Forest Laboratories, Inc.
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New York, New York 10022

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

CIT-MD-18
IND Number 22,368

September 01, 1999

Confidentiality Statement

Final Protocol Authorization Sign-off Sheet

(To be retained in the study file.)

The following have reviewed and authorize the conduct of Study CIT-MD-18 entitled *A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Citalopram in Children and Adolescents with Depression* according to the attached protocol dated September 01, 1999:

Submitted By:

Paul J. Tiseo Sept. 01, 1999
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Associate Medical Director-CNS
Medical Monitor

Authorized By:

9/10/99
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COMPLIANCE WITH GOOD CLINICAL PRACTICE

This clinical study is designed to comply with the International Conference on Harmonisation (ICH) Guidance on General Considerations for Clinical Trials (62 FR 6611, December 17, 1997) and Good Clinical Practice: Consolidated Guidance (62 FR 25692, May 9, 1997).

1. SYNOPSIS

Forest Laboratories, Inc.
Name of Finished Product: Citalopram HBr
Name of Active Ingredient: 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, HBr
Study Title: A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Citalopram in Children and Adolescents with Depression.
Protocol Number: CIT-MD-18
Development Phase: Phase III
Objective: The objective of this study is to evaluate the safety and efficacy of citalopram in children and adolescent outpatients (7-11 and 12-17 years of age, respectively), diagnosed with major depressive disorder.
Study Design: Multicenter, randomized, double-blind, placebo-controlled, flexible-dose, stratified by age.
Number of patients/Number of centers: 160 patients/20 centers
Indication and main criteria for inclusion: Male and female pediatric outpatients, 7-17 years of age inclusive, with a diagnosis of Major Depressive Disorder (DSM-IV: 296.xx).
Test Products: Citalopram 20mg tablets and placebo tablets. *Doses:* Citalopram 20 – 40 mg/day, by mouth
Duration of treatment: One week of single-blind placebo lead-in followed by eight weeks of double-blind treatment.
Evaluations: *Diagnosis:* Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime (K-SADS-PL) *Primary Efficacy:* Children's Depression Rating Scale – Revised (CDRS-R). *Secondary Efficacy:* Clinical Global Impression (CGI)- Severity and Improvement subscales. K-SADS-P (depression module). Children's Global Assessment Scale (CGAS)
Safety: Clinical laboratory evaluations, adverse events, physical examinations, ECG's and vital signs.
Statistical Methods: The efficacy analyses will be based upon the last observation carried forward (LOCF) for all patients with post-baseline efficacy data who have received double-blind treatment. The primary efficacy parameter will be the CDRS-R. Three-way analysis of covariance (ANCOVA), with age-group, treatment group and center as the three factors, will be used for treatment comparisons.

2. SCHEDULE OF EVALUATIONS

Study visit	**Screen**	**Baseline**	**End of Week 1**	**End of Week 2**	**End of Week 4**	**End of Week 6**	**End of Week 8**
Visit number	1	2	3	4	5	6	7
Informed Consent	x						
Medical History - Psychiatric History	x						
Inclusion/Exclusion Criteria	x	x					
Physical Exam (with ECG)	x						x
Laboratory Evaluations	x						x
Analytical Sample							x
Urine drug screen	x						
Pregnancy test	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-Severity		x	x	x	x	x	x
CGI-Improvement			x	x	x	x	x
CGAS		x			x		x
K-SADS-P (depression module)		x					x
Drug Dispensing	x	x	x	x	x	x	
Concomitant Medication Check	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, will be conducted at the end of Week 8 visit for completers, or earlier, should the patient drop out of the study.*

3. LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine amino transferase
AST	Aspartate amino transferase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
BUN	Blood urea nitrogen
CDRS-R	Children's Depression Rating Scale – Revised
CFR	Code of Federal Regulations
CGAS	Children's Global Assessment Scale
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression – Improvement subscale
CGI-S	Clinical Global Impression – Severity subscale
CMH	Cochran-Mantel-Haenszel test
CRA	Clinical Research Associate
CRF	Case report form
CTM	Clinical Trial Manager
DHHS	Department of Health and Human Services
DSM-IV	Diagnostic and Statistical Manual – Fourth Edition
ECG	Electrocardiogram
ER	Emergency room
FDA	Food and Drug Administration
GCP	Good clinical practice
β-HCG	Human chorionic gonadotropin
ICH	International Conference on Harmonization
IND	Investigational new drug
IRB	Institutional Review Board
ITT	Intent-to-treat
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
LOCF	Last observation carried forward
MAO-I	Monoamine Oxidase Inhibitor
MDD	Major depressive disorder
NDA	New drug application
OC	Observed cases
PCS	Potentially clinically significant
RBC	Red blood cell
SAE	Serious Adverse Event
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TSH	Thyroid Stimulating Hormone
WBC	White blood cell

4. 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 TCA's (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.

Citalopram is currently approved for marketing in 68 countries for the treatment of either depression or depression and panic disorder. To date, it has been prescribed for 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.

4.1 Pediatric depression

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

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

5. OBJECTIVE

The primary objective of this study is to evaluate the safety and efficacy of citalopram in children (7-11 years) and adolescent (12-17 years) outpatients with major depressive disorder.

6. STUDY DESIGN AND DURATION

This study will be conducted as a randomized, double-blind, placebo-controlled, multicenter, parallel-group, flexible-dose study comparing citalopram (20–40 mg/day) to placebo in pediatric outpatients diagnosed with *major depressive disorder* (DSM-IV criteria). The study population will be equally stratified between children (ages 7 to 11) and adolescents (ages 12 to 17). A total of 160 patients will be randomized to double-blind treatment.

