0053212). In the escitalopram group, Patient 0203223 had an MDD duration of 6.5 weeks, and Patient 0303213 had an MDD duration of 11 weeks. Two patients, one per treatment group (placebo Patient 0463201, escitalopram Patient 0353201), had a screening CDRS-R score below 45 (total score was 44 in both).

There were 16 deviations related to study drug, including consumption of an incorrect dose of study drug by five escitalopram patients (4 patients took 2 tablets per day, and 1 patient took ½ tablet per day) and discontinuation of study drug dosing for 5 or more days by six placebo patients and five escitalopram patients.

There were nine deviations related to concomitant medications that were limited or prohibited by Appendix II of the Protocol (7 placebo, 2 escitalopram; Appendix 16.1.1).

During the study, no placebo patients and 1.9% (3/155) of escitalopram patients were prematurely discontinued from the study by the Investigator for a protocol violation (Table 14.1.4). For all three of these patients (0213205, 0213206, and 0333203), noncompliance with study drug and/or visits was reported by the Investigator at the time of discontinuation.

10.5 EXTENT OF EXPOSURE

10.5.1 Study Drug

The extent of exposure for patients in each treatment group is presented in Table 10.5.1-1. The mean treatment duration was 52.8 days for the placebo group and 52.1 days for the escitalopram group. The number of tablets per day received was similar in the two groups, with an overall mean dosage of 13.2 mg/d in the escitalopram group. The dosage was increased in most patients (76.4% placebo, 68.4% escitalopram). The corresponding individual patient data are presented in Listing 16.2.4.1.

Table 10.5.1-1. Extent of Exposure: Safety Population

		Placebo (N = 157)	*Escitalopram (N = 155)*
Treatment duration, days	mean ± SD	52.8 ± 11.6	52.1 ± 12.8
	median	56	56
	min, max	5, 67	3, 67
Overall mean dosage	mg/d (mean ± SD)	—	13.2 ± 2.9
	tablets/d (mean ± SD)	1.4 ± 0.3	1.3 ± 0.3
Patients with dose increase, n (%)		120 (76.4)	106 (68.4)
Patient-years		22.7	22.1

Treatment duration = last date of double-blind study drug before down-taper – first date of double-blind study drug + 1. Patient-years = total exposure to study drug in years.

Cross-reference: Tables 14.3.1.1, 14.3.1.2, 14.3.1.4.

10.5.2 Prior and Concomitant Medications

A summary of prior or concomitant medications in the Safety Population is presented in Tables 14.3.2.1 and 14.3.2.2, respectively. During the study, 73.9% of placebo patients and 71.0% of escitalopram patients received at least one concomitant medication. The most common concomitant medications (used by ≥ 10% of patients in either group) were analgesics, antibacterials for systemic use, antihistamines for systemic use, anti-inflammatory/antirheumatics, and drugs for obstructive airway diseases. The use of common concomitant medications was similar between treatment groups.

The corresponding individual patient data are presented in Listing 16.2.5.1.

10.6 MEASUREMENTS OF TREATMENT COMPLIANCE

A summary of patient compliance with double-blind study drug is displayed by treatment group and visit in Table 14.3.3. Overall treatment compliance was similar between groups (93.5% placebo, 93.7% escitalopram). The corresponding individual patient data are presented in Listing 16.2.4.2.

11.0 EFFICACY EVALUATION

All efficacy analyses were based on the ITT Population, which was defined as all patients who received at least one dose of double-blind study drug and had at least one postbaseline assessment of the CDRS-R.

11.1 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

11.1.1 Analyses of Efficacy

11.1.1.1 Primary Efficacy Parameter

The primary efficacy parameter was the change from baseline to Week 8 in CDRS-R total score. Table 11.1.1.1–1 presents the results of the ANCOVA analysis for this primary endpoint, using the LOCF approach. The change from baseline to Week 8 in the escitalopram group was clinically and statistically significant and greater than that in the placebo group (LSMD = –3.4, p = .022).

Table 11.1.1.1–1. Primary Analysis: Change From Baseline to Week 8 in CDRS-R Total Score: ITT Population

	Placebo (N = 157)	***Escitalopram (N = 154)***	***LSMD (95% CI)***	***p-value***
	Mean ± SEM	*Mean ± SEM*		
Baseline	56.0 ± 0.7	57.6 ± 0.7	–	–
Change at Week 8 (LOCF)[a]	–18.4 ± 1.1	–22.4 ± 1.1	–3.4 (–6.2, –0.5)	.022

a Analysis is based on an analysis of covariance model for change from baseline with treatment group and study center as factors and baseline value as covariate.

CDRS-R = Children's Depression Rating Scale–Revised; CI = confidence interval; ITT = Intent-to-Treat; LOCF = last observation carried forward; LSMD = least squares mean difference.

