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TREATMENT : CONFIDENTIAL
SOURCE : Charles Flicker
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PAGECOUNT = 67
PLTF_SUMMARY :

intro
prev child studies
pk studies
dose
lot # for unblinds cit
vital sign norms ref
Worsening at week 8
signif effect @ wk 4
= 20 mg
Pt s20 age 10, dispensing error cit
hypomania, akathisia, agitation, suicidality
narratives
lab tables

CGAS
simple phobia
adult plasma levels

11/27/01

Memorandum

To: Charlie Elicker, James Jin, Julie Kilbane, Paul Tiseo, Jane Wu

CC: Eric Schlackman (memo only)

From: Bill Heydorn BH

Date: October 17, 2001

Re: Review of first draft of CIT-MD-18 Study Report

Attached for your review is the first draft of the CIT-MD-18 Study Report. Note that there are a number of queries included in the text. Please supply any information you have that can assist us in addressing these queries.

Please review and return comments to me by October 25.

Thank you.

Forest Laboratories, Inc.
909 Third Avenue
New York, New York 10022

STUDY Report for
Protocol No. CIT-MD-18

Title: A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Citalopram in Children and Adolescents with Depression

Abbreviated Title: Citalopram ~~Flexible-Dose Study~~ Pediatric Depression

Name of Study Drug: Citalopram ~~HBr~~
Indication: Major Depressive Disorder
Study Phase: III
Initiation Date: 31 Jan 2000
Completion Date: 10 Apr 2001

The study was carried out in compliance with the International Conference on Harmonization (ICH)-E6 Good Clinical Practice Guideline.

Report Date: October 15, 2001

Confidentiality Statement

SYNOPSIS

Name of sponsor/company: Forest Laboratories, Inc.	
Title of study: A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Citalopram in Children and Adolescents with Depression	
Protocol No.: CIT-MD-18	
Study period: 31 Jan 2000 (Date of first enrollment) 10 Apr 2001 (Date of last completion)	**Development Phase:** III
Objectives: The primary objective of this study was to evaluate the safety and efficacy of citalopram (20–40 mg/day) compared with placebo in children (7-11 years) and adolescent (12-17 years) outpatients with major depressive disorder (MDD).	
Study design: Randomized, double-blind, placebo-controlled, multicenter, parallel-group, 2-arm, flexible dose study consisting of a 1-week single-blind placebo lead-in and an 8-week double-blind treatment phase in pediatric outpatients diagnosed with MDD (DSM-IV criteria).	
Number of patients: One hundred seventy-four (174) patients received at least one dose of double-blind study medication (safety population).	
Study centers: 21 US centers.	
List of investigators: A list of investigators is presented in Appendix II.	
Diagnosis and main criteria for inclusion: Male or female children (7 to 11 years) and adolescent (12 to 17 years) outpatients, who met DSM-IV criteria for MDD.	
Study drug and dosage strength: Citalopram - 20 mg tablets and placebo capsules. **Dosage groups:** Citalopram 20 mg/day or citalopram 40 mg/day; placebo. **Mode of administration:** All study drugs were administered orally. **Lot numbers:** Citalopram - lot nos. XXXXX; placebo - lot no. XXXXX.	
Duration of treatment: One week of single-blind placebo treatment and 8 weeks of double-blind treatment.	

Criteria for evaluation:

Efficacy: Primary - Children's Depression Rating Scale - Revised (CDRS-R).

Secondary – Clinical Global Impression – Severity subscale (CGI-S);
Clinical Global Impression – Improvement subscale (CGI-I);
Children's Global Assessment Scale (CGAS);
Kiddie Schedule for Affective Disorders and Schizophrenia – Present (depression module) (K-SADS –P depression module).

Safety: Recording of adverse events (AEs), standard laboratory measurements, physical examination, vital signs evaluation, and electrocardiograms (ECGs).

Statistical methods:

Patient disposition, demographics, and safety analyses were based on the safety population, which included all patients who received double-blind treatment.

Efficacy analyses were based on the ITT population, which included all patients in the safety population who had at least one post-baseline efficacy assessment on the CDRS-R. All tests were two-sided with a 5% significance level for main effects and a 10% significance level for interaction terms.

The primary efficacy parameter was the change from baseline in CDRS-R score at week 8. Comparison of citalopram and placebo were performed using an analysis of covariance (ANCOVA) additive model with treatment, study center, and age group as factors and baseline score as covariate. ~~The p-values for between-treatment comparisons, the differences in least squares means between treatment groups, and their 95% confidence intervals are presented. The interaction between treatment and baseline score was examined. An ANOVA model was used if the interaction was significant at the 10% level.~~ The primary efficacy analysis used the last observation carried forward (LOCF) approach.

All secondary efficacy parameters except the CGI-I score were analyzed using the same ANCOVA model as for the primary efficacy parameter. A three-way analysis of variance (ANOVA) model was used for the CGI-I score, since this parameter records improvement relative to baseline and baseline score is not applicable. Additional by visit analyses were carried out for all efficacy parameters, using both the LOCF and observed cases (OC) approach.

Additional analyses were performed on the CGI-I responders defined by a CGI-I scale improvement rating of "very much improvement" or "much improvement" and the CDRS-R responders defined by a CDRS-R score of ≤ 28. The Cochran-Mantel-Haenszel (CMH) test controlling for center and age group was applied for between treatment comparison with respect to the numbers of CGI-I and CDRS-R responders. These analyses were carried out using the Last Observation Carried Forward (LOCF) approach at week 8.

Additional by-visit analyses were carried out for all primary, secondary, and additional efficacy parameters using additive ANCOVA or ANOVA models for continuous parameters and CMH test for categorical parameter. In addition to the LOCF approach, the Observed Case (OC) approach was used, where only observed values were used for analyses. Week 8 analyses were carried out using the LOCF approach.

Summary – Conclusions:

Patient Disposition:

A total of ~~178 patients were randomized to double-blind treatment,~~ 174 patients entered the double-blind treatment period and received study drug, 89 in the citalopram group and 85 in the placebo group. These patients were included in all safety and efficacy analyses. ~~Of the 178 patients randomized to double-blind treatment, 4 patients in the citalopram group were lost to follow-up and are not included in the safety or intent-to-treat (ITT) population.~~ A total of 138 (79%) patients completed the study, 80% of patients in the citalopram group and 79% of patients in the placebo group.

Demography: In the placebo group, 38 patients were 7-11 years of age and 45 patients were 12-17 years of age. In the citalopram group, 45 patients were 7-11 years of age and 44 patients were 12-17 years of age. Mean age in both treatment groups was 12 years.

Demographic characteristics were similar between the treatment groups. The majority of subjects in both treatment groups were female (53% for citalopram and 54% for placebo) and Caucasian (81% and

73%, respectively). ~~Mean age in both treatment groups was 12 years.~~

Efficacy results:
Citalopram treatment showed a statistically significant improvement in the CDRS-R score as early as week 1 (p=0.011), which persisted over the entire treatment period using the LOCF approach (p≤0.038). Additionally, the response rate for the CDRS-R responders at week 8 for the LOCF analyses showed a statistically significant treatment effect in favor of citalopram (p=0.041). Similar results were observed using the OC scores with the exception of the week- 8 timepoint. The OC analyses for this parameter approached statistical significance at week 8 (p= 0.097). All other efficacy parameters showed a consistent numerical trend in favor of citalopram treatment, but failed to reach statistical significance at week 8. Except for the CGI-I responder score, all other parameters with evaluations at week 6 reached statistical significance in favor of citalopram treatment at this timepoint. The by-visit evaluations for these parameters show a marked improvement in the placebo scores at the week 8-timepoint, suggesting a placebo effect. No explanation is currently available for this observation. This large placebo effect may be, in part, responsible for the lack of statistical significance in favor of citalopram at week 8.

Safety results:
This study showed that citalopram was safe and well tolerated in children and adolescents with MDD. Seventy-five (84.3%) patients in the citalopram and 59 (69.4%) patients in the placebo group reported TEAEs. No clinically significant difference in TEAE profile was observed between treatment groups, between children and adolescents, or between male and female patients receiving citalopram. The most frequent TEAEs (>8%) in the citalopram group were headache, rhinitis, nausea, and abdominal pain. In the placebo group, headache and pharyngitis were most commonly reported. Three TEAEs with an incidence of at least twice that observed with placebo were reported in the citalopram group: influenza-like symptoms, fatigue, and diarrhea. The most frequent ongoing psychiatric disorders occurring in 3 or more patients, were dysthymia and enuresis in the citalopram group and encopresis and enuresis in the placebo group. The majority of TEAEs were mild or moderate in severity in both treatment groups. No deaths occurred during the study. One serious TEAE (impulsive behavior) was reported in the placebo group. Ten patients were discontinued because of TEAEs. The incidence of discontinuation due to TEAEs was similar between the citalopram (5.6%) and placebo (5.9%) groups. Analysis of laboratory, vital sign, body weight, and ECG parameters revealed a low incidence of PCS values for both treatment groups. The mean changes from baseline were small in magnitude and clinically unremarkable.

The safety findings support the conclusion that citalopram is safe and well tolerated in children and adolescents with MDD. No new safety concerns were identified relative to the safety review of citalopram in the New Drug Application (NDA) 20-822 or the citalopram package insert. According to the citalopram package insert, the most frequent TEAEs in adults treated with citalopram were nausea (21%), dry mouth (20%), somnolence (18%), and insomnia (15%) and the only common TEAE occurring at twice the incidence of placebo-treated patients was ejaculation disorder in males. This study showed that in children and adolescents these TEAEs occurred at a frequency of <5.0% except for nausea (14%). However, headache and rhinitis were reported at a higher frequency in children and adolescents (19% and 14%, respectively) than in adults (<2% and 5%, respectively). Since this study was conducted in children and adolescents (mean age 12 years) ejaculation disorder was an unlikely TEAE to occur in this population, and none was reported. On the other hand influenza-like symptoms, fatigue, and diarrhea were reported with twice the incidence in children and adolescents treated with citalopram compared with children and adolescents treated with placebo.

Conclusion:
The results of this study demonstrate the safety, tolerability, and antidepressant efficacy of citalopram in the treatment of MDD in children and adolescents.

Date of the report: Month DD, YYYY

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LIST OF PANELS

separate list for population analyzed

LIST OF TABLES

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LIST OF PATIENT NARRATIVES

1 – Serious Adverse Event Narratives

Patient No.
137

2 – Adverse Event Discontinuation Narratives

del?

Patient No.	Patient No.
137	144
507	193
519	229
550	534
574	561

Patient 137 discontinued because of a serious adverse event, and the patient narrative is included in the serious adverse event section.

LIST OF APPENDICES

Dis

LIST OF ABBREVIATIONS

AE	Adverse event
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
ATC	Anatomical Therapeutic Chemical
βHCG	Human chorionic gonadotropin
BUN	Blood urea nitrogen
°C	Degrees Celsius
CDRS-R	Children's Depression Rating Scale – Revised
CGAS	Children's Global Assessment Scale
CFR	Code of Federal Regulations
CGI	Clinical Global Impressions
CGI-I	Clinical Global Impressions – Improvement scale
CGI-S	Clinical Global Impressions – Severity scale
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRF	Case report form
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hg	Mercury
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intent-to-treat
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime
K-SADS-P	Kiddie Schedule for Affective Disorders and Schizophrenia – Present
LNL	Lower normal limit
LOCF	Last observation carried forward
LSM	Least squares mean
MDD	Major Depressive Disorder
NDA	New Drug Application
OC	Observed cases
PCS	Potentially clinically significant
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SI	System International
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TEAE	Treatment-emergent adverse event
UNL	Upper normal limit
WBC	White blood cell
WHO	World Health Organization
WHOART	World Health Organization Adverse Reaction Dictionary

1.0 ETHICAL CONSIDERATIONS

1.1 Institutional Review Board (IRB)

The study protocol, the informed consent form, and information sheet advertisements were approved by Institutional Review Boards (IRBs) at each study center in conformance with 21 Code of Federal Regulations (CFR), Part 56.

A list of IRBs for this study is provided in Appendix I.3 del?

1.2 Ethical Conduct of the Study

The study was conducted in full compliance with Food and Drug Administration (FDA) guidelines for Good Clinical Practices (GCP) and in accordance with the ethical principles that have their origins in the Declaration of Helsinki and 21 CFR, Part 56.

1.3 Patient Information and Consent

Patients ~~and/or guardians~~, after having the study explained to them, gave voluntary ~~and written informed consent~~ before participating in any study-related procedures. Each ~~patient and~~/or guardian was provided with a written informed consent statement that complied with 21 CFR, Parts 50 and 312. Each ~~patient and~~/or guardian read, assented understanding, and signed an instrument of informed consent having had an opportunity to discuss it with the clinical investigator before signing, and was made aware that ~~he/she~~ could withdraw from the study at any time.

assent parent parent patient ~~he~~

2.0 INVESTIGATORS

This study was performed at 21 study centers located in the United States. At each center, the Principal Investigator was responsible for ensuring that the investigation was conducted according to the signed Investigator Agreement, the protocol, and Good Clinical Practice guidelines.

A list of investigators, including their affiliations and curricula vitae, are included in Appendix II. Full financial disclosure was obtained from all investigators and subinvestigators.

3.0 INTRODUCTION

Citalopram is a highly selective serotonin reuptake inhibitor that has minimal or no effect upon the reuptake of other biogenic amines such as norepinephrine and dopamine (1). Furthermore, citalopram has little effect on cholinergic and histaminergic receptors, and as a result, anti-cholinergic and anti-histaminergic side effects are far less common with citalopram than with tricyclic antidepressants (1).

Human pharmacological studies indicate that citalopram has a bioavailability of approximately 80% and is eliminated with a half-life of 35 hours, consistent with a once daily dosing regimen. With repeated daily administration, citalopram plasma levels achieve steady-state in one week and show a linear relationship to the dose administered. Citalopram pharmacokinetics are not influenced by food intake.

The safety and efficacy of citalopram in adults has been established in clinical trials including over 20,000 citalopram-treated patients. The side effect profile of citalopram at doses of 20-60 mg/day indicates that citalopram is well tolerated and presents no undue risk to patients.