The study will consist 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 will be 9 weeks.

The study will involve a total of 7 clinic visits: Screening, Baseline, and at the end of Weeks 1, 2, 4, 6 and 8. The diagnosis of *major depressive disorder* (DSM-IV), must be confirmed at the Screening visit using the *Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (K-SADS-PL*, see Section 8.1). The primary efficacy evaluation *(Children's Depression Rating Scale-Revised)* will be conducted at each clinic visit beginning with the Screening visit. A blood sample for the measurement of steady-state citalopram concentrations in plasma will be taken at the end of Week 8 visit.

Patients who complete this study will be eligible to participate in a 24-week open-label extension study.

7. STUDY POPULATION

Patients aged 7 to 17 years inclusive and with a diagnosis of *major depressive disorder* who fulfill all of the inclusion criteria and none of the exclusion criteria listed below are eligible for enrollment. The nature and purpose of this study must be explained to both the patient and their guardian (parent or caregiver) and written informed consent must be obtained from the guardian prior to the initiation of any study-specific procedures.

7.1 Inclusion Criteria

1. Male or female outpatients between 7 and 17 years of age.
2. The patient must meet DSM-IV diagnostic criteria for *major depressive disorder*. The duration of the current *major depressive episode* must be at least four weeks at the Baseline visit.
3. Patients must have 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 ECG results must be normal at Screening, or if abnormal, must be deemed clinically insignificant by the Investigator and documented in the case report form as such.
5. Female patients of childbearing potential must have a negative serum β–HCG at Screening.
6. Prior to the conduct of any study-specific procedures, the patient must provide assent to participation and the parent or legal guardian must provide written informed consent.
7. Patients must be 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 who is capable of providing information about the patient's condition must agree to accompany the patient to all clinic visits.

7.2 *Exclusion Criteria*

1. Patients with any primary psychiatric diagnosis other than *major depressive disorder.*
2. Patients who meet 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 test 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 are pregnant or breast feeding.
9. Females of childbearing potential who are not practicing, or not willing to practice, a reliable method of birth control.
10. Patients with a medical condition that might interfere with the conduct of the study, confound interpretation of the study results, or endanger 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 is a history of such disease but the condition has been stable for more than 1 year and is judged by the Investigator not to interfere with the patient's participation in the study, the patient may be included, with the documented approval of the Medical Monitor.)

11. Patients with a history of seizure.
12. Patients who have been treated with any antidepressant or anxiolytic medication within 2 weeks of the Baseline visit (4 weeks for fluoxetine).
13. Patients who have been treated with any neuroleptic or stimulant (e.g., methylphenidate) *within 6 months prior to the Screening visit.*
14. Patients requiring concomitant treatment with any psychotropic drug (except zolpidem for sleep), or any drug with a psychotropic component (see Appendix II).
15. Patients requiring concomitant treatment with any prescription or over-the-counter medications that are classified as *not allowed* by this protocol (see Appendix II).
16. Patients who have been in a previous investigational study of *citalopram.*
17. Patients who have received treatment with *any* investigational drug within 30 days or 5 half lives (whichever is longer), prior to study entry.
18. Patients with a history of hypersensitivity reaction to *citalopram (Celexa)* or other SSRIs.
19. Patients who have previously failed to respond to an adequate trial of citalopram or to adequate trials of two other SSRIs.
20. Patients who have initiated psychotherapy or behavior therapy within 3 months prior to the Screening visit, or who plan to inititate or change such therapies during the course of the study.
21. Patients who are unable to swallow tablets.
22. Patients who are considered a suicide risk (active suicidal ideations), who have made a serious suicide attempt within the past year, or who have ever been hospitalized because of a suicide attempt.
23. Patients who in the Investigator's opinion might not be suitable for the study.

8. STUDY PROCEDURES

8.1 Diagnostic Assessment

Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (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 will be used in this study to establish that the patient meets DSM-IV criteria for major depressive disorder during the present episode, and to rule out other psychiatric diagnoses.

8.2 Efficacy Measures

The following instruments will be used to assess efficacy. To ensure the sensitivity and reliability of the assessments, the same Investigator (clinician) should assess a particular patient at each evaluation. *Efficacy ratings are not to be administered if the patient is not accompanied by the identified parent or caregiver.*

8.2.1 Primary Efficacy Measure

Children's Depression Rating Scale - Revised: 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 MDD (range is 17-113).

The CDRS-R will be administered at all clinic visits, including Screening, and will be administered separately to both the patient and the identified parent or caregiver.

8.2.2 Secondary Efficacy Measures

- *Clinical Global Impression– Severity* subscale*:* At Baseline, and at each visit after Baseline, global *severity* will be assessed on a scale of 1 to 7.
- *Clinical Global Impression– Improvement* subscale*:* Global *improvement* will be assessed at each clinic visit following the Baseline visit. Improvement will be 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".
- *Kiddie Schedule for Affective Disorders and Schizophrenia-Present (depression module).* The K-SADS-P depression module will be completed at Baseline and at study termination to evaluate response to treatment.
- *Children's Global Assessment Scale (CGAS):* The CGAS will be completed at Baseline, the end of Week 4 and at study termination to evaluate overall functioning.

8.3 Safety Assessments

8.3.1 Adverse Events

At each clinic visit (starting with Baseline), patients are to be queried regarding any adverse events (AE's) they may have experienced since their last visit (see Section 13).