Cross-reference: Tables 14.4.1.1, 14.4.3.1A.

Results of the OC and MMRM sensitivity analyses for the primary efficacy parameter are presented in Table 11.1.1.1–2. In the OC analysis, the escitalopram group was numerically superior to the placebo group, but the difference was not significant (p = .071). The MMRM analysis showed a statistically significant improvement in the escitalopram group relative to the placebo group (LSMD = –3.1, p = 0.035).

Table 11.1.1.1–2. Sensitivity Analyses: Change From Baseline to Week 8 in CDRS-R Total Score: ITT Population

	Placebo (N = 157)		Escitalopram (N = 154)		LSMD (95% CI)	p-value
	n	*Mean ± SEM*	*n*	*Mean ± SEM*		
CDRS-R baseline	157	56.0 ± 0.7	154	57.6 ± 0.7	–	–
Change at Week 8 (OC)[a]	135	–20.1 ± 1.2	129	–23.8 ± 1.2	–2.8 (–5.8, 0.2)	.071
Change at Week 8 (MMRM)[b]	153	–19.6 ± 1.2	154	–22.7 ± 1.1	–3.1 (–6.0, –0.2)	.035

a OC analysis is based on an analysis of covariance model with treatment group and study center as factors and baseline value as covariate

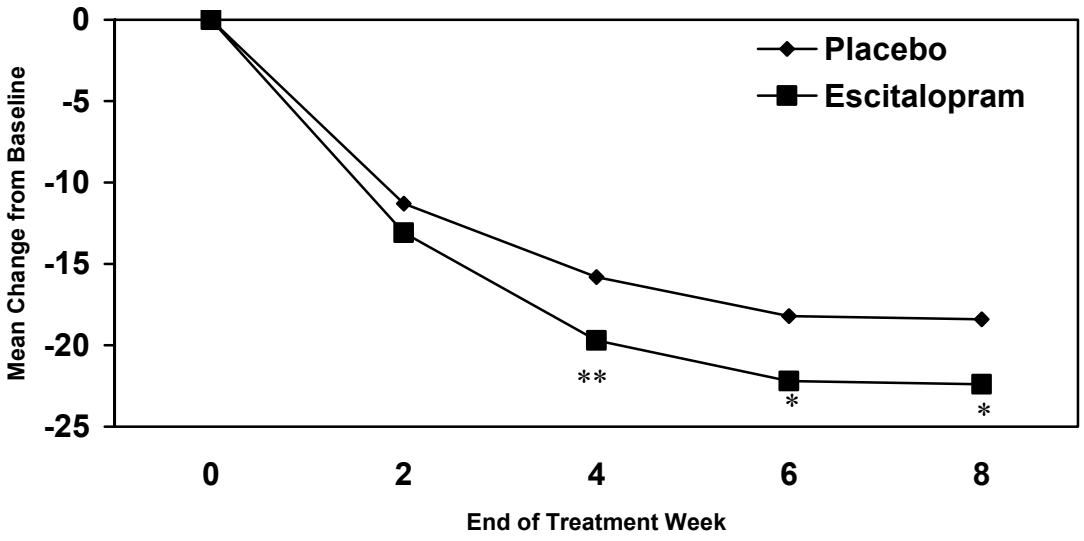
b MMRM analysis included visit, treatment group, treatment-group-by-visit interaction, and study center as factors, baseline value as covariate, and an unstructured covariance matrix. For the MMRM, least squares mean and standard error for the least squares mean are presented.

CDRS-R = Children's Depression Rating Scale–Revised; CI = confidence interval; ITT = Intent-to-Treat; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; OC = observed cases.

Cross-reference: Tables 14.4.1.1, 14.4.3.1B; Table 16.1.9.3.1.

By-visit data for change from baseline in CDRS-R total score are shown in Figure 11.1.1.1–1 and presented in Table 14.4.3.1A (LOCF analyses). Statistically significant improvement in the escitalopram group relative to the placebo group was seen at Week 4 and was maintained through Week 8, with statistical significance at all time points.

Figure 11.1.1.1–1. Change From Baseline in CDRS-R by Visit: LOCF Analysis, ITT Population



*p < .05; **p < .01

Individual patient data for the CDRS-R are presented in Listing 16.2.6.1. Descriptive statistics by visit for LOCF and OC analyses are presented in Tables 14.4.3.1A and 14.4.3.1B, respectively.

11.1.1.2 Secondary Efficacy Parameter

Table 11.1.1.2–1 presents the results for the CGI-I score at Week 8, the secondary efficacy endpoint. At Week 8, statistically significant improvement was seen in the escitalopram group relative to the placebo group in both the LOCF (LSMD = –0.3, p = .008) and OC analyses (LSMD = –0.3, p = .023).