The antidepressant efficacy of citalopram in adults has been clearly demonstrated in placebo-controlled double-blind trials. These trials have demonstrated statistically and clinically significant improvements relative to placebo for citalopram at doses of 20-60 mg/day. The consistent antidepressant effect of citalopram in placebo-controlled studies was also seen in subpopulation analyses of patients categorized by race, gender, age, and depression characteristics at baseline. In addition, two 6-month, placebo-controlled continuation studies have shown citalopram to be significantly more effective than placebo in the prevention of depression relapse.

has been the treatment of depression more than 70
Citalopram ~~is currently~~ approved for ~~marketing~~ in countries ~~for the treatment of either depression or depression and panic disorder~~. To date, it has been prescribed for more than 30 ~~approximately 12~~ million patients in clinical practice. ~~A detailed description of the chemistry, pharmacology, efficacy, and safety of citalopram is provided in the Investigator's Brochure and Package Insert.~~ **~~[Forest, is 12 million still the correct number?]~~**

Our knowledge about depression in children and adolescents has increased considerably during the past 20 years, and it has now been demonstrated that depression in childhood occurs with the same characteristics as in adults (2, 3). During puberty, the frequency of depression increases markedly (4). Furthermore, the ratio between the sexes in the pediatric population is the same as that observed in adults (5). The increasing numbers of children and adolescents suffering from depression have been observed both in family studies and in epidemiological studies (6, 7). In addition, the cumulative risk of having depression before a certain age has increased successively in younger cohorts (8, 9).

Numerous tricyclic antidepressants, including amitriptyline (10), imipramine (11), desipramine (12) and nortriptyline (13) have been studied in double-blind trials of depressed patients under 21 years of age, and none have been found to produce significantly greater improvement than placebo. In contrast to these trials, a recently published placebo-controlled study of the selective serotonin uptake inhibitor (SSRI)

fluoxetine in the treatment of pediatric depression (14) demonstrated a significantly greater improvement in fluoxetine-treated patients compared with placebo-treated patients.

The present study was designed to evaluate the safety and efficacy of citalopram in child and adolescent outpatients diagnosed with major depressive disorder (MDD). ~~A summary of the available safety and efficacy data on citalopram treatment in children and adolescents can be found in the Investigator's Brochure.~~

4.0 STUDY OBJECTIVES

The primary objective of this study was to evaluate the safety and efficacy of citalopram (20–40 mg/day) compared with placebo in children (7-11 years) and adolescent (12-17 years) outpatients with MDD.

5.0 INVESTIGATIONAL PLAN

5.1 Study Design and Rationale

The clinical trial was conducted as a randomized, double-blind, placebo-controlled, multicenter, parallel-group, 2-arm, flexible dose study comparing citalopram (20-40 mg/day) with placebo in pediatric outpatients diagnosed with MDD (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] criteria). ~~If at the Week 4 visit (or at anytime thereafter), the investigator felt that the therapeutic response was not satisfactory and the patient did not experience dose-limiting adverse events (AEs), the dose could have been increased from 20mg/day to 40 mg/day.~~ The study population was to be equally stratified between children (ages 7 to 11) and adolescents (ages 12 to 17). A total of 160 patients were to be randomized in a 1:1 ratio to double-blind treatment. The study consisted of a 1-week, single-blind placebo lead-in period followed by an 8-week double-blind treatment period, ~~The~~ total duration of ~~the study was~~ 9 weeks.

The study involved a total of seven clinic visits: Screening, baseline, and at the end of weeks 1, 2, 4, 6 and 8. The diagnosis of MDD ~~(DSM-IV) was to be confirmed at the screening visit using the~~ Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (K-SADS-PL). The primary efficacy evaluation (Children's Depression Rating Scale-Revised) was ~~to be~~ conducted at each clinic visit, ~~beginning with the screening visit. A blood sample for the measurement of steady-state citalopram concentrations in plasma was to be taken at the end of the week 8 visit.~~

Patients who completed this study were eligible to participate in a 24-week open-label extension study.

Detailed descriptions of each study visit and the schedule of evaluations can be found in Section 5.5. The protocol for this study is provided in Appendix I.1, and a sample case report form (CRF) is provided in Appendix I.2.

The safety and effectiveness of citalopram have not been established in pediatric patients. ~~Since childhood depression has been shown to occur with the same characteristics as in~~ Because of the established efficacy and tolerability of citalopram in the treatment of adult depressed patients, it is likely to be used in the treatment of depressed patients under 18 years of age. It is therefore important that the safety and efficacy of citalopram be systematically evaluated in this population.

adults, and since depression increases markedly during puberty, there is a pressing need for a safe and effective treatment for childhood and adolescent depression. Results of recent trials of selective serotonin uptake inhibitors in the treatment of pediatric depression have demonstrated promising results. Based on the efficacy of citalopram in the treatment of adults with depression, the current study was conducted to assess the safety and effectiveness in the treatment of childhood depression.

No safety issues have been identified in adult populations at daily doses of 20 to 60 mg citalopram. The daily dose range of 20 to 40 mg chosen for the current study is based on the safety profiles obtained from clinical studies in adults as well as post-marketing information.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

To be included in the study, patients had to satisfy all of the following criteria:

1. Male or female outpatient between 7 and 17 years of age;
2. The patient must have met DSM-IV diagnostic criteria for MDD. The duration of the current major depressive episode must have been at least 4 weeks at the baseline visit;
3. Patient must have had a Children's Depression Rating Scale-Revised (CDRS-R) score of 40 or greater at both the screening and baseline visits;
4. Physical examination, laboratory tests and electrocardiogram (ECG) results must have been normal at screening, or if abnormal, must have been deemed clinically insignificant by the investigator and documented in the CRF as such;
5. Female patients of childbearing potential must have had negative serum human chorionic gonadotropin (β–HCG) test results at screening;
6. Prior to the conduct of any study-specific procedures, the patient must have provided assent to participation and the parent or legal guardian must have provided written informed consent;
7. Patients must have been able to speak, read, and understand English sufficiently to understand the nature of the study and to allow completion of all study assessments;
8. A parent or caregiver capable of providing information about the patient's condition must have agreed to accompany the patient to all clinic visits.

5.2.2 Exclusion Criteria

Patients who met any of the following criteria were disqualified from participation in the study:

1. Patients with any primary psychiatric diagnosis other than MDD;

2. Patients who met DSM-IV criteria for attention deficit-hyperactivity disorder, posttraumatic stress disorder, bipolar disorder, pervasive developmental disorder, mental retardation, conduct disorder or oppositional defiant disorder;

3. Patients with any psychotic features;

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

5. A history of substance abuse, including alcohol, within the past year;

6. Patients who tested positive for alcohol or any other prohibited medication on the urine drug screen collected at the screening visit;

7. A history of anorexia nervosa or bulimia within the past year;

8. Females who were pregnant or breast feeding;

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

10. Patients with a 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 hematological, endocrine, cardiovascular (including any rhythm disorder), neurological, 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 to interfere with the patient's participation in the study, the patient may have been included, with the documented approval of the Medical Monitor);

11. Patients with a history of seizure;

12. Patients who had been treated with any antidepressant or anxiolytic medication within 2 weeks of the baseline visit (4 weeks for fluoxetine);

13. Patients who had been treated with any neuroleptic or stimulant (e.g., methylphenidate) within 6 months prior to the screening visit;

14. Patients who required concomitant treatment with any psychotropic drug (except zolpidem for sleep), or any drug with a psychotropic component ~~(see Appendix I1)~~;

15. Patients who required concomitant treatment with any prescription or over-the-counter medications that were ~~classified as "not allowed"~~ by ~~this~~ the protocol (see Appendix I1);

16. Patients who had been in a previous investigational study of citalopram;

17. Patients who had received treatment with any investigational drug within 30 days or 5 half lives (whichever was longer), prior to study entry;

18. Patients with a history of hypersensitivity reaction to citalopram (Celexa) or other SSRIs;

19. Patients who had previously failed to respond to an adequate trial of citalopram or to adequate trials of two other SSRIs;

20. Patients who had initiated psychotherapy or behavior therapy within 3 months prior to the screening visit, or who planned to inititate or change such therapies during the course of the study;

21. Patients who were unable to swallow tablets;

22. Patients who were considered a suicide risk (active suicidal ideations), who had made a serious suicide attempt within the past year, or who had ever been hospitalized because of a suicide attempt;

23. Patients who, in the investigator's opinion, might not have been suitable for the study.

5.3 Treatments

5.3.1 Identity of Investigational Products

Citalopram (20 mg) and placebo medication were supplied by Forest Laboratories, Inc. (New York, NY) as film-coated, white tablets of identical appearance. For the single-blind lead-in period, patients were to be supplied with placebo tablets only. For the double-blind treatment period, identically appearing tablets contained either 20 mg of citalopram or placebo. Medication was supplied in bottles containing either 10 tablets ~~for the lead-in and the first 4 weeks of double-blind treatment~~, or 40 tablets ~~for the remaining 4 weeks of the treatment period~~.

All study medication bottles were labeled with the protocol number, visit number, instructions to take tablets as directed, and storage and warning information. Additionally, bottles for double-blind medication were labeled with a patient number. Prior to dispensing the medication, the investigator wrote the patient's initials, the center number, and the date on the label. Study medication was kept in an appropriate, secure area. All drug supplies were stored at controlled room temperature, 59°F - 86°F (15°C - 30°C), and protected from heat and moisture.

The lot numbers, dosage strengths, and expiry dates of the citalopram and the corresponding placebo tablets used in this trial are shown in Panel 1.

Panel 1. Study Drug Lot Numbers

Study Medication	Dosage Strength	Encapsulated Tablet Lot No.	~~Original Tablet~~ Lot No.	Expiry Date*
Citalopram	20 mg			
Placebo	NA			

* Based on 12 month stability data.

[Forest, please provide missing information for Panel 1.]

5.3.2 Method of Assigning Patients to Treatment Groups

Each study site was provided with double-blind drug supplies corresponding to two different sequences of patient numbers. Patients between 7 and 11 years of age were sequentially assigned numbers between 101 and 299. Patients between 12 and 17 years of age were sequentially assigned numbers between 501 and 699.

Appendix IV provides the randomization scheme and codes.

5.3.3 Dosing Regimen

The dosing regimen is presented in Panel 2. Patients who met all of the eligibility criteria at screening were dispensed one bottle containing 10 placebo tablets prior to departing from the clinic. Patients were instructed to take one tablet each evening until they returned 1 week later for the baseline visit.

Patients who met all of the eligibility criteria at the end of the single-blind lead-in period (baseline visit) were assigned a randomization number and dispensed the corresponding bottle of study medication for week 1 of double-blind treatment. Patients were instructed to take one tablet each evening, beginning on the day that the study medication was dispensed. (Dosing ~~may have subsequently been~~ could be switched to the morning if preferred.) In accordance with their assigned treatment, patients received either one placebo tablet or one tablet of 20 mg citalopram through the end of week 4.

At the end of week 1, patients were to return to the clinic bringing their unused study medication with them for drug accountability. Henceforth, patients were to return their unused study medication at each clinic visit.

At the end of the week-1 visit, patients were dispensed another bottle containing 10 tablets of either placebo or active (20 mg citalopram) medication and were to continue taking one tablet daily during week 2 of the study.

At the end of week 2, patients were dispensed two bottles of medication (each containing 10 tablets of either placebo or 20 mg citalopram), and were instructed to continue taking one tablet daily during weeks 3 and 4 of the study.

At the end of the week-4 and week-6 visits, patients were dispensed one bottle containing 40 tablets of either placebo or active (20 mg citalopram) medication. Patients who exhibited a satisfactory therapeutic response by the week-4 visit were to continue taking one tablet of medication daily. However, if at the week-4 visit (or at anytime thereafter),

the clinician determined that the therapeutic response was not satisfactory and the patient was not experiencing dose-limiting AEs, the dose ~~could have been~~ be increased and the patient ~~was to be~~ instructed to take two tablets daily (placebo or 40 mg citalopram). All study medication still was to be taken as a single daily dose.

The dose of medication could have been decreased at any time because of AEs. However, the daily dose for this study was never to be less than one tablet or greater than two tablets.

Panel 2. Dosing Regimen

~~Dosage~~ Group		~~20 mg/day~~ citalopram		placebo	
Study Week	Blinding	Minimum Dose	Maximum Dose	Minimum Dose	Maximum Dose
Screening	single-blind	1 placebo tablet		1 placebo tablet	1 placebo tablet
Week 1 – 4	double-blind	1 citalopram 20 mg tablet	1 citalopram 20 mg tablet	1 placebo tablet	1 placebo tablet
Week 5-8	double-blind	1 citalopram 20 mg tablet	2 citalopram 20 mg tablets	1 placebo tablet	2 placebo tablets

a: If at the week-4 visit (or at anytime thereafter), the clinician determined that the therapeutic response was not satisfactory and the patient was not experiencing dose-limiting AEs, the dose could have been increased and the patient was instructed to take two tablets daily (placebo or 40 mg citalopram).

5.3.4 Blinding

A list of patient randomization numbers and the corresponding assigned treatment was generated by Forest Laboratories, Department of Biostatistics, and retained in electronic format. A hard copy was retained by the Department of Drug Safety Surveillance in a secure, locked area.

Double-blind medication was labeled with a tear-off panel that, once opened, revealed the treatment corresponding to the patient randomization number. The tear-off panel for the double-blind medication was placed, unopened, in the patient's CRF. In case of emergency, the tear-off panel could ~~have~~ be opened, ~~or Forest Laboratories could have been called,~~ to reveal the study medication assignment of any patient.

The tear-off panel identifying the treatment was to be opened only in the event that an emergency necessitated identification of the medication for the welfare of the patient. If the blind was broken for any reason, Forest Laboratories was to be notified immediately. Any patient for whom the blind had been broken was to be immediately discontinued from the study and no further efficacy evaluations were to be performed. If at all possible, an attempt was to be made to discuss the case with the study Medical Monitor prior to unblinding the medication.

No double-blind treatment assignment was unblinded by this procedure ~~or by any other procedure~~ before database lock. **[Forest, please confirm or correct.]**

Because of a drug packaging error, 9 patients assigned to citalopram treatment were initially dispensed 20 mg citalopram tablets that were ~~not~~ distinguishable in color from the placebo tablets ~~in that they were pink in color rather than white~~ at study centers. All study medication shipments including potentially unblinding information were replaced in full.

including psychotropic medication during the previous 5 (?) years and any other medication during the previous 3 months. 27

5.4 Prior and Concomitant Therapy

A medication history was to be obtained from the patient at the time of screening. ~~All medication that the patient was taking at the time of the screening visit was to be recorded on the concomitant medication form in the CRF~~. In addition, any subsequent changes in these medications or their doses, or any new ~~medications introduced~~ during the course of the study, was to be recorded in the CRF. The study protocol (Appendix I.1) provides a list of drugs that were allowed and not allowed as concomitant medications ~~for this study~~. In addition, patients were ~~to be~~ instructed to abstain from alcohol during the study.