8.3.2 Laboratory Determinations

Blood and urine specimens for laboratory determinations will be collected at the Screening visit and the final visit (end of Week 8 or upon early termination). Specimens will be submitted for analysis as per the instructions of the central laboratory. The following parameters will be measured:

Hematology: hemoglobin, hematocrit, RBC count, WBC count (with differential), platelet count.

Chemistry: alkaline phosphatase, albumin, BUN, calcium, cholesterol, chloride, creatinine, glucose, potassium, ALT (SGPT), AST (SGOT), sodium, total bilirubin, total protein, uric acid.

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

Urine Drug Screen: conducted at Screening only.

Thyroid function profile: TSH (Screening only).

Pregnancy test: Serum β-HCG will be measured at Screening in all female patients of childbearing potential.

8.3.3 Vital Signs

Vital signs, including body weight, systolic and diastolic blood pressure and radial pulse rate, will be obtained at every visit. Blood pressure and pulse determinations will be conducted after the patient has been seated for 5 minutes. *Height will be recorded at the Screening visit and at the end of Week 8 visit (or early termination).*

8.3.4 Physical Examination

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

8.3.5 Electrocardiogram

An electrocardiogram (ECG) will be done at Screening and at the end of Week 8 (or early termination) visit. The ECG will be a complete, standardized 12-lead recording. ECG's will be

evaluated by the Investigator or a qualified consultant and attached to the appropriate page in the case report form.

8.4 Clinical Findings at Termination

Any clinical findings in the final examination, or at premature discontinuation for any reason, including clinically significant laboratory abnormalities, must be followed until the condition returns to pretrial status or can be explained as being unrelated to study drug. A follow-up visit should be scheduled within 28 days of termination if necessary.

8.5 Schedule of Assessments

8.5.1 Screening visit (Visit 1)

- Review study with patient and guardian – obtain assent from patient and written informed consent from guardian.
- Obtain medical and psychiatric history.
- Conduct diagnostic interview (K-SADS-PL).
- Review concomitant medications.
- Perform physical examination (including ECG, height and vital signs).
- Obtain blood sample for laboratory determinations (and ß-HCG if applicable).
- Obtain urine sample for drug screen and laboratory determinations.
- Conduct CDRS-R
- Assess eligibility via review of inclusion/exclusion criteria.
- Dispense "Visit 1" medication for single-blind placebo lead-in period.

8.5.2 Baseline visit (Visit 2)

- Review inclusion/exclusion criteria
- Review study procedures with both patient and guardian.
- Check vital signs.
- Review concomitant medications.
- Review adverse events.
- Assess drug accountability for single-blind placebo period.
- Conduct primary efficacy evaluation (CDRS-R).

- Conduct secondary efficacy evaluations (CGI-*Severity,* K-SADS depression module and CGAS).
- Assign randomization number.
- Dispense "Visit 2" medication for the first week of double-blind treatment.

8.5.3 End of Week 1 visit (Visit 3)

- Check vital signs.
- Review concomitant medications.
- Review adverse events.
- Assess drug accountability.
- Conduct primary efficacy evaluation (CDRS-R).
- Conduct secondary efficacy evaluations (CGI-*Severity,* CGI-*Improvement*).
- Dispense "Visit 3" medication for the second week of double-blind treatment.

8.5.4 End of Week 2 visit (Visit 4)

- Check vital signs.
- Review concomitant medications.
- Review adverse events.
- Assess drug accountability.
- Conduct primary efficacy evaluation (CDRS-R)
- Conduct secondary efficacy evaluations (CGI-*Severity,* CGI-*Improvement*).
- Dispense "Visit 4" medication for Weeks 3 and 4 of double-blind treatment.

8.5.5 End of Week 4 visit (Visit 5)

- Check vital signs.
- Review concomitant medications.
- Review adverse events.
- Assess drug accountability.
- Conduct primary efficacy evaluation (CDRS-R)

- Conduct secondary efficacy evaluations (CGI-*Severity*, CGI-*Improvement* and CGAS).
- *Determine if dose increase is clinically warranted* (see Section 9.2).
- Dispense "Visit 5" medication for Weeks 5 and 6 of double-blind treatment.

8.5.6 End of Week 6 visit (Visit 6)

- Check vital signs.
- Review concomitant medications.
- Review adverse events.
- Assess drug accountability.
- Conduct primary efficacy evaluation (CDRS-R)
- Conduct secondary efficacy evaluations (CGI-*Severity*, CGI-*Improvement*).
- *Determine if dose increase or decrease is clinically warranted* (see Section 9.2).
- Discuss participation in the open-label extension study with patient and guardian.
- Dispense "Visit 6" medication for Weeks 7 and 8 of double-blind treatment.

8.5.7 End of Week 8 visit (Visit 7) – Study Termination (or early termination)

- Review concomitant medications.
- Review adverse events.
- Assess drug accountability.
- Perform physical examination (including ECG, height and vital signs).
- Obtain blood sample for laboratory *and* analytical determinations.
- Obtain urine sample for laboratory determinations.
- Conduct primary efficacy evaluation (CDRS-R)
- Conduct secondary efficacy evaluations (CGI-*Severity*, CGI-*Improvement*, CGAS and K-SADS-P (depression module).