Table 11.1.1.2–1. CGI-I Score at Week 8: ITT Population

	Placebo (N = 157)		*Escitalopram (N = 154)*		*LSMD (95% CI)*	*p-value*
	n	*Mean± SEM*	*n*	*Mean ± SEM*		
CGI-I at Week 8 (LOCF)[a]	157	2.5 ± 0.1	154	2.2 ± 0.1	–0.3 (–0.6, –0.1)	.008
CGI–I at Week 8 (OC)[a]	135	2.3 ± 0.1	130	2.1 ± 0.1	–0.3 (–0.6, –0.0)	.023

a Analysis is based on ANCOVA model with treatment group and study center as factors and baseline CGI-S score as covariate.

CGI-I = Clinical Global Impressions–Improvement; CI = confidence interval; ITT = Intent to Treat; LOCF = last observation carried forward; LSMD = least squares mean difference; OC = observed cases.

Cross-reference: Table 14.4.2.1.

By-visit data for CGI-I and descriptive statistics are presented in Tables 14.4.3.2A and B. Individual patient data are presented in Listing 16.2.6.2.

11.1.1.3 Additional Efficacy Parameters

The additional efficacy parameters included change from baseline to Week 8 in CGI-S and CGAS, CGI-I response (CGI-I ≤ 2), CDRS-R response (≥ 40% reduction from baseline), and CDRS-R remission (CDRS-R ≤ 28).

Table 11.1.1.3–1 presents the change from baseline to Week 8 in CGI-S and CGAS. At Week 8, statistically significant improvement in CGI-S was seen in the escitalopram group relative to the placebo group using both the LOCF (LSMD = –0.4; p = .007) and OC (LSMD = –0.3; p = .022) approaches. On the CGAS at Week 8, a numerically higher improvement was seen in the escitalopram group relative to the placebo group; the difference was borderline significant in the OC analysis (p = .056).

Table 11.1.1.3–1. Change From Baseline to Week 8 in CGI-S and CGAS: ITT Population

	Time point	*Placebo*		*Escitalopram*		*LSMD (95% CI)*	*p-value*
		N	*Mean – SEM*	*N*	*Mean – SEM*		
CGI-S	Baseline	157	4.4 – 0.0	154	4.6 – 0.1	–	–
	Change at Week 8 (LOCF)[a]	157	–1.4 – 0.1	154	–1.8 – 0.1	–0.4 (–0.6, –0.1)	.007
	Change at Week 8 (OC)[a]	135	–1.6 – 0.1	130	–2.0 – 0.1	–0.3 (–0.6, –0.1)	.022
CGAS	Baseline	157	51.9 – 0.4	154	51.9 – 0.5	–	–
	Change at Week 8 (LOCF)[a, b]	152	12.4 – 1.0	149	14.7 – 1.0	2.2 (–0.4, 4.8)	.103
	Change at Week 8 (OC)[a, b]	135	13.6 – 1.0	130	16.1 – 1.0	2.4 (–0.1, 4. 9)	.056

a Analyses are based on an analysis of covariance model for change from baseline with treatment group and study center as factors and the corresponding baseline value as covariate.

b On the CGAS, a score increase denotes improvement.

CGAS = Children's Global Assessment Scale; CGI-S = Clinical Global Impressions–Severity; CI = confidence interval; ITT = Intent to Treat; LOCF = last observation carried forward; LSMD = least squares mean difference; OC = observed cases.

Cross-reference: Tables 14.4.3.3A and B, 14.4.3.4A and B.

Table 11.1.1.3–2 presents response and remission rates at Week 8. More patients responded to escitalopram treatment relative to placebo; in an LOCF analysis the difference was statistically significant for CGI-I responders (64% vs 53%, p = .029).

Table 11.1.1.3–2. CDRS-R and CGI-I Response and Remission Rates: ITT Population

	Parameter	*Placebo n/N (%)*	*Escitalopram n/N (%)*	*p-value* [a]
CDRS-R response (≥ 40% reduction from baseline in CDRS-R total score)	Week 8, LOCF	76/157 (48.4)	91/154 (59.1)	.063
	Week 8, OC	73/135 (54.1)	81/129 (62.8)	.184
CDRS-R remission (CDRS-R total score ≤ 28)	Week 8, LOCF	56/157 (35.7)	64/154 (41.6)	.150
	Week 8, OC	53/135 (39.3)	57/129 (44.2)	.217
CGI-I response (CGI-I ≤ 2)	Week 8, LOCF	83/157 (52.9)	99/154 (64.3)	.029
	Week 8, OC	80/135 (59.3)	89/130 (68.5)	.098

a Analyses are based on a logistic regression with treatment group as the factor and appropriate baseline score as the covariate.

CDRS-R = Children's Depression Rating Scale–Revised; CGI-I = Clinical Global Impressions–Improvement; LOCF = last observation carried forward; OC = observed cases.