A history of non-drug treatments was also recorded during the screening visit.

5.5 Study Procedures

Panel 3 presents the study procedures conducted at the screening and baseline visits and throughout the double-blind treatment period. A copy of the CRF is provided in Appendix I.2.

summarize psychotropic, ~~ect~~, investigational drug, psychotherapy exclusions

Panel 3. Study Flow Chart of Procedures and Determinations

			Double-Blind Treatment: End of Week				
Visit Name	**Screen**	**Baseline**	**1**	**2**	**4**	**6**	**8**
Visit Number	*1*	*2*	*3*	*4*	*5*	*6*	*7*
ASSESSMENT							
Informed Consent	X						
Inclusion / Exclusion Criteria	X	X					
Medical History – Psychiatric History	X						
Physical Exam (with ECG)	X						X
Laboratory Evaluations	X						X
Analytical Sample							X
Pregnancy Test	X						
Urine Drug Screen	X						
Vital Signs	X	X	X	X	X	X	X
Diagnostic Evaluation (K-SADS-PL)	X						
Primary Efficacy Evaluation: CDRS-R	X	X	X	X	X	X	X
CGI-S		X	X	X	X	X	X
CGI-I			X	X	X	X	X
CGAS		X			X		X
K-SADS-P (depression module)		X					X
Drug Dispensed	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Final Evaluation*							X

* The final evaluation, including all procedures scheduled for the end of week 8, was to be conducted at the end of week 8 for patients who completed the study or at the time a patient discontinued from the study.

5.5.1 Screening Visit (Visit 1)

The placebo screening phase was used for evaluation of potential study patients for inclusion in the study. At the screening visit, study procedures were reviewed with the patient and guardian and documentation of informed consent was obtained. The

following data were collected and procedures were performed at the screening visit. See efficacy and safety measurements in Sections 5.5.5 and 5.5.6 for detailed descriptions of each parameter.

1. Psychiatric and medical history;
5. ~~Conduct~~ Diagnostic interview (K-SADS-PL);
4. ~~Review~~ Concomitant medications;
2. ~~Perform~~ Physical examination (including ECG, height and vital signs);
3. ~~Obtain blood sample for~~ Laboratory determinations (including ~~and~~ ß-HCG if applicable); and urine drug screen
~~6. Obtain urine sample for drug screen and laboratory determinations;~~
6. ~~Conduct~~ CDRS-R;
7. ~~Assess eligibility via~~ Review of inclusion/exclusion criteria.

Eligible patients were dispensed single-blind placebo tablets. Results from the laboratory and ECG evaluations were reviewed during the 1-week single-blind placebo lead-in phase.

5.5.2 Baseline Visit (Visit 2)

The baseline visit was used to determine whether patients were eligible to continue into the double-blind treatment phase of the study. Baseline efficacy assessments were obtained for the CDRS-R, Clinical Global Impressions –Severity (CGI-S), Kiddie Schedule for Affective Disorders and Schizophrenia – Present (K-SADS-P) depression module and Children's Global Assessment Scale (CGAS), ~~and~~ Drug accountability ~~were assessed.~~ Vital signs were measured and AEs and concomitant medication use were recorded. was conducted on the returned single-blind medication.

If patients were determined to be eligible to continue into the double-blind phase, they were assigned the next available randomization number, in ascending sequential order, and were dispensed the corresponding double-blind study medication for the first week of double-blind treatment.

5.5.3 Double-Blind Study Visits (Visits 3 to 8)

After the baseline visit at the end of the placebo lead-in, study visits were conducted after 1, 2, 4, 6, and 8 weeks of double-blind treatment. The following procedures were performed at each visit:

1. ~~Check~~ Vital signs;
2. Review of concomitant medications;
3. Review of AEs;

4. ~~Assess~~ Drug accountability;

5. ~~Conduct primary efficacy evaluation (CDRS-R)~~, CGI-S, and CGI-I.

~~6. Conduct secondary efficacy evaluations (CGI-S, Clinical Global Impression – Improvement [CGI-I]).~~

Additionally, at the end of week 4 (Visit 5) the CGAS was assessed. Patients returned previously dispensed bottles of double-blind study medication and, except at the final visit, were dispensed new bottles of double-blind study medication. ~~Additionally, it was determined if an adjustment in the dose of study medication was necessary (increase at Visit 5 and increase or decrease at Visit 6).~~ The following additional assessments were made at the final visit (end of week 8):

1. Physical examination including ECG ~~vital signs~~ and height;

2. Laboratory determinations;

~~3. 12-lead ECG recording;~~

4. Plasma sample for determination of citalopram ~~and primary metabolite~~ concentrations;

5. ~~Conduct primary efficacy evaluation (CDRS-R);~~

~~6. Conduct secondary efficacy evaluations (CGI-S, CGI-I,~~ CGAS and K-SADS-P depression module).

5.5.4 Premature Discontinuation

All patients who discontinued prematurely were to be seen for a final evaluation, which consisted of all assessments scheduled for the final visit (end of week 8). ~~Any clinical findings in the final examination, or at premature discontinuation for any reason, including clinically significant laboratory abnormalities, were to be followed until the condition returned to pretrial status or could have been explained as being unrelated to study drug. A follow-up visit was to be scheduled within 28 days of termination if necessary.~~

5.5.5 Diagnostic Assessment

The full K-SADS-PL

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. It evaluates both past and current episodes and was used in this study to establish that ~~the~~ patients met DSM-IV criteria for MDD ~~during the present episode~~, and to rule out other psychiatric diagnoses. ~~This diagnostic interview~~ was administered at the screening visit only.

5.5.5 Efficacy Measurements

The following instruments were used to assess efficacy (see Panel 3). To ensure the sensitivity and reliability of the assessments, the same Investigator (clinician) was to

assess a particular patient at each evaluation. Efficacy ratings were not to be administered if the patient was not accompanied by the identified parent or caregiver.

5.5.5.1 Primary Efficacy Measure

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 that evaluate the presence and severity of symptoms commonly associated with depression in childhood. A total CDRS-R score ≥ 40 is consistent with a diagnosis of a MDD ~~with a score from 17 to 113.~~ The CDRS-R was administered at all clinic visits, including screening, and was administered separately to both the patient and the identified parent or caregiver.

5.5.5.2 Secondary Efficacy Measures

5.5.5.2.1 Clinical Global Impression ~~Severity Subscale~~

At baseline, and at each visit after baseline, global severity was assessed on a scale of 1 to 7.

~~5.5.5.2.2 Clinical Global Impression Improvement Subscale~~

Global improvement was assessed at each clinic visit following the baseline visit. Improvement was assessed on a 7-point Lichert scale which is anchored at a score of 4 (no change) and with a score of 1 correlating with "very much improved" and a score of 7 correlating with "very much worse."

5.5.5.2.3 Kiddic Schedule for Affective Disorders and Schizophrenia-Present (depression module) a component of the full K-SADS-PL administered at screening for diagnostic purposes

The K-SADS-P depression module was completed at baseline and at study termination to evaluate response to treatment.

5.5.5.2.4 Children's Global Assessment Scale

The CGAS was completed at baseline, the end of week 4, and at study termination to evaluate overall functioning.

5.5.6 Safety Measurements

Patients were seen by a physician at every visit and the evaluation documented. The following evaluations were performed at the designated visits (see Sections 5.5.1-3 for a detailed description of when each measurement was performed):

5.5.6.1 Adverse Events

Reports of AEs were collected ~~after general questioning~~ or patient representative at all study visits, or during any contact with a patient subsequent to the first administration of single-blind study medication. An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study medication, whether or not considered related to study medication.

Adverse events included:

1. Changes in the general condition of the patient;
2. Subjective symptoms offered by or elicited from the patient;
3. Objective signs observed by the investigator or study personnel;
4. All concurrent diseases that occured after the start of the trial, including any change in severity or frequency of pre-existing diseases;
5. All investigator identified clinically relevant laboratory abnormalities or physical findings that occured during the trial.

Adverse findings not considered clinically significant that were related to routine laboratory evaluations, physical or neurological exams, vital signs, or ECGs were not to be recorded on the AE reporting page. They were instead to be recorded on the relevant CRF page.

Pregnancies were to be reported to Forest Laboratories, Inc. within 24 hours and were to be followed to term.

For each AE, the investigator provided an assessment of the seriousness, severity, timing, and causal relationship to study drug of the event. All actions taken with regard to study drug and any other treatment measures were documented and detailed.

For all AEs judged to be serious, the investigator or other study personnel were required to inform Forest Laboratories, Inc. immediately (within 24 hours). A serious adverse event (SAE) was one that:

1. Resulted in death;
2. Was an immediate threat to life;
3. Required in-patient hospitalization, or prolongation of existing hospitalization;
4. Resulted in persistent or significant disability/incapacity;
5. 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 if, 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.

When assessing the causality and the severity of the AE, investigators assessed the events as related, possibly related, or not related to study drug administration and as mild, moderate, or severe.

The investigator was required to follow up any clinical findings occurring at the final examination, or at premature discontinuation for any reason, including clinically significant laboratory abnormalities, until the condition returned to pretrial status or could be explained as being unrelated to study drug. A follow-up visit was conducted 28 days after termination, if necessary.

5.5.6.2 Vital Signs and Body Weight

Vital signs, including body weight, systolic and diastolic blood pressure and radial pulse rate, were recorded at every visit. Blood pressure and pulse determinations were recorded after the patient had been seated for 5 minutes. Height was recorded at the screening visit and at the end of week 8 visit (or early termination).

5.5.6.3 Laboratory Evaluations

Blood and urine samples for laboratory tests were collected at screening and at the final visit (end of week 8 or upon early termination). Values obtained at screening were used to determine whether a patient could be included in the study. The investigator assessed the clinical significance of any values outside the reference range and patients with abnormalities judged to be clinically significant were excluded. All reference ranges are presented in Listing 15 of Appendix IX. The following laboratory tests were conducted on the samples obtained:

1. Hematology: Hematology included red blood cell (RBC) count, white blood cell (WBC) count with differential, hemoglobin, hematocrit, and platelet count;

2. Chemistry: Blood chemistry screen included sodium, potassium, calcium, chloride, glucose, blood urea nitrogen (BUN), creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), cholesterol and uric acid;

3. Urinalysis: Urinalysis included specific gravity, pH, acetone, albumin, glucose, WBC/hpf, RBC/hpf, casts/lpf, protein, and ketones;

4. Urine drug screen, thyroid function test, and serum β-HCG pregnancy test (for women of childbearing potential only), were conducted at screening only; Positive results on the urine drug screen or pregnancy test excluded patients from participating in the study.

A central laboratory was also used to evaluate all urine and blood samples, which were collected, processed, and stored according to the instructions provided by the laboratory. The contact address for this laboratory is:

Quest Diagnostics (formerly SmithKline Beecham Clinical Laboratories)
7600 Tyrone Avenue
Van Nuys, CA 91405.

[Forrest, please confirm or correct.]

5.5.6.4 Electrocardiogram

A 12-lead ECG was performed at screening and the end of week 8 or upon early termination. The overall interpretation was categorized as normal, abnormal but not clinically significant, or clinically significantly abnormal. Patients with a clinically significant ECG abnormality at screening were excluded from participating in the study.

A central ECG laboratory, eResearch Technology, provided a telephonic ECG machine and trained appropriate site staff to transmit ECG data to their central ECG laboratory for their interpretation. The cardiologist at eResearch Technology reviewed the ECG and signed the final report, which was sent back to the study site for the investigator's verification and signature. The contact address for the ECG laboratory is:

not central

eResearch Technology (formerly known as Premier Research Worldwide)
30 South 17th Street
Philadelphia, PA 19103-4001.

[Forest, please confirm or correct.]

5.5.6.5 Physical Examination

A complete physical examination was performed at the screening visit and at the end of the week 8 evaluation (or upon early termination). General physical well-being was ~~to be~~ assessed by evaluating the head, eyes, ears, nose, throat, neck, heart, chest, lungs, abdomen, extremities, peripheral pulses, skin, and other physical conditions of note.

5.5.7 ***Premature Discontinuation*** <more to 5.5.4>

Any enrolled patient who ceased participation in the study, regardless of circumstances, before completion of the protocol (prior to the week 8 visit) was considered prematurely discontinued. For each discontinued patient, the investigator identified one of the following as the primary reason for discontinuation:

1. An AE;
2. An insufficient therapeutic response;
3. A protocol violation, including lack of compliance;
4. Patient withdrawal of consent;
5. The patient was "lost to follow-up";
6. Other reasons, such as administrative reasons.

Upon discontinuation, patients were administered all assessments scheduled for the end of the week 8 visit. ~~Patients who discontinued after beginning double-blind treatment were not to be replaced.~~

5.6 Pharmacokinetics

A blood sample for the measurement of citalopram steady-state concentrations in plasma was to be collected at the end of week 8 (or early termination) visit along with the blood samples for laboratory determinations. If possible, the sample was to be collected between 8-14 hours after the last dose of study medication was taken. Blood samples were collected in 10 ml Vacutainers and ~~plasma was harvested and stored as described in the protocol (Appendix II).~~ separated by refrigerated centrifuge at 4°C at 1500G for 5 minutes. At least 2 ml of plasma was transferred to a polypropylene tube, immediately frozen and stored at −70°C.

The concentration of citalopram, escitalopram, R-citalopram, and their metabolites was determined on the basis of a validated assay with a lower limit of quantitation of ng/ml.

5.7 Data Quality Assurance

5.7.1 Investigator Site Training and Monitoring

Before study site initiation, representatives of Forest Laboratories, Inc. met with the investigators and site personnel to familiarize them with the protocol, CRFs, and procedures for proper source documentation. After the enrollment of the first patient, the investigator permitted the Forest representative, a Clinical Research Associate (CRA), to periodically monitor the progress of the trial on site. The investigator made available to the CRA CRFs as well as source documents, the patient's medical records, and signed consent forms. The investigator reviewed the CRFs, provided missing or corrected data, ~~corrected data,~~ and signed the appropriate CRF page(s). The CRA arranged for the return of CRFs to Forest Laboratories, Inc. A copy of each CRF was retained by the investigator.

5.7.2 Data Entry

Case report form data were double-entered into a validated database system. A combination of manual and programmatic edit checks were used to review the data for completeness, logic, and adherence to study protocol. Any resulting queries were addressed by the study site and returned to Forest Laboratories, Inc. for review. If necessary, the database was updated to reflect the new or changed information. A complete audit trail recorded the date, time, and reason for all changes made to the database. Treatment codes were unblinded only after all issues had been resolved and the database was locked.

[Forest, please confirm or correct.]