9. STUDY DRUG

9.1 Study Medication

Citalopram (20 mg) and placebo medication will be supplied by Forest Laboratories as film-coated, white tablets of identical appearance. For the single-blind lead-in period, patients will be supplied with placebo tablets only. For the double-blind treatment period, identically appearing tablets will contain either 20mg of citalopram or placebo. Medication will be supplied in bottles containing either 10 tablets for the lead-in and the first four weeks of double-blind treatment, or 40 tablets for the remaining four weeks of the treatment period.

9.2 Dosing Regimen

Patients who meet all of the eligibility criteria at Screening will be dispensed one bottle containing 10 placebo tablets prior to departing from the clinic. Patients will be instructed to take one tablet each evening until they return one week later for the Baseline visit.

Patients who meet all of the eligibility criteria at the end of the single-blind lead-in period (Baseline visit) will be assigned a randomization number and dispensed the corresponding bottle of study medication for Week 1 of double-blind treatment. Patients will be instructed to take one tablet each evening, beginning on the day that the study medication is dispensed. (*Dosing may subsequently be switched to the morning if preferred.*) In accordance with their assigned treatment, patients will receive either one placebo tablet or one tablet of 20mg citalopram.

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

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

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

At the end of Week 4 and Week 6 visits, patients will be dispensed *one* bottle containing 40 tablets of either placebo or active (20mg citalopram) medication. Patients who are exhibiting a satisfactory therapeutic response by the Week 4 visit will continue to take one tablet of medication daily. *However, if at the Week 4 visit (or at anytime thereafter), the clinician feels that the therapeutic response is not satisfactory and the patient is not experiencing dose-limiting adverse events,, the dose may be increased and the patient should be instructed to take two tablets daily* (placebo or 40mg citalopram). All study medication must still be taken as a single daily dose.

The dose of medication may be decreased at any time because of adverse events. However, the daily dose for this study can never be less than one tablet or greater than two tablets.

9.3 Patient Numbering and Identification

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

9.4 Packaging

All study medication will be provided by Forest Laboratories Inc. (New York, NY). Medication will be supplied in bottles containing either 10 tablets or 40 tablets and labeled with the protocol number, visit number and instructions to take tablets as directed. Double-blind medication will also be labeled with a patient number. In addition, all labels will include storage and warning information. *Prior to dispensing the medication, the Investigator must write the patient's initials, the center number and the date on the label.*

9.5 Storage, Issue, and Return of Study Medication

Study medication must be kept in an appropriate, secure area (for example, a locked cabinet in a locked room). All drug supplies must be stored at controlled room temperature, 59°F - 86°F (15°C - 30°C), and protected from heat and moisture.

The Investigator will be responsible for recording the receipt and storage of all drugs supplied and for overseeing the dispensing of these supplies. In addition, all unused study medication must be returned, and unit counts must be performed whenever medication is returned. All study medication must be accounted for in the case report form and on the medication inventory sheet provided.

At the end of the study, all unused drug supplies and empty drug bottles must be returned to Forest at the following address:

Forest Laboratories, Inc.
500 Commack Road
Commack, NY 11725
Attn: Asst. Director, PR&D Logistics

9.6 Medication Compliance Checks

At each clinic visit after Screening, the patient must bring their medication bottle to the site to be inventoried.

9.7 Unblinding Procedures

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

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

The tear-off panel identifying the treatment should be opened only in the event that an emergency necessitates identification of the medication for the welfare of the patient. If the blind is broken for any reason, Forest Laboratories must be notified immediately.

Any patient for whom the blind has been broken will immediately be discontinued from the study and no further efficacy evaluations will be performed.

If at all possible, an attempt should be made to discuss the case with the study medical monitor *prior* to unblinding the medication.

10. CONCOMITANT MEDICATION

A medication history will be obtained from the patient at the time of Screening. All medication that the patient is taking at the time of the Screening visit must 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, must also be recorded in the CRF. APPENDIX II provides a list of drugs that are allowed and not-allowed as concomitant medications for this study. In addition, patients will be instructed to abstain from alcohol during this study.

11. ANALYTICAL SAMPLE COLLECTION

A blood sample for the measurement of citalopram steady-state concentrations in plasma will be collected at the end of Week 8 (or early termination) visit along with the blood samples for laboratory determinations. *If possible, the sample should be collected between 8-14 hours after the last dose of study medication was taken.* Blood samples will be collected in 10-ml Vacutainers and plasma will be harvested and stored as described in Appendix III.

12. STATISTICAL EVALUATION

12.1 Objectives

12.1.1 Primary objective

The primary objective is to compare the efficacy of citalopram (20-40mg/day) to placebo in children (7-11 years) and adolescents (12-17 years) with major depressive disorder. The primary endpoint is change from baseline in CDRS-R score at Week 8.

12.1.2 Secondary objectives

The secondary objectives are:

1. To further compare the efficacy of citalopram to placebo in depressed children and adolescent patients. The endpoints for the secondary objectives are the CGI-Improvement score, and change from baseline in CGI-Severity score, K-SADS-P (*depression module*) score and CGAS score at Week 8.
2. To evaluate the safety of 20- 40 mg/day citalopram in children and adolescents.

12.2 Patient Populations

12.2.1 Randomized population

The Randomized population will consist of all patients randomized into this study.

12.2.2 Safety population

The Safety population will consist of all randomized patients who receive at least one dose of double-blind study medication.

12.2.3 Intent-to-Treat population

The Intent-to-Treat (ITT) population will consist of all patients in the Safety population who complete at least one post-baseline efficacy evaluation of the primary efficacy variable.