Cross-reference: Tables 14.4.3.5A and B, 14.4.3.6A and B, 14.4.3.7A and B.

By-visit response rates are presented in Tables 14.4.3.5A and B and 14.4.3.6A and B. Corresponding individual patient data are presented in Appendices 16.2.6.1 and 16.2.6.2.

11.1.2 Statistical/Analytical Issues

The statistical analysis followed the analysis prospectively defined in the SAP (Section 9.7.1, Appendix 16.1.9.1).

11.1.3 Tabulation of Individual Response Data

Individual response data are summarized in the tables presented in Section 14.0.

11.1.4 Drug Dose, Drug Concentration, and Relationships to Response

A blood sample for the measurement of the plasma concentration of escitalopram and S-DCT was collected at Visit 8 (or early termination). Descriptive statistics for the plasma concentration of escitalopram and S-DCT are presented in Table 14.6.1, and individual plasma concentration data are presented in Listing 16.3.1. The concentrations of escitalopram and S-DCT (mean ± SD) in patients who received 10-20 mg/d escitalopram were 19.3 ± 21.51 ng/mL and 8.9 ± 6.52 ng/mL, respectively.

The ratio of mean escitalopram plasma concentration to S-DCT concentration is in agreement with data from another study in pediatric patients (Study CIT-PK-07). Based on Study CIT-PK-07, mean plasma levels of escitalopram and S-DCT in this study were generally lower than average steady-state plasma concentrations expected for a 20-mg/d dosage and higher than those expected for a 10-mg/d dosage. Blood samples for analysis were collected at various times postdose, with five samples taken 6 to 16 days postdose.

11.1.5 Drug-Drug and Drug-Disease Interactions

Drug-drug and drug-disease interactions were not evaluated in this study.

11.1.6 By-Patient Displays

Individual patient data are presented in Appendix 16.2.

11.1.7 Efficacy Conclusions

With multiple clinically and statistically significant differences between placebo and escitalopram, the results of this study demonstrate efficacy of escitalopram in treating MDD in pediatric patients (12-17 years). On the primary efficacy parameter, the change from baseline to Week 8 in CDRS-R, statistically significant improvement was seen in the escitalopram group relative to the placebo group using both LOCF (LSMD = –3.4 , p = .022) and MMRM (LSMD = –3.1, p = .035) approaches. Significant improvement was also seen in the secondary efficacy parameter, CGI-I at Week 8, for the escitalopram group relative to the placebo group using both LOCF (LSMD = –0.3, p = .008) and OC (LSMD = –0.3, p=.023) approaches.

Significant differences ($p < .05$), consistent with greater improvement in the escitalopram group relative to the placebo group, were also seen for the additional efficacy parameters CGI-S change from baseline (LOCF, OC) and CGI-I response (LOCF).

Table 14.4.1.1
Change from Baseline in CDRS-R at Week 8
ITT Population

Visit		Placebo (N=157)		Escitalopram (N=154)		LSMD (Esc - Placebo) (95% CI) [1]	P-value
		Actual	Change	Actual	Change		
Week 8 (LOCF)	Mean	37.6	-18.4	35.1	-22.4		
	SD	14.28	13.42	13.60	14.11		
	SEM	1.14	1.07	1.10	1.14		
	Median	34.0	-20.0	31.0	-25.0		
	Min, Max	17.0,75.0	-50.0,18.0	17.0,81.0	-53.0,21.0		
	n	157	157	154	154		
	LS Mean (se)		-18.8 (1.27)		-22.1 (1.22)	-3.356 [-6.226, -0.486]	0.022
Week 8 (OC)	Mean	35.7	-20.1	34.0	-23.8		
	SD	13.55	12.96	12.81	13.72		
	SEM	1.17	1.12	1.13	1.21		
	Median	32.0	-22.0	31.0	-26.0		
	Min, Max	17.0,75.0	-50.0,18.0	17.0,70.0	-53.0,21.0		
	n	135	135	129	129		
	LS Mean (se)		-21.9 (1.29)		-24.6 (1.24)	-2.787 [-5.811, 0.237]	0.071
Week 8 (MMRM)	LS Mean (se)		-19.6 (1.16)		-22.7 (1.14)	-3.129 [-6.031, -0.227]	0.035 [2]

Notes: 'LSMD' indicates the difference in least squares mean. CI = Confidence Interval.
[1] Analyses are based on ANCOVA model for change from baseline with treatment group and study center as factors and baseline value as covariate.
[2] Analyses are based on MMRM for change from baseline with visit, treatment group, treatment by visit interaction and study center as factors and baseline value as covariate. The covariance matrix is assumed unstructured.
SD = Standard Deviation, SEM = Standard Error of the Mean, Min = Minimum, Max = Maximum, and se = Standard Error of LS Mean.

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