6.0 STATISTICAL METHODS

The complete statistical analysis plan is presented in Appendix V.

6.1 Statistical Objectives

6.1.1 Primary Statistical Objective

The primary objective of this study was to compare the efficacy of citalopram (20-40 mg/day) to placebo in children (7-11 years) and adolescents (12-17 years) with MDD. The primary efficacy parameter was the change from baseline in the CDRS-R score at week 8.

6.1.2 Secondary Statistical Objectives

The secondary statistical objectives of this study were:

1. To further compare the efficacy of citalopram to placebo in children and adolescents with MDD using ~~the change from baseline to week 8 in~~:
   - CGI-S;
   - K-SADS-P; and
   - CGAS; ~~and~~
   - CGI-I score ~~at week 8~~.

2. To evaluate the safety of 20 – 40 mg/day citalopram in children and adolescents;

6.1.3 Additional Statistical Objectives

To further compare the efficacy of citalopram with placebo, the following efficacy parameters were examine:

- CGI-I responder defined by a CGI-I ~~scale~~ improvement rating of "very much improvement" or "much improvement", and
- CDRS-R responder defined by a CDRS-R score ≤ 28.

Cochran-Mantel-Haenszel (CMH) test controlling for center and age group was applied for between treatment comparison with respect to the numbers of CGI-I and CDRS-R responders. These analyses were carried out using the Last Observation Carried Forward (LOCF) approach at week 8.

Additional by-visit analyses were carried out for all primary, secondary, and additional efficacy parameters using additive analysis of covariance (ANCOVA) or analysis of variance (ANOVA) models for continuous parameters and CMH test for categorical parameter. In addition to the LOCF approach, the Observed Case (OC) approach was used, where only observed values were used for analyses.

6.2 Patient Disposition

6.2.1 Patient Populations

Patient populations were defined as follows:

- Randomized population - The randomized population consisted of all patients randomized in the study.
- Safety population - The safety population consisted of all randomized patients who received at least one dose of the double-blind study medication, ie, all treated patients.
- Intent-to-Treat (ITT) Population - The ITT population consisted of all patients in the safety population with at least one post-baseline efficacy assessment of the primary efficacy variable (CDRS-R score).

The number of patients in each study population was summarized by treatment group, age group, and study center.

6.2.2 Premature Discontinuation

The number (percentage) of patients in the safety population who prematurely discontinued from the study was summarized by treatment group, age group, and reason for discontinuation as recorded in the termination page of the CRF.

6.3 Demographics and Other Baseline Characteristics

~~All the summaries were presented by treatment group and age group.~~

Demographic parameters (age, gender, and race) and other baseline characteristics (weight and height) were summarized for the safety and ITT populations. Depression history was summarized for the safety population, including the following items: disease course, duration of MDD, duration of current episode, age at onset of MDD, previous antidepressant treatment, and response to and tolerance of previous antidepressant treatments. The baseline scores of the efficacy parameters were summarized for the ITT population. The incidence of ongoing secondary psychiatric disorders and the incidence of previous or ongoing secondary psychiatric disorders were summarized. Descriptive statistics, including the number (N), mean and standard deviation (SD), median, and range were presented for continuous variables and frequency distributions (count and percent) were presented for categorical variables.

Comparability between treatment groups was tested using a three-way analysis of variance (ANOVA) model with age group, treatment and study center as factors for continuous variables. Cohran-Mantel-Haenszel (CMH) tests controlling for age group and study center were used for categorical variables.

6.4 Efficacy

Efficacy analyses were based on the ITT population. All tests were two-sided with 5% significance level for main effects and 10% significance level for interaction terms.

The analyses were carried out using the LOCF approach. In addition to LOCF, an OC approach was used, in which only observed values were analyzed.

6.4.1 Primary Efficacy Parameter

The primary efficacy parameter was the change from baseline to week 8 in the CDRS-R score. Comparison between citalopram and placebo was performed using an analysis of covariance (ANCOVA) model with treatment, study center, age group as factors and the baseline score as covariate. ~~The p-value for between-treatment comparison is presented along with the differences in least squares means between the two treatment groups and 95% confidence intervals.~~

The interaction between treatment and baseline score was examined. An ANOVA model was used if the interaction was significant at the 10% level.

6.4.2 Secondary Efficacy Parameters

To further test the efficacy of citalopram ~~20-40 mg/day~~ relative to placebo, the secondary parameters listed in Section 6.1.2 were analyzed. An ANCOVA model, as described for the primary efficacy parameter, was used to analyze the change from baseline ~~at week 8~~ in these parameters except for the CGI-I. A three-way ANOVA model was used for the CGI-I score ~~at week 8~~, since this parameter, by definition, records improvement relative to baseline and is not measured at baseline.

~~*6.4.3 Additional Efficacy Parameters*~~

~~To further test the efficacy of citalopram treatment relative to placebo treatment,~~ the numbers of CGI-I responders and CDRS-R responders were compared using the CMH test controlling for center and age group ~~at week 8~~.

~~Additional~~ by-visit analyses (LOCF and OC) were conducted for all efficacy parameters using additive ANCOVA or ANOVA models for continuous parameters and the CMH test for categorical parameters.

6.4.4 Descriptive Statistics

Descriptive statistics (N, mean, SD, standard error of mean [SEM], median, and range) were presented for all continuous efficacy parameters by treatment group, age group, and visit. Changes from baseline were summarized and plotted. Frequency distributions were also presented for CGI-I by treatment, age group, and visit.

6.4.5 Examination of Treatment-By-Age Group Interaction

The consistency in treatment effect across age groups was examined using an ANCOVA ~~model~~ or ANOVA model with treatment, study center, age group, interaction between treatment and age group as factors and ~~for~~ ANCOVA, baseline score as covariate. ~~The p-values for treatment interaction with the age group were presented.~~ These analyses were carried out using the LOCF approach at week 8 for all continuous efficacy parameters.

6.4.6 Examination of Treatment-By-Center Interaction

The consistency in treatment effect across centers was examined through graphical presentations using the LOCF approach at week 8. Small centers, ie, centers with ~~less than two~~ patients in at least one treatment group in the ITT population were not included.

6.4.7 Examination of Treatment-By-Baseline Score Interaction

The significance of treatment-by-baseline score interaction was tested at 10% level using an ANCOVA model with treatment, study center, age group, interaction between treatment and baseline score as factors and baseline score as covariate. ~~The p-values for treatment interaction with baseline score were presented.~~ These analyses were carried out using the LOCF approach at week 8 for all continuous efficacy parameters ~~except for CGI-I~~.

If the treatment-by-baseline score interaction ~~was~~ significant ~~in the above ANCOVA model~~, the results from ANOVA model with treatment, study center, age group as factors ~~were used~~ ~~to~~ be used instead.

6.4.8 Missing Data

Missing values were imputed using the LOCF approach. Missing assessments at post-baseline visits were imputed by the last observed non-missing value immediately prior to the missing value. If the missing value occurred at week 1, the baseline value was carried forward for week 1, provided at least one subsequent post-baseline assessment was available. For each efficacy parameter, only the total score, not individual items, was carried forward.

6.4.9 Visit Windows

Panel 4 presents the visits assigned for efficacy and safety analyses corresponding to the range of treatment days (window) over which an actual study visit may have occurred. Days on drug (double-blind study medication) were calculated as (visit date – first date on double-blind study medication +1). If there was more than one visit within a visit window, the one closer to the scheduled date was used for that visit. If there were two visits with equal distance from the scheduled visit date within a visit window, the later one was used.

Panel 4. Visit Time Windows

Visit	Scheduled Visit Day[a]	Window
Week 1	Day 7	Days 1 – 10
Week 2	Day 14	Days 11 – 21
Week 4	Day 28	Days 22 – 35
Week 6	Day 42	Days 36 – 48
Week 8	Day 56	Days 49 – 77

a: Day 1 is the first day of double-blind study medication.

6.4.10 Pooling of Centers

Study sites with ≤ 2 patients in any treatment group in the ITT population were pooled into a single center.

[Forest, does this apply?]

6.5 Safety

Safety analyses were performed on the safety population (i.e., all patients who received study drug).

(or number of tablets taken)

6.5.1 Extent of Exposure

The duration of exposure to double-blind study medication, ~~mean daily tablet~~, and mean daily dose were summarized by treatment group and age group for the safety population.

6.5.2 Adverse Events

All AEs were coded using the World Health Organization Adverse Reaction Terminology (WHOART) Dictionary, version 1998/04. An AE that occurred during the

double-blind study medication period was defined as a "treatment emergent" adverse event (TEAE) if either it was not present at baseline or it was present at baseline, but increased in severity during the double-blind treatment period. If the severity assessment for an AE was missing pre-baseline, then "mild" was assigned. If the severity assessment was missing post-baseline, "severe" was assigned.

[Forest, please confirm or correct WHOART version used.]

The number and percentage of patients with at least one TEAE during the double-blind treatment period were summarized by system organ class (body system), preferred term, gender, treatment group, age group, and Investigator's assessment of the severity and relationship to the double-blind study medication. The incidence of treatment-limiting AEs (events contributing to premature discontinuation) were also tabulated. Individual patient listings were compiled for all patients who discontinued the study due to AEs or experienced a SAE and included study center, gender, age, and days to onset of the event. Individual patient narratives were generated describing the chronology, context, details, and outcome of all SAEs or discontinuations because of an AE.

6.5.3 Vital Signs

Sitting pulse, systolic and diastolic blood pressure, body weight and height were assessed at every visit in this study. The ~~range of values~~ criteria listed in Panel 5 were used to identify potentially clinically significant (PCS) vital signs. A post-baseline value was regarded as a PCS value if it met both the criterion value and the change relative to baseline. For each parameter, the number (percentage) of patients with any PCS values were tabulated for each treatment group, along with supportive listings.

The criteria used for the adolescent age group were the same as those used for adult outpatients, whereas the criteria for the patients between 7 and 11 years of age were adjusted in accordance with the normative vital sign values described for this age group. A secondary analysis was conducted in which the criteria for the adolescent patients were applied to all patients.

need ref. Peterson?

6.6 Pharmacokinetics

Plasma concentrations for citalopram and its active enantiomer escitalopram and for their metabolites demethylcitalopram (DCT), didemethylcitalopram (DDCT), S-demethylcitalopram (S-DCT), and S-didemethylcitalopram (S-DDCT) were summarized by dose, by age group, and overall. Correlation analyses were conducted to examine the relationship between both citalopram plasma concentration and escitalopram plasma concentration and patient age, body weight, and change from baseline in CDRS-R score.

Panel 5. Criteria for Potentially Clinically Significant Vital Signs

Variable	Criterion Value	Change Relative to Baseline
Age 12 - 17		
Systolic Blood Pressure	≥180 mmHg	Increase of ≥ 20
	≤ 90 mmHg	Decrease of ≥ 20
Diastolic Blood Pressure	≥105 mmHg	Increase of ≥ 15
	≤ 50 mmHg	Decrease of ≥ 15
Pulse	≥120 bpm	Increase of ≥ 15
	≤ 50 bpm	Decrease of ≥ 15
Weight	not applicable	Change of ≥ 7%
Age 7 - 11		
Systolic Blood Pressure	≥130 mmHg	Increase of ≥ 20
	≤ 75 mmHg	Decrease of ≥ 20
Diastolic Blood Pressure	≥100 mmHg	Increase of ≥ 15
	≤ 40 mmHg	Decrease of ≥ 15
Pulse	≥130 bpm	Increase of ≥ 15
	≤ 55 bpm	Decrease of ≥ 15
Weight	not applicable	not applicable

Note: A post-baseline value was regarded as a PCS value if it met both the criterion value and the change relative to baseline.

Descriptive statistics were presented for each parameter by visit including the final visit for each treatment group and age group. Changes from baseline were also summarized. Only patients with a baseline assessment and at least one post-baseline assessment were included in the summary. Results from the screening visit were used if baseline the assessment was missing.

6.5.4 Laboratory Parameters

The number (percentage) of patients with post-baseline PCS values was tabulated for each parameter by treatment group and age group using the criteria presented in Panel 6. All results ~~are~~ were presented in System International (SI) units. Listings were prepared for patients with post-baseline PCS values.

verify same units as 94404 report provide US unit conversion?

Panel 6. Criteria for Potentially Clinically Significant Laboratory Values

Laboratory Parameter	SI Units	PCS Criteria Low Values	PCS Criteria High Values
Hematology			
Hemoglobin	g/dL	≤ 0.9*LNL	
Hematocrit	%	≤ 0.9*LNL	
Eosinophils	%		≥ 10
Neutrophils Segs	%	≤ 15	
Platelet Count	10^9/L	≤ 75	≥ 700
White Cell Count	10^9/L	≤ 2.8	≥ 16
Chemistry			
Alkaline Phosphatase	IU/L	--	≥ 3*UNL
ALT (SGPT)	IU/L	--	≥ 3*UNL
AST (SGOT)	IU/L	--	≥ 3*UNL
Blood Urea Nitrogen	mmol/L	--	≥ 10.7
Calcium	mmol/L	≤ 1.75	≥ 3.0
Cholesterol	mmol/L	--	≥ 7.8
Creatinine	µmol/L	--	≥ 175
Potassium	mmol/L	≤ 3.0	≥ 5.5
Sodium	mmol/L	≤ 125	≥ 155
Total Bilirubin	µmol/L	--	≥ 34.2
Urinalysis			
Protein		--	Increase of ≥ 2
Glucose		--	Increase of ≥ 2

LNL= Lower normal limit of laboratory reference range.
UNL= Upper normal limit of laboratory reference range.

Descriptive statistics ~~are~~ were presented by treatment group and age group for each parameter at the screening visit, final visit, and the change from screening at the final visit. Only patients with a screening assessment and at least one post-baseline assessment were included in the tabulation.

6.5.5 Electrocardiogram

For each ECG parameter, the number (percentage) of patients with PCS values was tabulated by age group and treatment group based on the criteria presented in Panel 7. Listings were prepared for patients with PCS values.

Panel 7. Criteria for Potentially Clinically Significant ECG Values

ECG Variable	Units	PCS Criteria
PR Interval	msec	≥ 250
QT_C Interval	msec	>500

Descriptive statistics are presented by treatment group and age group for each parameter at the screening, final, and the change from screening at the final visit. Only patients with a screening assessment and at least one post-baseline assessment were included in the summary. The incidence of ECG abnormalities at the final visit was also summarized.

6.5.6 Physical Examination

For each organ class, the number (percentage) of patients with an abnormal finding at the final visit was tabulated by treatment group and age group. Only patients with a normal or missing value (not done) at screening ~~for an organ class~~ were included in the summary ~~for that organ class~~.