12.3 Analysis of Demographics and Other Baseline Characteristics

Demographic parameters, and other baseline characteristics will be summarized by age group (children, adolescents) and treatment group. For each age group, imbalance between treatment groups will be tested using two-way ANOVA additive model with treatment and study center as the factors for continuous variables, and Cochran-Mantel-Haenszel (CMH) test controlling for study center for categorical variables.

12.4 Extent of Exposure

Extent of exposure to study medication will be presented in terms of treatment duration and mean daily dose.

12.5 Efficacy Analyses

All efficacy analyses will be based on the ITT population, i.e., patients who took at least one dose of study medication and had at least one post-baseline efficacy assessment of CDRS-R score. All tests will be two-sided, with 5% significance level for main effects, and 10% significance level for interaction terms.

Primary analyses will be performed using the *Last Observation Carried Forward* (LOCF) approach. In these analyses, the last observed value before the missing value will be carried forward to impute the missing value. If the missing value occurs at Week 1, the baseline value will be carried forward to Week 1 provided at least one subsequent post-baseline assessment is available. The *observed cases* (OC) approach will be used for supportive analyses, where only observed values will be used for analyses.

12.5.1 Primary Efficacy Parameters

Change from baseline in CDRS-R score at Week 8 will be used as the primary efficacy parameter. Descriptive statistics will be calculated by visit. Comparison between citalopram and placebo will be performed using three-way analysis of covariance (ANCOVA) with age group, treatment group and center as the three factors, and the baseline CDRS-R score as covariate.

12.5.2 Secondary Efficacy Parameter(s)

The secondary efficacy parameters are:

- CGI – Improvement subscale score.
- Change from baseline in CGI – Severity score.
- Change from baseline in K-SADS-P (*depression module*) score.
- Change from baseline in CGAS score.

For each parameter, descriptive statistics will be calculated by visit. Comparison between citalopram and placebo will be performed using the same approach as for the primary efficacy parameter. Two-way ANOVA will be used for CGI-I, since improvement relative to Baseline is inherent in the score.

12.6 Safety Analyses

The safety analyses will be performed using the safety population as defined in Section 12.2.2.

12.6.1 Adverse Events

For each age group, the number (percentage) of patients with treatment emergent adverse events (TEAE's) will be tabulated by body system, preferred term, and treatment group. Within a specific category, the patient is to be counted only once if the patient had more than one event reported. Listings will be provided for all patients with serious adverse events and all patients who have discontinued prematurely due to adverse experiences.

12.6.2 Laboratory Parameters

The number (percentage) of subjects with post-baseline *potentially clinically significant* (PCS) values of laboratory parameters will be tabulated by treatment group. For each laboratory parameter, summary statistics will be presented by age group and treatment group.

12.6.3 Vital Signs

For each age group, the number (percentage) of patients with post-baseline PCS values of vital signs will be tabulated by treatment group. Summary statistics will be presented for each parameter by age group, treatment group and visit.

12.6.4 ECG Parameters

The number (percentage) of subjects with post-baseline PCS values will be tabulated by age group and treatment group. For each parameter, summary statistics will also be presented by age group and treatment group.

12.7 Sample Size Considerations

The primary efficacy variable is the change from baseline in CDRS-R score at Week 8. Assuming an effect size (treatment group difference relative to pooled standard deviation) of 0.5, a sample size of 80 patients in each treatment group will provide at least 85% power at an alpha level of 0.05 (two-sided).

12.8 Computer Methods

Statistical analyses will be performed using SAS (version 6.12 or newer) under a UNIX operating system.

13. ADVERSE EVENTS

13.1 Definition of an Adverse Event

An adverse event (AE) is 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 include:

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

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

13.2 Definition of a Serious Adverse Event

The Investigator or other study personnel must immediately (within 24 hours) inform Forest Laboratories, Inc. of all serious adverse events that occur in study patients.
A serious adverse event is one that:

- Results in death.
- Is an immediate threat to life.
- Requires inpatient hospitalization, or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly or birth defect.

In addition to the above, important medical events that have not resulted in death, are not life-threatening, or do not require hospitalization may be considered serious adverse drug experiences when, based upon appropriate medical judgment, they are considered to jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Such medical events would be included under the following criterion:

- Is an intervention required to prevent permanent impairment/damage ?
    - Emergency room treatment or evaluation for signs and symptoms of potentially serious adverse events (e.g., unwitnessed loss of consciousness, allergic bronchospasm requiring intensive treatment

at home or in ER, blood dyscrasias or convulsions that do not result in hospitalization, anaphylactoid reactions, or the development of drug dependence or drug abuse). However, emergency room visits that can be defined as routine outpatient care (e.g., suture removal, treatment for a sprained ankle, earache, etc.) do not meet this criterion and do not require immediate notification.

- Symptomatic overdose that results in a serious outcome
- Intentional overdose/suicide attempt —with or without any sign or symptom—when considered to be a threat to life.
- Neoplasia (benign or malignant) if judged to be medically serious.

Although not a serious AE in itself, exposure to drug during pregnancy—even if no AE is produced in the mother—should be reported within 24 hours, and the pregnancy followed to outcome.

13.3 Definition of an Unexpected Adverse Event

An unexpected adverse event is any adverse drug experience, the specificity or severity of which is not consistent with adverse events described in the Investigator's Brochure or the Package Insert.