6.5.7 Concomitant Medications

Concomitant medications were coded using the WHOART dictionary. The number (percentage) of patients who took concomitant medications was summarized by drug class (based on the Anatomical Therapeutic Chemical [ATC] codes), age group, and treatment group.

Medications taken during the screening period up to and including the baseline day, and all medications taken during the double-blind treatment period including drugs started prior to the start of double-blind study medication and continued during the treatment period were tabulated by treatment group and age group. Drugs started after the stop of double-blind study medication were not summarized.

6.6 Pharmacokinetics <insert from p. 22>

6.7 Sample Size Considerations

The primary efficacy parameter was the change from baseline in CDRS-R score at week 8. Assuming an effect (treatment group difference relative to pooled standard deviation) of 0.5, a sample size of 80 patients in each treatment group was used to provide 85% power using a two-sided t-test with alpha level of 0.05.

6.8 Computer Methods

Statistical analyses were performed using SAS (version 6.12) under a UNIX operating system. PROC Univariate was used for descriptive statistics and PROC FREQ was used for frequency distribution and CMH test with centers as strata. PROC MIXED was used for analysis of covariance and analysis of variance with the options DIFF and confidence

interval (CI) to compute the difference of least squares means (LSM) and 95% confidence interval, respectively.

7.0 CHANGES IN THE CONDUCT OF THE STUDY AND PLANNED ANALYSES

In the protocol it was specified that a three-way additive ANCOVA model, without the treatment-by-baseline score interaction, was to be used for the analysis of the primary efficacy parameter. ~~The protocol was sent to the FDA for review. To address a comment from the agency, the analysis method was amended by Forest Laboratories, Inc.~~ In response to the FDA (dated February 14, 2000), Forest Laboratories, Inc. ~~proposed to test the significance of treatment-by-baseline score interaction at the 10% level using an~~ ANCOVA model with treatment, study center, age group, and the interaction between treatment and baseline score as factors and baseline score as covariate. If the interaction was significant, the results from ~~the~~ an ANOVA model with treatment, study center, and age group as factors was to be used instead.

Nine patients (Patients 105, 113, 114, 505, 507, 506, 509, 513, and 514) ~~accidentally received~~ were mistakenly dispensed medication with potentially unblinding information 1 week of ~~unblinded study drug treatment~~ (tablets had the incorrect color coating). Therefore, in addition to the per-protocol analysis, a post-hoc ~~LOCF~~ analysis, ~~excluding these 9 patients,~~ was performed on ~~the~~ an ITT sub population ~~for the mean change from baseline in CDRS-R. **[Forest, please confirm or correct.]**~~ that excluded these 9 patients.

8.0 PATIENT DISPOSITION

Patient disposition data are summarized by treatment group and center in Table 1.1, Appendix IX, Listing 1, and Panel 8. Appendix Table 1A provides the distribution of individual randomized patients by center. ~~A list of non-treated patients who prematurely discontinued and reason for discontinuation is provided in Appendix Table 1B.~~ ~~178 patients were randomized, 93 patients into the citalopram group and 85 patient into the placebo group.~~ Four patients randomized ~~into the~~ additional to citalopram ~~group~~ were but were lost to follow-up and never received study drug ~~(Patients 104, 119, 211, and 505). These 4 patients were not included in the safety or ITT populations~~ (Appendix Table 1B ~~and Appendix IX, Listing 1).~~ ~~Of the~~ 174 patients ~~who~~ received double-blind study drug, of whom 89 received citalopram and 85 received placebo. These patients were included in all safety and efficacy analyses. Among the 89 patients treated with citalopram, 45 were between 7 and 11 years of age and 44 were between 12 and 17 years of age. Among the 85 patients treated with placebo 38 were between 7 and 11 years of age and 47 were between 12 and 17 years of age. ~~In addition,~~ and so the safety populations and ITT population were identical.

comments on the protocol from

modified the primary statistical analysis to an ~~0.1~~ 0.5 level, at the 10% level

Panel 8. Patient Disposition

Reason	Placebo			Citalopram		
	Children (N=38)	Adolescents (N=47)	Total (N=85)	Children (N=48)	Adolescents (N=45)	Total (N= 93)
Patients Randomized	38	47	85	48	45	93
Lost to Follow-up	0	0	0	3	1	4
Safety Population	38	47	85	45	44	89
ITT Population	38	47	85	45	44	89

Cross-reference: Table 1.1 and Appendix IX, Listing 1.

Panel 9 presents the number of patients who discontinued prematurely by treatment group and reason, using the safety population as the total sample. A total of 138 (79%) patients completed the study, 80% of patients in the citalopram group and 79% of patients in the placebo group. There was no significant difference between the two treatment groups or between age groups within and between the two treatment groups in the overall percentage of patients who discontinued from the study prematurely. The rates of discontinuation by individual reason were also similar between treatment groups, the most frequent being adverse event and lost to follow-up, each of which occurred in 5.6% of citalopram treated patients and 5-9% of placebo treated patients.

Where is the analysis?

Panel 9. Reasons for Patient Discontinuation: Number (%)

Reason	Placebo			Citalopram		
	Children (N=38)	Adolescents (N=47)	Total (N=85)	Children (N=45)	Adolescents (N=44)	Total (N=89)
Total Completers	30 (78.9)	37 (78.7)	67 (78.8)	36 (80.0)	35 (79.5)	71 (79.8)
Total Withdrawn For Any Reason	8 (21.1)	10 (21.3)	18 (21.2)	9 (20.0)	9 (20.5)	18 (20.2)
Adverse Event	1 (2.6)	4 (8.5)	5. (5.9)	3 (6.7)	2 (4.5)	5 (5.6)
Insufficient Therapeutic Response	0	1 (2.1)	1 (1.2)	2 (4.4)	0	2 (2.2)
Protocol Violation	2 (5.3)	1 (2.1)	3 (3.5)	0	2 (4.5)	2 (2.2)
Withdrawal of Consent	0	2 (4.3)	2 (2.4)	0	2 (4.5)	2 (2.2)
Lost to Follow-Up	4 (10.5)	1 (2.1)	5 (5.9)	2 (4.4)	3 (6.8)	5 (5.6)
Other	1 (2.6)	1 (2.1)	2 (2.4)	2 (4.4)	0	2 (2.2)

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

Table 1.3 lists the patients who discontinued prematurely by treatment group, reason for discontinuation, number of days on drug, and day of last visit.

Section 12.2.3 provides detailed information on patients who prematurely withdrew from the study due to AEs. Narratives for each of these patients can be found in the Patient Narrative Section at the end of this report.

9.0 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

9.1 Demographics

However, patients between 7 and 11 years of age were predominantly male (58%), whereas the adolescent patients were predominantly female (64%)

Demographic data for the safety population are summarized by treatment and age groups in Table 2.1, Appendix IX, Listing 2, and Panel 10. Subgroup analyses of demographic data by treatment for the safety population are summarized in Appendix Table 2A for children and in Appendix Table 2B for adolescents. Demographic characteristics were similar between the treatment groups. The majority of subjects in both treatment groups were female (58% for citalopram and 54% for placebo) and Caucasian (81% and 73%, respectively). Mean age in both treatment groups was 12 years. Among the children, the mean age in the citalopram group was 9.3 years and the mean age in the placebo group was 9.6 years. Among the adolescents, the mean age in the citalopram group was 14.9 years and the mean age in the placebo group was 14.1 years.

Panel 10. Demographic Characteristics

Characteristic		Placebo			Citalopram		
		Children (N=38)	Adolescents (N=47)	Total (N=85)	Children (N=45)	Adolescents (N=44)	Total (N=89)
Age, years	Mean (SD)	9.6 (1.3)	14.1 (1.8)	12.1 (2.8)	9.3 (1.1)	14.9 (1.7)	12.1 (3.1)
	Median	10.0	14.0	12.0	9.0	15.0	11.0
	Min, Max	7;11	12;17	7;17	7;11	12;17	7;17
Sex, n (%)	Female	16 (42.1)	30 (63.8)	46 (54.1)	19 (42.2)	28 (63.6)	47 (52.8)
	Male	22 (57.9)	17 (36.2)	39 (45.9)	26 (57.8)	16 (36.4)	42 (47.2)
Race, n (%)	Caucasian	31 (81.6)	31 (66.0)	62 (72.9)	36 (80.0)	36 (81.8)	72 (80.9)
	Non-Caucasian	7 (18.4)	16 (34.0)	23 (27.1)	9 (20.0)	8 (18.2)	17 (19.1)
Weight, lbs	Mean (SD)	97.6 (38.0)	148.2 (60.3)	125.6 (57.2)	98.9 (43.0)	149.1 (46.2)	123.7 (51.0)
	Median	95.8	138.5	116.0	88.6	143.3	117.0
	Min, Max	48;219	72;396	48;396	50;247	75;280	50;280

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

~~Demographic data and other baseline characteristics of the ITT population, presented in Table 2.2, were similar to those of the safety population.~~ A patient listing of demographic and baseline data for all randomized patients is provided in Appendix IX, Listing 2.

The subgroup analyses, presented in Appendix Tables 2A and 2B, showed that statistically significantly (p=0.028) more Caucasian adolescents were enrolled in the citalopram group (36/44, 82%) than in the placebo group (31/47, 66%). The significant difference in race for children was not considered clinically meaningful. No other significant differences were observed for any other demographic subgroup parameter. However, it should be noted that this study was not powered to determine differences within the age subgroups (children and adolescents). The sample size was calculated based on the anticipated effect size for the primary efficacy variable.

Among the children, the onset of MDD had occurred while they were 7 years of age, on average, and the onset of MDD among the adolescents was at a mean age of approximately 12.

9.2 Patient History

Table 2.3 presents the depression history of the safety population by treatment group and age group. Subgroup analyses of the depression history by treatment for the safety population are summarized in Appendix Table 3A for children and in Appendix Table 3B for adolescents.

There were no apparent differences between treatment groups. The percentage of patients who ~~had experienced a single previous~~ were experiencing their first episode of depression was 78.7% ~~for patients~~ in the citalopram group and 82.4% ~~for patients~~ in the placebo group. The mean duration of MDD was approximately 2 years and the average age of onset was 10 years for both treatment groups. Twenty percent of patients in the citalopram group and 18% of patients in the placebo group had previously received antidepressant treatment, and approximately 15% of patients in the citalopram group and 16% of patients in the placebo group had a history of treatment nonresponse.

The subgroup analyses, presented in Appendix Tables 3A and 3B, showed that statistically significantly ($p=0.030$) more children in the citalopram group (9/45, 20%) than children in the placebo group (1/38, 3%) had recurrent disease course. For adolescents the difference in disease episode duration approached statistical significance between the two treatment groups ($p=0.054$), with adolescents in the citalopram group experiencing longer episodes (22.5 months) than adolescents in the placebo group (15.7 months). No other significant differences were observed for any other depression history subgroup parameter.

The psychiatric, suicide, medical, and psychotropic drug treatment histories of patients in the safety population also were similar between treatment groups and were typical of this patient population.

Individual patient listings of psychiatric history, suicide history, medical history, psychotropic drug treatment, and nondrug psychiatric treatment histories can be found in Appendix IX, Listings 3, 4, 5, 6, and 7, respectively.

9.3 Efficacy Variables at Baseline

Efficacy variables for the ITT population at baseline are presented in Table 2.4 and Panel 11. The mean baseline scores in each treatment group are indicative of ~~patients with~~ moderate to severe depressive symptomatology producing significant functional impairment, consistent with a diagnosis of major depressive disorder. No statistically significant differences between groups were observed for any efficacy parameter at baseline.

The incidence of ongoing secondary psychiatric disorders and of previous or ongoing secondary psychiatric disorders is presented by treatment group and age group in Appendix Tables 9A and 9B. The overall incidence of ongoing psychiatric comorbidity was 16.9% in the citalopram group and 9.4% in the placebo group; the overall incidence of psychiatric comorbidity at present or by history was 25.8% in the citalopram group and 15.3% in the placebo group. The most frequent ongoing secondary psychiatric disorders were enuresis (6 patients) and dysthymia (5 patients). Encopresis, separation anxiety disorder, social anxiety disorder, anxiety disorder NOS, and specific phobia (?) were also present in more than one patient.

Panel 11. Efficacy Variables at Baseline [Mean (SD)]

Efficacy Parameter	Placebo			Citalopram			p-value[a]
	Children (N=38)	Adolescents (N=47)	Total (N=85)	Children (N=45)	Adolescents (N=44)	Total (N=89)	
CDRS-R	56.8 (10.3)	58.6 (11.8)	57.8 (11.1)	60.0 (10.9)	57.5 (10.9)	58.8 (10.9)	0.653
CGI-S	4.3 (0.5)	4.4. (0.6)	4.3 (0.5)	4.4 (0.7)	4.3 (0.5)	4.4 (0.6)	0.721
CGAS	51.9 (5.8)	51.6 (7.9)	51.8 (7.0)	50.6 (7.4)	52.0 (8.0)	51.3 (7.7)	0.579
K-SADS-P Depression Module	28.2 (3.4)	29.1 (6.8)	28.7 (5.0)	28.6 (5.6)	29.2 (5.1)	28.9 (5.3)	0.977

a p-values for between-treatment comparisons are from three-way ANOVA with factors of treatment, age group, and center.
ITT population
Cross-reference: Table 2.4 and Appendix IX, Listing 8.

10.0 EFFICACY EVALUATION

All efficacy analyses are based on the ITT population. Tables 3.1 through 3.8, 4.1A through 4.5B, and 5.1A through 5.5B present the results of the efficacy analyses as the means, medians, SD, and ~~means~~ SEM, the p-value for the overall ~~and pairwise~~ treatment effects, the difference of the LSM with 95% CIs, ~~and p-values for the treatment by center interaction for the comparison of citalopram with placebo.~~

10.1 Children's Depression Rating Scale – Revised

The primary efficacy parameter was the change from baseline in the CDRS-R score after 8 weeks of double-blind treatment. Table 3.1 and Panel 12 present the results from the LOCF analysis for the change from baseline to week 8. The p-value for the treatment by baseline score interaction is presented in Table 3.8. The LOCF analysis by visit is presented in Table 4.1A. Descriptive statistics by visit are presented in Tables 5.1A (LOCF) and 5.1B (OC). The OC analysis by visit is presented in Table 4.1B.