13.4 Reporting Adverse Events

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

All adverse events must be recorded on the appropriate AE reporting page of the patient's CRF. All adverse events must be reported, whether or not they are considered causally related to study medication. For every AE, the Investigator must provide an assessment of the severity, chronicity, causal relationship to study medication, and seriousness of the event; document all actions taken with regard to study medication; and detail any other treatment measures taken for the AE. The Investigator or other study personnel must immediately (within 24 hours) inform Forest Laboratories, Inc. of any AE considered serious or otherwise significant as described in Section 13.2 above. Reporting should not be delayed pending resolution or outcome of an event. If an outcome for an adverse event is not available at the time of the initial report, patient follow-up should proceed until such time as an outcome is known.

Notification may be via telephone or pager, and facsimile transmission of a written report. The following Forest Medical Monitor or Clinical Trial Manager is to be contacted:

Medical Monitor: *Paul J. Tiseo, Ph.D.*
Associate Medical Director, CNS Development
212.224.6929 (work)
212.717.4120 (home)

Clinical Trial Manager: *Joan E. Barton, MS, MPH*
212.224.6791
Fax: (212) 750-9152

Forest Laboratories' Medical Emergency Pager No. (917) 313-4198

In the event that none of the above are available, contact:
John Sullivan
Director, Drug Safety Surveillance
Phone: (201) 386-2006
Pager: (917) 205-2961

13.5 Causality Assessment of Adverse Events

For all AEs, the Investigator will provide an assessment of causal relationship to study medication. The causality assessment must be recorded on the appropriate AE reporting page of the patient's CRF. Causal relationship will be classified according to the following criteria:

Related	Reasonable temporal relation to study medication administration, AND cannot be reasonably explained by other factors (such as the patient's clinical state, concomitant therapy, and/or other interventions), or application/injection site reaction.
Possibly Related	Relationship to study medication cannot be ruled out.
Not Related	Data are available to identify a clear alternative cause for the reaction (e.g., positive test for viral antigen in a case of suspected drug-induced hepatitis, hemorrhage due to mechanical injury).

13.6 Assessment of Severity

The Investigator will provide an assessment of the severity of each adverse reaction by recording a severity rating on the appropriate AE reporting page of the patient's CRF. (Severity, which is a description of the intensity of manifestation of the AE, is distinct from seriousness, which

implies a patient outcome or a required treatment measure associated with a threat to life or functionality.) Severity will be assessed according to the following scale:

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

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

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

14. PREMATURE DISCONTINUATION

A discontinuation occurs when an enrolled patient ceases participation in the study, regardless of circumstances, prior to the Week 8 visit. All patients prematurely discontinuing from the trial, regardless of cause, must be seen for a final evaluation. In addition, patients who discontinue after beginning double-blind treatment will not be replaced.

The *final evaluation* is defined as the completion of all the evaluations scheduled for the final visit (*end of Week 8*). Patients refusing to come in for a final visit must be requested in writing (registered letter) to return for a visit and to return all study medication. A copy of the letter must be kept by the Investigator together with the source documentation.

Drug treatment may be terminated for the following reasons:

- An adverse event.
- Insufficient therapeutic response.
- A protocol violation, including lack of compliance.
- Patient withdrawal of consent
- The patient is "lost to follow-up."
- Other reasons, such as administrative reasons.

15. DATA RECORDING AND DOCUMENTATION

All data collected in the context of this study will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (copies of CRFs and regulatory documents) will be retained at the study site, along with adequate source documentation according to FDA

IND/NDA requirements. All study records must be available for inspection by Forest Laboratories or their authorized representatives and the FDA.

16. MONITORING

A representative of Forest Laboratories, Inc. will meet with the Investigator and his/her staff prior to the entrance of the first patient to review the procedures to be followed in conducting the study and recording the findings in the CRFs. After the enrollment of the first patient, the Investigator will permit the Forest representative, a Clinical Research Associate (CRA), to periodically monitor the progress of the trial on site. The Investigator will make available to the CRA CRFs as well as source documents, the patient's medical records, and signed consent forms. The Investigator will review the CRFs, provide missing or corrected data, and sign the appropriate CRF page(s). The CRA will arrange for the return of CRFs to Forest Laboratories, Inc. A copy of the CRF will be retained by the Investigator.

17. AMENDMENTS TO THIS PROTOCOL

Any amendment to this protocol will be provided to the Investigator in writing by Forest Laboratories. No changes may be implemented before the amended protocol has been approved by the Institutional Review Board (IRB) and the signature page, signed by the Investigator, has been received by Forest Laboratories, Inc. Deviations are permitted only if absolutely necessary for the safety or clinical management of the patient, and must be immediately reported to Forest Laboratories, Inc.

18. ETHICAL CONSIDERATIONS

18.1 Patient Confidentiality

All patient records will be identified only by initials and code number. Patients' names are not to be transmitted to Forest Laboratories, Inc. The Investigator will keep a Master Patient List on which the identification number and full name of each patient is kept.

18.2 Institutional Review Board (IRB)

This study will be carried out in full compliance with FDA guidelines for Good Clinical Practices (GCPs). Approval by the IRB prior to the start of the study will be the responsibility of the Investigator. A copy of the approval letter must be supplied to Forest Laboratories, Inc. along with a roster of IRB members or DHHS General Assurance number. During the course of the study, the Investigator shall make timely and accurate reports to the IRB on the progress of the trial, at intervals not exceeding 1 year, and notify the IRB of serious adverse events or other significant safety findings.

18.3 Patient Informed Consent

The study will be explained to each prospective patient and their parent or legal guardian before the patient participates in any study-related procedures. The patient must demonstrate assent to the procedures and written informed consent must be obtained from the parent or legal guardian. Copies of the informed consent should be given to the patient and the signed originals placed in the Investigator's study files. Elements of informed consent conforming to the Declaration of Helsinki are provided in *Appendix I.*

19. INVESTIGATOR OBLIGATIONS

19.1 Documentation

The Investigator must provide the following to Forest Laboratories, Inc. prior to the start of the study:

- A completed and signed Form FDA 1572. If during the course of the trial any changes are made that are not reflected on the 1572, a new 1572 form must be completed and returned to Forest Laboratories, Inc. for submission to the FDA.
- Curriculum vitae for the Principal Investigator and all Sub-Investigators listed on Form 1572, including a copy of each physician's license.
- A copy of the original approval for conducting the trial from the IRB. Renewals must be submitted at yearly intervals, if the study is ongoing. All subsequent modifications must be submitted and approved by the IRB as described in Section 17 above.
- A copy of the IRB-approved informed consent form.
- A list of IRB members or DHHS General Assurance Number.
- The Investigator's Statement page of this protocol signed and dated by the Investigator.
- Laboratory Certifications

19.2 Performance

The Investigator must demonstrate reasonable efforts to obtain qualified patients for the study and to conduct the evaluations and examinations described in this protocol to the best of his/her abilities.

19.3 Use of Investigational Materials

The Investigator acknowledges that the drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Principal Investigator or Sub-Investigators listed on Form FDA 1572. No study medication will be sent to the site until all regulatory documents, including IRB approval, are received at Forest

Laboratories. Study medication must be stored in a safe and secure location. At study initiation, a representative from Forest Laboratories, Inc. will inventory the drug at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies on the forms provided by Forest Laboratories. This is separate from the dispensing records maintained for each patient in the CRFs. All unused medications must be returned to Forest Laboratories, Inc. It is the Investigator's responsibility to ensure that patients return their medication to the site.

19.4 Case Report Forms

All data relating to the trial will be recorded on CRFs to be provided by Forest Laboratories, Inc. The CRFs are to be completed at the time of the patient's visit, with the exception of results of tests performed outside the Investigator's office. The data entered in the CRFs must be legible, complete, and recorded using black ink. All physical examinations must be performed by a physician and the principal Investigator or documented sub-Investigator must see the patient at every visit. The Investigator is responsible for verifying that all data entries in the CRFs are accurate and correct as documented by his/her signature on the appropriate page(s) of the CRF.

19.5 Retention and Review of Records

The Investigator must maintain the documentation relating to this study. If Forest Laboratories, Inc. or the Food and Drug Administration (FDA) wish to review any documentation relating to the study, the Investigator must permit access to such records.

Federal regulations require that the Investigator retain a copy of all records (e.g., informed consents, laboratory reports, source documents, study medication dispensing records) that support CRFs of this study for whichever of the following is shortest:

- A period of 2 years following the date of approval by the FDA of the study medication for the purposes that were the subject of the investigation; or,
- A period of 5 years following the date on which the results of the investigation are submitted to the FDA in support of, or as part of, an application for a research or marketing permit for the study medication for the purposes that were the subject of the investigation.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by Forest Laboratories, Inc. that the entire clinical investigation (not merely the Investigator's portion) is completed, terminated, or discontinued; or, 2 years following withdrawal of the IND or NDA.

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Forest Laboratories, Inc. must be notified in writing of the name and address of the new custodian.

20. REPORTING AND PUBLICATION

All data generated in this study are the property of Forest Laboratories, Inc. An integrated clinical and statistical report will be prepared at the completion of the trial.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and Forest Laboratories, Inc.

21. REFERENCES

1. Hyttel J. (1994). Pharmacological characterization of selective serotonin reuptake inhibitors (SSRIs), *Int. Clin. Psychopharmacology* 9:19-26.

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11. Strober M., Freeman R., Rigali J. (1990). The Pharmacotherapy of Depressive Illness in Adolescence: I. An Open Label Trial of Imipramine. *Psychopharmacol. Bull.* 26:80-84.

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Arch. Gen Psychiatry 54, 1031-1037.

22. INVESTIGATOR'S STATEMENT

I agree to conduct the trial in accordance with the protocol, and with all applicable government regulations and Good Clinical Practice Guidance.

..../ / .....
Investigator's Signature Date

.....
Typed Name of Investigator

APPENDIX I:
Elements of Informed Consent

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained from all patients participating in clinical research studies or the patient's legally authorized representative. This consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and identification of any procedures that are experimental; and the expected duration of the patient's participation.
- A description of any reasonably foreseeable risks or discomforts to the patient.
- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount he/she will receive and the schedule of payment (to assure neither coercion nor undue influence).
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient.
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA, Forest Laboratories, Inc., the Institutional Review Board, or an authorized contract research organization may inspect the records.
- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of, or where further information may be obtained.
- An explanation of whom to contact, including the appropriate telephone number, for answers to pertinent questions about the research and research patient's rights, and whom to contact in the event of a research-related injury to the patient. (NOTE: In some cases it may be necessary to identify some person other than the Investigator as the contact. The guidance of the IRB may be required.)
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.
- A statement of consent, e.g., "I agree to participate...."
- A place for the research patient's signature and date of signature.
- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus, if the patient is or may become pregnant) that are currently unforeseeable.

- Anticipated circumstances under which the patient's participation may be terminated by the Investigator without regard to the patient's consent.
- Any additional costs to the patient that may result from participation in the research.
- The consequences of a patient's decision to withdraw from the research and procedures for orderly termination of participation by the patient.
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient.
- The approximate number of patients involved in the study.