At week 8, the LOCF analysis comparing the mean change from baseline in CDRS-R in the citalopram and placebo groups demonstrated a statistically significant ~~overall~~ treatment effect in favor of citalopram (p=0.038). This treatment effect was already apparent at week 1 (p=0.011) and ~~persisted over the entire treatment period (p≤0.038).~~ was observed at all subsequent clinic visits (p≤0.05; see Panel 13). Similar effects were seen in the children and adolescent subgroups, as evidenced by the lack of a treatment-by-age group interaction (p=0.136, Appendix Table 5). The treatment effect was also independent of baseline severity of depression, as indicated by the lack of a treatment-by-baseline interaction (p=0.116). Similar results were found for the OC analyses at weeks 1, 4, and 6 (p≤0.021). At week 2 the difference between the treatment groups approached statistical significance in favor of citalopram (p=0.060). However, even though citalopram treatment exhibited a numerically greater improvement than placebo treatment at week 8, the difference between the groups was not statistically significant (p=0.167).

Analyses using the OC approach likewise demonstrated significantly greater improvement in the citalopram group than the placebo group, with significant citalopram – placebo differences (p≤0.05) observed at weeks 1, 4, and 6.

The response rate at week 8 (with response defined as CDRS-R ≤ 28) was significantly higher in the citalopram group (36.0%) than the placebo group (23.5%) in the LOCF analysis (p=0.041)

CI(s) resp? adj x tx? baseline x tx

Panel 12. Change from Baseline to Week 8 in CDRS-R [Mean ± SEM]

~~Analysis~~	Placebo ~~Total~~ (N=85)	Citalopram ~~Total~~ (N=89)	p-value[a]
Mean ± SEM	-16.5 ± 1.6	-21.7 ± 1.6	0.038
~~Median~~	~~-17.0~~	~~-20.0~~	
~~Range~~	~~-55; 14~~	~~-67; 7~~	

a ~~ANOVA~~ p-value is based on the three-way ANCOVA model with treatment, age group, and center as factors and baseline score as covariate.
ITT population
Cross-reference: Tables 3.1, 4.1A, and Appendix IX, Listing 8.

~~The mean change from baseline in the CDRS-R scores at each week using the LOCF dataset are presented graphically in Panel 13.~~

Panel 13. CDRS-R Change from Baseline Over Time

Insert Figure 1.1.

[Forest, please provide Figure 1.1 in electronic format.]

Appendix Table 6 presents the results from the LOCF analysis for the change from baseline to week 8 excluding data from the 9 patients ~~(Patients 105, 113, 114, 505, 506, 507, 509, 513, and 514) who accidentally received 1 week of unblinded study drug treatment (tablets had the incorrect color coating). At week 8, the LOCF post-hoc~~ analysis comparing the mean change from baseline in CDRS-R in the citalopram and placebo groups ~~approached a statistically significant overall treatment effect in favor of citalopram (p=0.052).~~

[Forest, please confirm or correct wording concerning incorrect study drug administration.]

Appendix Table 7A presents the ~~LOCF~~ and Appendix Table 7B the OC analysis showing a 50% decrease from baseline in CDRS-R scores, by visit and treatment group. No statistically significant differences were observed for weeks 1 through 8 between the two treatment groups for either analysis. However, at week 4, both analyses approached statistical significance in favor of citalopram (LOCF, p=0.074 and OC, p=0.063).

The SAS outputs for the analysis of change from baseline in CDRS-R by visit are provided in Appendix Tables 15 and 16 for the LOCF analysis and OC analysis, respectively.

10.2 Secondary Parameters

10.2.1 Clinical Global Impressions ~~Improvement~~

~~Table 3.2 presents the analysis of the change from baseline to week 8 in the CGI-I score using the LOCF analysis. By-visit analysis results are presented in Table 4.2A (LOCF) and 4.2B (OC), respectively.~~ Descriptive statistics by visit for LOCF and OC analyses are presented in Tables 5.2A and 5.2B, respectively. Individual patient data are provided in Appendix IX, Listing 8.

For the CGI-I score, the LOCF analysis comparing the mean change from baseline to week 8 between the citalopram and placebo groups demonstrated an overall treatment effect numerically in favor of citalopram. However, the improvement in the CGI-I score did not reach statistical significance (p=0.257). Similar results were observed for the OC analysis. By-visit analyses demonstrated that citalopram resulted in numerically greater improvement in the CGI-I score over placebo for both the LOCF and OC analyses at every visit, but the differences were not statistically significant, except for week 6 (p=0.006, LOCF and p=0.009, OC).

~~10.2.2 Clinical Global Impressions Severity~~

Table 3.3 presents the analyses of the change from baseline to week 8 in the CGI-S score using the LOCF approach. Results of the by-visit analyses are presented in Table 4.3A (LOCF) and Table 4.3B (OC). Descriptive statistics by visit are presented in Tables 5.3A (LOCF) and 5.3B (OC). Individual patient data are provided in Appendix IX, Listing 8.

For the CGI-S score, the LOCF analysis comparing the mean change from baseline to week 8 between the citalopram and placebo groups demonstrated a numerical overall greater improvement in favor of citalopram. However, this effect did not reach statistical significance (p=0.266). Similar results were observed in the analysis using the OC approach.

By-visit analyses demonstrated that citalopram produced a statistically significantly greater improvement in the CGI-S score than placebo for the LOCF analysis at weeks 1 to 6 (p≤0.023). The OC analysis showed a greater statistically significant improvement in the CGI-S score for citalopram compared with placebo at weeks 1, 4, and 6 (p≤0.034). At week 2, the OC analysis approached statistical significance (p=0.057) in favor of citalopram.

10.2.3 Childrens Global Assessment Scale

Table 3.4 presents the results from the LOCF analysis of the CGAS rating at week 8. Table 4.4A presents the results of the LOCF analysis by visit, and Table 4.4B presents the results of the OC analysis. Descriptive statistics by visit for CGAS are presented in Tables 5.4A (LOCF) and 5.4B (OC), respectively. Individual patient data are provided in Appendix IX, Listing 8.

10.2.3 K-SADS-P Depression Module
The K-SADS-P depression module was administered at screening, baseline, and the end of week 8. Results from the LOCF analysis are presented in Table 3.5 and 4.5A. Results from the OC analysis are presented in Table 4.5B.

For CGAS, the LOCF analysis comparing the mean change from baseline to week 8 between the citalopram and placebo groups demonstrated a numerical overall treatment effect in favor of citalopram. However, this effect did not reach statistical significance (p=0.309). Similar results were observed for the OC analysis. By-visit analyses demonstrated that citalopram produced a statistically significant treatment effect over placebo at week 4 (p=0.019, LOCF and p=0.028, OC).

10.3 Additional Parameters

The additional efficacy parameters included the K-SADS-P depression module, CGI-I responders, CDRS-R responders, and treatment-by-baseline interaction. The analyses of the change from baseline to week 8 for these parameter are presented in Tables 3.5 through 3.8, using the LOCF approach. By-visit analyses for the K-SADS-P depression module, the CGI-I responders, and the CDRS-R responders are presented in Tables 4.5A through 4.7A (LOCF) and 4.5B through 4.7B (OC). Descriptive statistics at each visit for the K-SADS-P depression module are presented in Tables 5.5A (LOCF) and 5.5B (OC). Additionally, Appendix Table 8A presents the LOCF and Appendix Table 8B the OC analyses for the K-SADS-P responders at week 8. Individual patient data are provided in Appendix IX, Listing 8. On the K-SADS-P depression module, numerically greater improvement was observed in the citalopram groups relative to the placebo group in both the LOCF and OC analysis, but the difference did not reach statistical significance.

For the CDRS-R responders, a statistically significant treatment effect in favor of citalopram was observed for the LOCF analysis at week 6 (p=0.033) and week 8 (p=0.041). The OC analysis at week 6 (p=0.037) also showed statistically significant improvement in favor of citalopram; the difference in treatment tended towards statistical significance at week 8 (p=0.097). For the LOCF and OC analyses of the K-SADS-P responders at week 8, no statistically significant differences were observed between treatment groups.

For all other additional parameters, a consistent numerical trend in favor of citalopram treatment was observed.

10.3 Treatment-By-Baseline Interaction from the week 8 ANCOVA using the LOCF approach

10.4 Treatment-By-Age Group Interaction

The significance of the Treatment-by-age group interaction is summarized in Appendix Table 5 for the LOCF approach. No significant differences were observed for the treatment-by-age group interactions for the CDRS-R, CGI-I, CGI-S, CGAS, and K-SADS-P scores. No interaction was found for each efficacy variable.

10.5 Efficacy Conclusions

Citalopram treatment showed a statistically significant improvement in the CDRS-R score as early as week 1 (p=0.011), which persisted over the entire treatment period using the LOCF approach (p≤0.038). Additionally, the response rate for the CDRS-R responders at week 8 for the LOCF analyses showed a statistically significant treatment effect in favor of citalopram (p=0.041). Similar results were observed using the OC scores with the exception of the week-8 timepoint. The OC analyses for this parameter approached statistical significance at week 8 (p= 0.097). All other efficacy parameters showed a consistent numerical trend in favor of citalopram treatment, but failed to reach statistical significance at week 8. Except for the CGI-I responder score, all other parameters with evaluations at week 6 reached statistical significance in favor of citalopram treatment at this timepoint. The by-visit evaluations for these parameters

show a marked improvement in the placebo scores at the week 8-timepoint, suggesting a placebo effect. No explanation is currently available for this observation. This large placebo effect may be, in part, responsible for the lack of statistical significance in favor of citalopram at week 8.

11.0 PHARMACOKINETICS AND PHARMACODYNAMICS

Descriptive statistics for plasma concentrations of citalopram and its metabolites, by previous dose, are summarized in Appendix Table 13A. Summaries of the mean plasma concentrations of escitalopram and its enantiomers are provided in Appendix Table 13B. Panel 14 presents the plasma concentrations of citalopram, its metabolites, and enantiomers by citalopram concentration and overall age group. Citalopram is metabolized to demethylcitalopram (DCT) (29.4 ng/mL), and didemethylcitalopram (DDCT) (5.2 ng/mL), with the unchanged citalopram (67.6 ng/mL) as the predominant compound in plasma after citalopram administration. The enantiomer analysis showed that the major component in plasma, after citalopram administration, was escitalopram (20.8 ng/mL) with S-DCT (11.6 ng/mL) and S-DDCT (1.5 ng/mL) being minor components. Given the high degree of variance in citalopram/escitalopram DCT/S-DCT, and DDCT/S-DDCT plasma concentrations, no meaningful differences between children and adolescents were observed in plasma concentrations of these components. Multiple-dose citalopram administration showed a linear and dose-proportional pharmacokinetic profile.

Panel 14 Overall Mean Plasma Concentration of Citalopram and its Metabolites

Analysis	Citalopram		Overall		
	20 mg	40 mg	Children	Adolescents	Total
	(N=26)	(N-36)	(N=30)	(N=32)	(N=62)
Citalopram (ng/mL)					
Mean ± SD	49.4 ±37.90	80.8 ± 69.07	72.0 ± 57.97	63.6 ± 62.02	67.6 ± 59.75
Range	1.00 – 124.89	1.00 – 289.77	1.00 – 289.77	1.00 – 279.18	1.00 – 289.77
DCT (ng/mL)					
Mean ± SD	20.6 ± 13.39	35.8 ± 23.70	35.5 ± 23.36	23.8 ± 17.69	29.4 ± 21.29
Range	1.00 – 54.09	1.00 – 85.73	1.00 – 85.73	1.00 – 67.36	1.00 – 85.73
DDCT (ng/mL)					
Mean ± SD	3.0 ± 1.76	6.8 ± 5.43	5.8 ± 5.32	4.6 ± 3.91	5.19 ± 4.65
Range	1.00 – 6.62	1.00 – 22.15	1.00 – 22.15	1.00 – 13.92	1.00 – 22.15
Escitalopram (ng/mL)					
Mean ± SD	15.5 ± 14.57	24.6 ± 27.01	19.7 ± 21.60	21.8 ± 24.43	20.8 ± 22.94
Range	0.50 – 49.25	0.50 – 110.33	0.50 – 109.18	0.50 – 110.33	0.50 – 110.33
S-DCT (ng/mL)					
Mean ± SD	8.0 ± 5.68	14.1 ± 9.71	13.90 ± 9.94	9.36 ± 6.91	11.6 ± 8.75
Range	0.50 – 22.12	0.50 – 43.58	0.50 – 43.58	0.50 – 27.91	0.50 – 43.58
S-DDCT (ng/mL)					
Mean ± SD	0.94 ± 0.52	1.88 ± 1.32	1.62 ± 1.35	1.4 ± 0.93	1.5 ± 1.15
Range	0.50 – 1.88	0.50 –4.76	0.50 – 4.76	0.50 – 3.34	0.50 –4.76

Note: Patients with plasma concentration level BLOQ were assigned values of 0.5 (half of LOG).
Cross-reference: Appendix Tables 13A and 13B and Appendix IX, Listings 24A and 24B.

A listing of citalopram, ~~citalopram~~ escitalopram, and metabolite, ~~and enantiomer~~ plasma concentrations at the final visit is provided in Appendix IX, Listings 24A and 24B.

The concentration of citalopram was approximately 13% higher in the children as compared to the adolescents. However, the correlation analyses revealed no significant correlation between age and citalopram concentration (r=-.059) or escitalopram concentration (r=.048). Body weight also appeared to be uncorrelated with either citalopram concentration (r=-.119). Improvement on the CDRS-R also showed no significant relationship to plasma levels of either citalopram (r=.123) or its active enantiomer escitalopram (r=.104).

~~Appendix Tables 14A and 14B present the dose-adjusted and unadjusted plasma concentration correlation analyses for age and weight by citalopram and escitalopram concentration, respectively. For the dose-adjusted correlation analysis a statistically significant difference in citalopram plasma concentration was observed with respect to weight (p=0.030). No statistically significant differences were observed for the unadjusted correlation analysis.~~

[Forest, what was compared here?]

12.0 SAFETY EVALUATION

12.1 Extent of Exposure

The mean duration of treatment for patients in each treatment group is presented in Table 6.1. Appendix Table 4A summarizes the distribution by final dose and treatment group, and Appendix Table 4B summarizes the modal daily dose by visit and treatment group. The average duration of treatment was 53 and 51 days for patients in the citalopram and placebo groups, respectively. Forty-one (46.1%) patients received 20 mg citalopram and 48 (53.9%) patients received 40 mg citalopram. The majority of patients in both treatment groups received 2 tablets per day; 48 (53.9%) patients in the citalopram group and 53 (62.4%) patients in the placebo group. With respect to the modal daily citalopram dose, 70 (78.7%) patients received 20 mg and 19 (21.3%) patients received 40 mg citalopram. Most patients received a modal dose of 1 tablet per day in both treatment groups; 70 (78.7%) patients in the citalopram group and 59 (69.4%) patients in the placebo group.

12.2 Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events

12.2.1 Deaths

No deaths occurred during the conduct of this study.

12.2.2 Serious Adverse Events

One patient experienced an SAE during the study. The patient is listed in Table 7.1. A brief discussion of the SAE for this patient is presented below. A narrative describing the SAE is provided in the Patient Narratives Section of this report. The CRF for this patient is located in Appendix X.

Patient 137, a 10-year-old male treated with placebo, showed impulsive behavior on Study Day 57. The event was considered by the investigator to be moderate in intensity and not related to study drug treatment. The impulsive behavior resolved spontaneously on the same day.

12.2.3 Discontinuations Due to Adverse Events

The incidence of discontinuations due to AEs is presented in Tables 1.2 and 7.2. A listing of patients who discontinued due to AEs is presented in Panel 15. Ten patients experienced 15 AEs that resulted in discontinuation from the study: 5 (5.6%) patients in the citalopram group and 5 (5.9%) patients in the placebo group. The most common AEs leading to discontinuation were aggravated depression, which occurred in 2 (2.4%) adolescents treated with placebo, and agitation, which occurred in 2 (2.2%) children in the citalopram group.

Panel 15. List of Patients who Discontinued due to Adverse Events

Treatment Group/ Patient Number	Age (yrs)	Sex	AE Start Day[a]	AE (Preferred Term)
PLACEBO				
507	13	Female	30	Rash
550	13	Male	29	Depression Aggravated
574	15	Female	5	Depression Aggravated
519	12	Female	41	Suicidal Tendency
137	10	Male	31	Personality Disorder
CITALOPRAM				
534	16	Female	24	Akathisia
561	16	Female	8	Fatigue
			8	Appetite Decreased
			8	Weight Decreased
144	10	Male	47	Hypomania
			53	Headache
			53	Abdominal Pain
193	9	Male	36	Agitation
229	7	Male	15	Agitation
			15	Concentration Impaired

a: AE Start Day = AE Start Date – Date of First Dose +1.
Safety population; cross-reference: Table 7.3.

Individual narratives for the patients listed in Panel 15 are provided in the Patient Narratives Section at the end of this report; the corresponding CRFs are located in Appendix X.

12.3 Adverse Events

The following sections present the incidence of TEAEs for the safety population by treatment and age groups, by body system, preferred term, severity, relationship to study drug, and sex.

12.3.1 Incidence of Treatment-Emergent Adverse Events

The number and percentage of patients who experienced a TEAE are summarized by treatment group, age group, body system, and preferred term in Tables 7.4. ~~Appendix Table 10A presents the total number of AEs by treatment and age group.~~ Panel 16 presents the number and percentage of patients who experienced a TEAE with an incidence of at least 5.0% in any treatment group ~~and the total number of AEs by treatment group~~; TEAEs are presented in order of decreasing frequency in the citalopram group. **[Forest, Tables 10A and 10B, show 77 patients with 236 AEs and 61 patients with 179 AEs. Tables 7.4 and 7.5 show 75 and 59 patients with AEs in the citalopram and placebo groups, respectively. Are Tables 10A and 10B based on patients with AEs or TEAE as Tables 7.5 and 7.6. To correlate AEs with number of patients, who experienced AEs, both sets of Tables have to be based on the same AE definition.]**

Seventy-five (84.3%) patients in the citalopram group reported 236 AEs and 59 (69.4%) patients in the placebo group reported 179 AEs. Among patients treated with citalopram, the most common TEAEs were gastrointestinal system disorders, respiratory system disorders, and central and peripheral nervous system disorders. Among patients treated with placebo, respiratory system disorders, central and peripheral nervous system disorders, and gastrointestinal system disorders were most common. Headache (17 patients, 19.1%), rhinitis (12 patients, 13.5%), nausea (12 patients, 13.5%), and abdominal pain (10 patients, 11.2%) were the most frequently reported TEAEs in the citalopram group. All other TEAEs in the citalopram group occurred in 6 or less patients. In the placebo group, headache (17 patients, 20.0%) and pharyngitis (7 patients, 8.2%) were the most frequently observed TEAEs. All other TEAEs in the placebo group occurred in 6 or less patient.

Additionally, three patients had TEAEs with an incidence greater than 5.0% (and less than 7.0%) and at least twice that observed with placebo were reported in the citalopram groups: influenza-like symptoms (citalopram 6.7% and placebo 0%), fatigue (citalopram, 5.6% and placebo 1.2%), and diarrhea (citalopram 5.6% and placebo 1.2%).

Overall, no clinically significant differences in the frequency of TEAEs were observed between the two age groups in either treatment group.

The overall incidence of TEAEs was 84.3% in the citalopram group and 69.4% in the placebo group. Other than headache (19.1% citalopram, 20.0% placebo), the most frequent TEAEs in both treatment groups were gastrointestinal and respiratory disorders. The ~~three~~ TEAEs that occurred with an incidence greater than 5% in the citalopram group and at least twice the incidence in the placebo group were rhinitis (13.5% citalopram, 5.9% placebo), nausea (13.5% citalopram, 3.5% placebo),
The most frequent psychiatric side effects in the citalopram group were insomnia (4.5%), agitation (3.4%), and irritability (3.4%). No sexual dysfunction was reported.

The overall incidence of TEAEs was 82.2% in citalopram-treated children and 86.4% in citalopram-treated adolescents. In the citalopram group, the only individual TEAEs that differed in incidence between age groups by at least 10% (i.e., 5 patients) were fever (11.1% in children, 0% in adolescents) and nausea (2.2% in children, 25.0% in adolescents).

Panel 16. Most Frequent Treatment Emergent Adverse Events (≥5.0%)

Preferred Term	Number (%) of Patients: Placebo Total (N=85)	Citalopram Total (N=89)
~~Total number of AEs~~	~~179~~	~~236~~
Patients with at least 1 TEAE	59 (69.4)	75 (84.3)
Headache	17 (20.0)	17 (19.1)
Rhinitis	5 (5.9)	12 (13.5)
Nausea	3 (3.5)	12 (13.5)
Abdominal Pain	6 (7.1)	10 (11.2)
Influenza-Like Symptoms	0	6 (6.7)
Pharyngitis	7 (8.2)	6 (6.7)
Fever	5 (5.9)	5 (5.6)
Fatigue	1 (1.2)	5 (5.6)
Vomiting	5 (5.9)	5 (5.6)
Diarrhea	1 (1.2)	5 (5.6)
Back Pain	3 (3.5)	5 (5.6)
Coughing	6 (7.1)	4 (4.5)
Upper Respiratory Tract Infection	6 (7.1)	4 (4.5)

Percentages are relative to number of patients (N) in safety population.
Cross-reference: Table 7.4, Appendix Table 10A, and Appendix IX, Listings 11, 12 and 13.

Listings of AEs for individual patients for the ~~single-blind~~ placebo lead-in and double-blind ~~comparative~~ treatment periods are presented in Appendix IX, Listings 11 and 12, respectively. Listing 13 in Appendix IX presents AEs by treatment group, body system, and preferred term. Most adverse events in both the citalopram and placebo groups were mild in intensity and more than 98% in both groups were mild or moderate in intensity.

12.3.2 Treatment-Emergent Adverse Events by Severity and Causality

The number of patients with TEAEs by severity, treatment group, and age group are shown in Tables 7.5, and the total number of AEs by severity, treatment group, and age group is shown in Appendix Table 10A. ~~The majority of patients had TEAEs that were considered mild or moderate in severity. Only 4 patients in the citalopram group and 3 patients in the placebo group each had 1 TEAE that was considered to be severe.~~

The number and percentage of patients with TEAEs by causality and treatment group is presented in Table 7.6, and the total number of AEs by causality, treatment group, and age group is shown in Appendix Table 10B. ~~Four (4/89, 4.5%) patients in the citalopram group had 6 TEAEs that were considered to be related to study treatment. None of the~~ Most adverse events were judged to be unrelated to the study medication.

patients in the placebo group had a treatment-related TEAE. Thirty-seven (37/89, 41.6%) patients in the citalopram group had 94 AEs, and 33 (33/85, 38.8%) patients in the placebo group had had 62 AEs that were considered to be possibly related to study drug treatment.

12.3.3 Treatment-Emergent Adverse Events by Sex

The number and percentage of patients with TEAEs are shown by sex and treatment group in Table 7.7. Appendix Tables 11A and 11B present the number and percentage of patients by sex for children and adolescents, respectively. The overall number of patients with TEAEs within each treatment group was similar between male and female patients.

Overall, the type and frequency of TEAEs reported for male and female patients were similar to those reported for the treatment group as a whole. Among patients treated with citalopram, the largest male-female difference in the incidence of an individual TEAE was observed for headache, which was reported for 26.2% of male versus 12.8% of female patients. Headache was also more frequently reported among female patients treated with placebo than males: 17.9% of placebo-treated males versus 21.7% of placebo-treated females. Abdominal pain tended to be more common among citalopram-treated males than females, whereas nausea, appetite loss, insomnia, and coughing tended to be more frequent among citalopram-treated females than males. Overall, no clinically important differences in the TEAE profile of citalopram were observed between male and female patients.

12.3.4 Incidence of Other Psychiatric Disorders

The number and percentage of patients with other ongoing psychiatric disorders and previous or ongoing psychiatric disorders are summarized by treatment group, age group, and preferred term in Appendix Table 9A and Appendix Table 9B, respectively. More patients treated with citalopram (15/89, 16.9%) than patients treated with placebo (8/85, 9.4%) experienced ongoing psychiatric disorders during the study. Furthermore, in the citalopram group, more children (9/45, 20.0%) than adolescents (6/44, 13.6%) had ongoing psychiatric disorders. The incidence of ongoing psychiatric disorders for children (3/38, 7.9%) and adolescents (5/47, 10.6%) in the placebo group was similar.. The most frequent ongoing psychiatric disorders, occurring in 3 or more patients, were dysthymia (5/89, 5.6%) and enuresis (4/89, 4.5%) in the citalopram group and encopresis (3/85, 3.5%) and enuresis (3/85, 3.5%) in the placebo group.

The incidence of previous and ongoing psychiatric disorders were similar to the incidence of ongoing psychiatric disorders in that more patients in the citalopram group (23/89, 25.8%) than patients in the placebo group (13/85, 15.3%) experienced such disorders. However, compared to the incidence of ongoing psychiatric disorders in the citalopram group (more children than adolescents had ongoing psychiatric disorders), the incidence of previous and ongoing psychiatric disorders among children (12/45, 26.7%) and adolescents (11/44, 25.0%) in the citalopram group was similar. In the placebo group, 6 (15.8%) children and 7 (14.9%) adolescents experienced previous or ongoing psychiatric disorders. The most frequent previous and ongoing psychiatric disorders, occurring in more than 3 patients, were dysthymia (5/89, 5.6%), attention deficit hyperactivity disorder (4/89, 4.5%), enuresis (4/89, 4.5%), and generalized anxiety

disorder (3/89, 3.4%) in the citalopram group and enuresis (4/85, 4.7%), encopresis (3/85, 3.5%), and social anxiety disorder (3/85; 3.5%) in the placebo group.

12.4 Vital Signs and Body Weight

Table 8.1 presents the incidence of all vital sign values by treatment group and age group that were identified as PCS on the basis of criteria in Panel 5. Table 8.2 lists the baseline value, the PCS value, and the final value for all patients with PCS values. Tables 8.3 through 8.7 present summary statistics of the actual value and the change from baseline for systolic blood pressure, diastolic blood pressure, pulse rate, body weight, and height, respectively. Data are presented by treatment group, age group, and by visit, including endpoint. Individual patient data listings of all recorded vital sign values are provided in Appendix IX, Listing 14.

There were few cases of PCS ~~Potentially clinically significant (PCA)~~ values for blood pressure ~~and~~ or pulse rate ~~were~~ rate. Two (2.2%) children in the citalopram group and 1 (1.2%) child in the placebo group had a PCS increase in systolic blood pressure. PCS decreases in systolic blood pressure occurred in 2 (2.2%) patients (1 child and 1 adolescent) in the citalopram group and in 1 (1.2%) adolescent in the placebo group. The mean change in systolic blood pressure at endpoint was –0.6 mmHg in the citalopram group and +2.2 mmHg in the placebo group. No patient in either treatment group had an increase in diastolic blood pressure. One (1.1%) adolescent in the citalopram group and 2 (2.4%) adolescents in the placebo group had decreases in diastolic blood pressure. The mean change in diastolic blood pressure at endpoint was –1.4 mmHg in the citalopram group and -0.8 mmHg in the placebo group. No patient had a PCS increase in pulse rate and 1 (1.1%) child had a PCS decrease in pulse rate (citalopram group). The mean change in pulse rate from baseline to endpoint was 1.4 bpm for both treatment groups.

and none of them continued to meet PCS criteria at the final visit.

None of the PCS values for vital signs were classified as AEs and no patient discontinued study drug due to PCS values. Only 1 adolescent in the citalopram group experienced a mild cardiovascular TEAE (flushing) that was considered by the investigator to be possibly related to study drug treatment. [A detailed narrative for this patient is presented in the Patient Narrative Section of this report.]

Why?

Potentially clinically significant increases in body weight ≥7% in adolescents were infrequent, occurring in 2 (4.5%) adolescents in the citalopram group and 2 (4.3%) adolescents in the placebo group. Potentially clinically significant decreases ≥7% in body weight occurred only in 1 (2.3%) adolescent in the citalopram group. Overall, there was no ~~clinically significant~~ mean change in body weight for patients in the citalopram group at endpoint; the mean change in ~~body weight for patients in~~ the placebo group ~~at endpoint~~ was 1.4 lb.

group exhibited a weight increase ≥ 7% and two children in the citalopram group exhibited a weight decrease ≥ 7%.

Appendix Table 12A presents the incidence of all vital sign values by treatment and age group that were identified as PCS on the basis of the adolescent criteria in Panel 5. Appendix Table 12B lists all patients with PCS vital sign values based on the adolescent criteria. ~~Similar PCS vital sign values were obtained for children using the adolescent PCS criteria.~~ One child in the placebo group and 2 children in the citalopram group had postbaseline systolic blood pressure readings between 75 and 90 mmHg that met the adolescent PCS criteria. Two children in the placebo group and 6 children in the citalopram group had postbaseline diastolic blood pressure readings between 40 and 50 mmHg that met the adolescent PCS criteria. One child in the citalopram

12.5 Clinical Laboratory Evaluation

Table 9.1 presents the incidence of all laboratory test results that were identified as PCS based on the criteria in Panel 6. Table 9.2 presents the screening value, the PCS value, and the final value for each patient who had a post-baseline laboratory test result that was considered PCS. Descriptive statistics for all laboratory parameters are presented, in SI units, in Table 9.3. For each treatment group, mean values and standard deviations are given at screening, at the final visit, and for the change from screening to the final visit. Individual patient data listings of screening and follow-up laboratory results and any investigator's comments are provided in Appendix IX, Listings 15 and 16.