A copy of the consent form must be given to the patient.

APPENDIX II:
Concomitant Medications (pg. 1 of 4)

Drugs Allowed (Y) and Not Allowed (N) as Concomitant medications in this study.

Drug Class	Usage (p.r.n.)	Chronic Use	Restrictions
Analgesics	(Y)	(Y)	Non-narcotic analgesics only
Anesthetics			
General	(N)	(N)	
Local	(Y)	(N)	
Anorexics	(N)	(N)	
Antacids	(Y)	(Y)	
Antianginal agents	(N)	(N)	
Antiarrhythmics	(N)	(N)	
Antiasthma agents	(Y)	(Y)	
Antibiotics	(Y)	Call	
Anticoagulants	(N)	(N)	
Anticonvulsants	(N)	(N)	
Antidepressants	(N)	(N)	
Antidiarrheal preparations	(Y)	(N)	Only Imodium (loperamide), Pepto-Bismol, and kaolin preparations are allowed.
Antifungal agents			
Systemic	(N)	(N)	
Topical	(Y)	(Y)	

APPENDIX II:
Concomitant Medications (pg 2 of 4)

Drugs Allowed (Y) and Not Allowed (N) as Concomitant medications in this study.

Drug Class	Usage (p.r.n.)	Usage Chronic Use	Restrictions
Antihistamines	(Y)	Call	Only Allegra (fexofenadne), Claritin (loratadine) and Zyrtec (cetrizine) are allowed. See cough and cold preps for combination products.
Antihypertensives	(N)	(N)	
Anti-inflammatory drugs	(Y)	(Y)	Indocin (indomethacin) and systemic corticosteroids are not allowed.
Anti-nauseants	(Y)	(N)	Only phosphoric acid preparations (Emetrol, Emecheck), Pepto-Bismol and cola syrup are allowed.
Anti-neoplastics	(N)	(N)	
Antipsychotics	(N)	(N)	
Antiviral agents	(Y)	(Y)[b]	Only Zovirax (acyclovir) is allowed.
Anxiolytics	(N)	(N)	
Cough/Cold preparations	(Y)	Call	Decongestants containing narcotics are not permitted. Use of preparations with pseudoephedrine or phenylpropanolamine are not permitted (see antihistamines)

APPENDIX II:
Concomitant Medications (pg 3 of 4)

Drugs Allowed (Y) and Not Allowed (N) as Concomitant medications in this study.

Drug Class	Usage (p.r.n.)	Chronic Use	Restrictions
Diuretics	(Y)	(N)	The use of diuretics is restricted to episodic use in the Tx of premenstrual symptoms.
H_2 Blockers	(Y)	(Y)[b]	Tagamet (cimetidine) is **not allowed**
Hormones	(N)	(Y)	Only oral contraceptives are allowed.
Hormone suppresants	(N)	(N)	
Hypoglycemic agents	(N)	(Y)[c]	Only oral hypoglycemic agents are allowed.
Hypolipidemics	(N)	(N)	
Insulin	(N)	(N)	
Laxatives	(Y)	(Y)[a]	Only fiber-based products and Colace (docusate sodium) are allowed.
Muscle relaxants	(N)	(N)	
Psychotropic drugs not otherwise specified (including herbal products)	(N)	(N)	
Sedatives/hypnotics	(Y)	(N)	Only zolpidem (no more than 3 times per week), at a maximum dose of 10 mg/day, is permitted for sleep.

APPENDIX II:
Concomitant Medications (pg 4 of 4)

Drugs Allowed (Y) and Not Allowed (N) as Concomitant medications in this study.

Drug Class	Usage (p.r.n.)	Chronic Use	Restrictions
Steroids			
Systemic	(N)	(N)	
Topical	(Y)	(Y)	
Inhalant	(Y)	(Y)	
Vaccines	(Y)	N/A	

[a] If being taken before admission to the study.
[b] If being taken for at least 3 months before study and dose is stabilized.
[c] If being taken for at least 6 months before study and dose is stabilized.

APPENDIX III
Handling and Storage of Blood Samples

PLASMA PREPARATION FOR DRUG CONCENTRATIONS

A blood sample will be collected for the determination of plasma concentrations of the enantiomers of citalopram and their respective metabolites at the end of Week 8 visit or upon early termination. This sample will be collected in a pre-chilled 10-ml lavender top Vacutainer® tube containing EDTA. The actual clock time of the blood draw will be recorded in the case report form, along with the date and time of the previous dose of study medication.

Blood samples will be separated by refrigerated centrifuge at 4° C at 1500 G for 5 minutes. Following centrifugation, a ***minimum*** of 2 ml of plasma will be transferred into a polypropylene tube and frozen immediately. The sample will be stored upright at -70° C until it is shipped. Both the Vacutainers® and the polypropylene storage tubes will be labeled with labels provided by the central laboratory.

SHIPMENT INSTRUCTIONS

The analytical sample will be shipped according to the instructions provided by the central laboratory.

- The sample should be placed into a styrofoam box that contains the appropriate amount of dry ice. Cartons and labels for shipping will be provided.
- Attach to the lid of the box an inventory of the sample(s) contained inside including the protocol number, your center number, the patient number and the sample tracking number.
- On the day of shipment, a copy of the inventory of the sample(s) contained inside the box should be faxed to:

  Joan Barton, MPH
  Clinical Trial Manager
  Forest Laboratories Inc.

  Fax number: 212.750.9152
  Telephone: 212.224.6791