Four patients in the citalopram group and 2 patients in the placebo group had PCS clinical laboratory values. Panel 17 presents the screening, PCS, and final values for these patients by treatment group and patient number. No patient was discontinued from the study because of a laboratory abnormality, and no AEs related to laboratory abnormalities were reported. The magnitude of the observed mean changes from screening to final value was not clinically noteworthy for any laboratory tests.

Panel 17. List of Patients with PCS Laboratory Parameters

Treatment Group/ Patient Number	Parameter (Unit)	Age (yrs)	Sex	Screening Value	PCS Value	Final Value
PLACEBO						
(2) 517	Hemoglobin (g/dL)	13	Female	11.90	10.10	10.1
(1) 516	Protein Urine	12	Female	Negative	2+	2+
CITALOPRAM						
(3) 565	ALT (IU/L)	15	Female	13.0	117.0	117.0
	AST (IU/L)			12.0	197.0	197.0
(2) 522	Potassium (mmol/L)	17	Female	4.8	5.7	5.7
(1) 114	Potassium (mmol/L)	8	Female	5.0	5.5	5.5
(4) 598	WBC (x 10^9/L)	14	Male	5.0	2.8	2.7

Safety population; cross-reference: Table 9.2 and Appendix IX, Listing 15.

12.6 Electrocardiograms

on the basis of the criteria in Panel 7

~~Post-baseline~~ ECGs were evaluated ~~for PR and QTc intervals~~ to identify any PCS values ~~based on the criteria in Panel 7~~. As shown in Tables 10.1 and 10.2, no PCS ~~events~~ values were found. ~~reported~~. In addition, no ECG test results were considered to be AEs.

The percentage of patients with an ECG abnormality at screening was 27.5% (22/80) in the citalopram group and 23.7% (18/76) in the placebo group.

The emergence of any ECG abnormalities, regardless of clinical importance, is summarized by treatment group in Table 10.3. ~~The differences between treatment groups were not clinically meaningful.~~ The percentage of patients who had a normal ECG at screening and an ECG assessed as abnormal at endpoint was 13.8% (11/80) in the citalopram group and 11.8% (9/76) in the placebo group. ~~One~~ child (No. 203) treated with placebo who had a normal ECG at screening (PRI=172 msec, QTI=388 msec, and QTc=445 msec), an abnormal, clinically significant ECG at ~~endpoint~~ the end of week 8 visit (PRI=144 msec, QTI=412 msec, and QTc=467 msec), and an abnormal not clinically significant ECG

These differences are not clinically meaningful. Only one patient had a clinically significant ECG abnormality, a

later
1 day ~~after the endpoint evaluation~~ (PR=118 msec, QT=428 msec, and QTc=488 msec).
~~For all other patients, the abnormal ECG at endpoint was not clinically significant.~~

Individual patient data listings of baseline and post-baseline ECG evaluation results are provided in Appendix IX, Listing 17. Individual patient data listings of ECG abnormalities are provided in Appendix IX, Listing 18.

Descriptive statistics for ECG parameters are presented in Table 10.4 for each treatment group; mean values and standard deviations are given at screening, at the final visit (endpoint), and for the change from screening to the final visit. The mean changes in ventricular heart rate, QRS interval, PR interval, QT interval, and QTc interval from screening to the final visit were ~~not clinically significant.~~ insubstantial and clinically unimportant.

12.7 Physical Examination

Table 11.1 presents the number and percentage of patients with an abnormal value at the final visit by treatment group for patients with a normal or missing value (not done) at screening. The incidence of abnormal physical findings was low and similar among treatment groups.

Individual patient data are provided in Appendix IX, Listings 19 and 20.

12.8 Concomitant Medication

Table 12.1 shows the concomitant medications received by patients in each treatment and age group after the screening visit and before randomization. A total of 43 (48.3%) patients in the citalopram group and 44 (51.8%) patients in the placebo group received concomitant medications between screening and randomization. ~~Overall, use of concomitant medications was similar in type and frequency of use between the treatment groups during this period and was typical for patients with MDD.~~ The most commonly used concomitant medications during this period were analgesics, antiinflammatory drugs, and vitamins.

Table 12.2 shows the concomitant medications received by patients in each treatment and age group after randomization. A total of 70 (78.7%) patients in the citalopram group and 63 (74.1%) patients in the placebo group received concomitant medications during the double-blind treatment period. Overall, the use of concomitant medications was similar between treatment groups during the double-blind treatment period and comparable to that during the baseline period. ~~Overall, the type and frequency of concomitant medication use were typical of patients with MDD.~~ The most commonly used concomitant medications were analgesics, antiinflammatory drugs, antibiotics, antihistamines, and vitamins.

Individual patient data are provided in Appendix IX, Listings 21 through 23.

12.9 Safety Conclusions

Results of this study show that citalopram was safe and well tolerated in children and adolescents with MDD. Seventy-five (84.3%) patients in the citalopram and 59 (69.4%) patients in the placebo group reported TEAEs. The most frequent TEAEs (>8%) in the citalopram group were headache, rhinitis, nausea, and abdominal pain. In the placebo group, headache and pharyngitis were most commonly reported. Three patients in the citalopram group had TEAEs with an incidence of at least twice that observed for patients in the placebo group: influenza-like symptoms, fatigue, and diarrhea. The most frequent

ongoing psychiatric disorders occurring in 3 or more patients were dysthymia and enuresis in the citalopram group and encopresis and enuresis in the placebo group. No deaths occurred during the study. One serious TEAE (impulsive behavior) was reported in the placebo group. Ten patients were discontinued because of TEAEs. The incidence of discontinuation due to TEAEs was similar between the citalopram (5.6%) and placebo (5.9%) groups. No clinically significant difference in TEAE profile was observed between treatment groups, between children and adolescents, or between male and female patients receiving citalopram. The majority of TEAEs were mild or moderate in severity in both treatment groups. Analysis of laboratory, vital sign, body weight, and ECG parameters revealed a low incidence of PCS values for both treatment groups. The mean changes from baseline were small in magnitude and clinically unremarkable.

13.0 DISCUSSION AND OVERALL CONCLUSIONS

This clinical trial was conducted as a randomized, double-blind, placebo-controlled, multicenter comparison of the efficacy of citalopram with placebo in the treatment of depression in children and adolescents.

The design and execution of the trial assured that the study results provided a valid, double-blind comparison of treatment effects. Randomization resulted in treatment groups that were comparable with respect to demography and symptomatology. The statistical analyses compared the change from baseline between the treatment groups. The statistical model included baseline scores as a covariate, thus adjusting for between-group variability in baseline scores. Active and placebo capsules were identical in appearance and were identically packaged. Thorough monitoring of study sites, including source documents and study drug inventory, together with quality assurance procedures for data management, ensured the integrity of the data collected. Thus, the structural integrity and execution of the study satisfied rigorous validity criteria for a prospective, double-blind, randomized, placebo-controlled, comparative treatment design.

Citalopram treatment showed a statistically significant improvement in the CDRS-R score as early as week 1 ($p=0.011$), which persisted over the entire treatment period using the LOCF approach ($p\leq0.038$). Additionally, the response rate for the CDRS-R responders at week 8 for the LOCF analyses showed a statistically significant treatment effect in favor of citalopram ($p=0.041$). Similar results were observed using the OC scores with the exception of the week-8 timepoint. The OC analyses for this parameter approached statistical significance at week 8 ($p= 0.097$). All other efficacy parameters showed a consistent numerical trend in favor of citalopram treatment, but failed to reach statistical significance at week 8. Except for the CGI-I responder score, all other parameters with evaluations at week 6 reached statistical significance in favor of citalopram treatment at this timepoint. The by-visit evaluations for these parameters show a marked improvement in the placebo scores at the week 8-timepoint, suggesting a placebo effect. No explanation is currently available for this observation. This large placebo effect may be, in part, responsible for the lack of statistical significance in favor of citalopram at week 8.

Results of this study showed that citalopram was safe and well tolerated in children and adolescents with MDD. Seventy-five (84.3%) patients in the citalopram and 59 (69.4%) patients in the placebo group reported TEAEs. No clinically significant difference in TEAE profile was observed between treatment groups, between children and adolescents, or between male and female patients receiving citalopram. The most frequent TEAEs (>8%) in the citalopram group were headache, rhinitis, nausea, and abdominal pain. In the placebo group, headache and pharyngitis were most commonly reported. Three TEAEs with an incidence of at least twice that observed with placebo were reported in the citalopram group: influenza-like symptoms, fatigue, and diarrhea. The most frequent ongoing psychiatric disorders occurring in 3 or more patients were dysthymia and enuresis in the citalopram group and encopresis and enuresis in the placebo group. The majority of TEAEs were mild or moderate in severity in both treatment groups. No deaths occurred during the study. One serious TEAE (impulsive behavior) was reported in the placebo group. Ten patients were discontinued because of TEAEs. The incidence of discontinuation due to TEAEs was similar between the citalopram (5.6%) and placebo (5.9%) groups. Analysis of laboratory, vital sign, body weight, and ECG parameters showed a low incidence of PCS values for both treatment groups. The mean changes from baseline were small in magnitude and clinically unremarkable.

The safety findings support the conclusion that citalopram is safe and well tolerated in children and adolescents with MDD. No new safety concerns were identified relative to the safety review of citalopram in the New Drug Application (NDA) 20-822 or the citalopram package insert. According to the citalopram package insert, the most frequent TEAEs in adults treated with citalopram were nausea (21%), dry mouth (20%), somnolence (18%), and insomnia (15%), and the only common TEAE occurring at twice the incidence of placebo-treated patients was ejaculation disorder in males. This study showed that, in children and adolescents, these TEAEs occurred at a frequency of <5.0% except for nausea (14%). However, headache and rhinitis were reported at a higher frequency in children and adolescents (19% and 14%, respectively) than in adults (<2% and 5%, respectively). Since this study was conducted in children and adolescents (mean age 12 years), ejaculation disorder was an unlikely TEAE to occur in this population, and none was reported. On the other, hand influenza-like symptoms, fatigue, and diarrhea were reported with twice the incidence in children and adolescents treated with citalopram compared with children and adolescents treated with placebo.

The results of this study demonstrate the safety, tolerability, and antidepressant efficacy of citalopram in the treatment of MDD in children and adolescents.

intro
prev child studies
pk studies
dose
lot # for unblind cit
vital sign norms ref prot stip say
Worsening at week 8 no order / duration of visit / inf cons, ECG, phys
signif effect @ wk 4
= 20 mg
Pt 520 age 10, dispensing error cit
hypomania, akathisia, agitation, suicidality
narratives
lab tables

Safety Conclusions

No deaths occurred during the conduct of the study. There was one serious adverse event, in a placebo treated patient, and one clinically significant ECG abnormality, also in a placebo treated patient. The rate of discontinuation for adverse events was 5.6% in the citalopram group and 5.9% in the placebo group. Treatment emergent adverse events with a higher incidence in the citalopram group than the placebo group were, typically, either gastrointestinal symptoms (nausea and diarrhea) or respiratory disorders. Few psychiatric adverse events were reported, with little sign of CNS stimulation or depression. More than 98% of adverse events in each treatment group were mild or moderate in intensity. Citalopram's adverse event profile was generally similar in child and adolescent patients and in male and female patients. Analysis of laboratory, vital sign, body weight, and ECG parameters revealed a low incidence of PCS values in both treatment groups; the mean changes from baseline were clinically unremarkable.

DISCUSSION AND OVERALL CONCLUSIONS

1. Present results vs. previous studies [ital]

The positive results obtained in the present study contradict the high failure rate found in antidepressant trials in patients under 18 years of age. Several factors may have contributed to the outcome of this study:

(a) Citalopram treatment was tolerated by more than 94% of the patients treated, and 80% of the citalopram patients completed the full 8-week study.

(b) As a consequence of good tolerability for the adult starting dose (20 mg/day) with flexible upward titration (to 40 mg/day), effective citalopram plasma concentrations were achieved.

(c) The CDRS-R is a sensitive and reliable efficacy instrument for depressed children and adolescents that utilizes convergent information from the child and parent/caregiver.

2. Time course of effect and dosing [ital]

The primary efficacy measure, the CDRS-R, revealed significantly greater improvement in the citalopram group relative to the placebo group at every clinic visit during double-blind treatment. Consistent citalopram-placebo differences were observed at the end of week 4, before patients could be titrated above 20 mg/day, suggesting that 20 mg/day is an effective antidepressant dose in children and adolescents. Less consistent effects on secondary efficacy measures at the end of week 8 are probably not attributable to patients

receiving 40 mg/day citalopram. Worsened scores from the end of week 6 to the end of week 8 in children receiving citalopram or placebo may have been due to the extensive set of procedures administered at the final visit.

3. Validity [ital]

The study was designed to provide a valid, prospectively randomized, double-blind comparison of the treatment effects of citalopram and placebo. A medication packaging error partially compromised the study blind for 9 of the 174 patients. Post-hoc analysis excluding these patients supported the results from the intent-to-treat analysis. It is concluded that the study results are valid and interpretable.

4. Age effects [ital]

The safety profile of citalopram was generally similar in the children and adolescents, even though nausea occurred as a treatment emergent adverse event in only one of 45 citalopram-treated children. The magnitude of the mean citalopram-placebo differences on the efficacy ratings were numerically higher in the adolescents than the children, but no significant treatment-by-age group interactions were observed, indicating that the citalopram treatment effect was not age dependent. Plasma concentrations of citalopram were higher in the children as compared to the adolescents, but no significant correlation was found between plasma concentrations and age or body weight.

5. Safety versus adults [ital]

The safety profile of citalopram in depressed children and adolescents in the present study was generally similar to the one described for depressed adults in citalopram NDA 20-822 and the citalopram package insert. No new medical issues were identified in this study. The incidence of psychiatric adverse events, such as somnolence and insomnia, and the incidence of sexual dysfunction was lower in citalopram-treated children and adolescents than citalopram-treated adults, but these differences may be attributable to the reporting characteristics of the two populations.

6. Overall conclusion [ital]

The results of this study support the conclusion that citalopram, 20-40 mg/day, is safe and efficacious in the treatment of major depressive disorder in children and adolescents.