# REVIEW AND EVALUATION OF CLINCIAL DATA

**NDA 20-822 (b) (4) 016**

**Sponsor: Forest Labs**

**Drug: Celexa. (citalopram hydrocloride)**

**Material Submitted: Pediatric Supplement (b) (4) 016**

**Date Submitted: 4/18/02**

**Date Received: 4/19/02**

**Medical Reviewer: Earl D. Hearst, MD**

## Executive Summary

### *I. Recommendations*

#### A. Recommendation (b) (4)

(b) (4)

#### B. Recommendation on Phase 4 Studies and/or Risk Management Steps

In our 7/12/02 memo we asked to the sponsor to submit open-label 24 week safety data from these studies at a later date.

## *II. Summary of Clinical Findings*

### A. Brief Overview of Clinical Program

Two pharmacokinetic (CIT-PK-07 and CIT-PK-13) and two clinical studies (94 404 and CIT-MD-18) were submitted.

. CIT -PK-07 "An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Patients with Depression."

. CIT -PK-13 "An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Patients with Depression."

. 94 404 "A Double-blind Study Comparing Citalopram Tablets and Placebo in the Treatment of Major Depression in Adolescents."

. CIT-MD-18 "A Randomized Double-Blind, Placebo-controlled Evaluation of the Safety and Efficacy of Citalopram in Children and Adolescents."

### B. Efficacy

Only one of the two clinical studies can be considered positive.

## . CIT-MD-18

On the primary efficacy parameter, the change from baseline in CDRS-R at Week 8, citalopram produced significantly greater improvement than placebo.

| **Change from Baseline to Week 8 in CDRS-R [Mean ± SEM]** | | | |
|---|---|---|---|
| | *Placebo (N=85)* | *Citalopram (N=89)* | *p-value* |
| Mean ± SEM | -16.5 ± 1.6 | -21.7 ± 1.6 | 0.038 |

The citalopram group exhibited significantly greater improvement than the placebo group beginning at Week 1 and at all subsequent clinic visits. Analysis of the response rate on the CDRS-R also revealed a significantly higher percentage of responders (CDRS-R ≤ 28 at study endpoint) in the citalopram group (36.0%) as compared to the placebo group (23.5%) (p=0.041).

## . 94 404

In this 12-week study, a therapeutic effect of citalopram in the treatment of adolescent depression as compared to placebo could not be found. The patients showed improvement on the efficacy scales as a function of time, but the placebo response was high and not different from that of citalopram.

### C. Safety

There are no significant safety issues in this population. See studies below.

## CIT-MD-18

No deaths occurred during the conduct of the study. The rate of discontinuation for adverse events was 5.6% in the citalopram group and 5.9% in the placebo group. There was one serious adverse event, in a placebo treated patient, and one clinically significant ECG abnormality, also in a placebo treated patient.

## 94 404

No deaths occurred during the study.

Withdrawals due to AEs occurred for 9% of the patients and were similarly distributed among treatment groups.

SAEs were reported by 16 patients in the placebo group and by 18 patients in the citalopram group. The majority of the patients with SAEs reported hospitalizations due to psychiatric disorders (9 patients in the placebo group and 14 patients in the citalopram group). In the placebo group, the other SAEs were surgical interventions (3 patients), epileptic fit, head trauma, medication error, and hospitalization for social reasons.
In the citalopram group, the other SAEs were dyspnea, non-suicidal overdose, hospitalization for social reasons, and abortion.

## CIT -PK-07

There were no deaths or serious adverse events reported. No patients discontinued from the study due to an adverse event.

There were no apparent clinically relevant differences in adverse event type or frequency between the adult and pediatric patients.

**CIT -PK-13**

There were no deaths or serious adverse events reported.
No patients discontinued from the study due to an adverse event.
There were no apparent clinically relevant differences in adverse event type or frequency between the adult and pediatric patients.

## D. Dosing

**CIT-MD-18**

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. The concentration of citalopram was approximately 13% higher in the children as compared to the adolescents.

94404

This was a multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled, flexible-dose study. At screening, patients were randomly assigned to 12 weeks of double-blind treatment with either citalopram 10mg daily or placebo. Based on the investigator’s clinical evaluation, there was a possibility of a 10mg dose increase for patients in the citalopram group at the end of Week 1 (to a maximum of 20mg), Week 2 (to a maximum of 30mg), Week 5 (to a maximum of 40mg), or Week 9 (to a maximum of 40mg). The mean citalopram serum concentrations at Week 12 were 130, 217, and 288nmol / L after treatment with 20, 30, or 40mg, respectively.

### E. Special Populations

94404

No consistent pattern in serum levels in males as compared to females was observed.

**CIT-MD-18**

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=-0.059; p=0.650) or escitalopram concentration (r=0.048; p=0.714). Body weight also appeared to be uncorrelated with either citalopram concentration (r=-0.218; p=0.089) or escitalopram concentration (r=-0.119; p=0.357). Improvement on the CDRS-R also showed no significant relationship to plasma levels of either citalopram (r=0.123; p=0.341) or its active enantiomer escitalopram (r=0.104; p=0.422).

### F. Exclusivity

Exclusivity has been granted based on the completion of these studies.

## CINICAL REVIEW:

### I. Introduction and Background

Forest Labs submitted this NDA supplement after receiving a written request to conduct pediatric studies for Celexa. (b) (4)

Reference is made to FDA's Written Request for pediatric information dated April 28, 1999. Reference is also made to Forest's correspondence to IND (b) (4) dated 5/17/99, -9/24/99, and 2/17/00; and FDA's responses dated 6/30/99 and 12/10/99, respectively. In addition, refer to Forest's proposal dated 3/20/00 and a telephone contact between Forest and FDA on 4/17/00, in which an additional protocol was accepted and subsequently submitted on 8/14/00.

## II. Clinical Data Sources

Two pharmacokinetic (CIT-PK-07 and CIT-PK-13) and two clinical studies (94 404 and CIT-MD-18) were submitted.

. CIT -PK-07 "An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Patients with Depression."

. CIT -PK-13 "An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Patients with Depression."

. 94 404 "A Double-blind Study Comparing Citalopram Tablets and Placebo in the Treatment of Major Depression in Adolescents."

. CIT-MD-18 "A Randomized Double-Blind, Placebo-controlled Evaluation of the Safety and Efficacy of Citalopram in Children and Adolescents."

## III. Clinical Review Methods

### A. Materials Consulted in Review

The study reports and raw data were reviewed. 54 paper volumes were submitted along with data sets in the EDR. Electronic study reports were also submitted.

### B. Evaluation of Financial Disclosure

Study 94404 in this application was sponsored by H. Lundbeck. H. Lundbeck has done due diligence to try and obtain financial disclosure for investigators for study 94404. The legal department has researched through the archives and was unable to find anything as the study was initiated prior to the financial disclosure regulation. There were two investigators in study (b) (6) who did have financial arrangements that required disclosure. A description of each investigator's relevant financial arrangements and a Form 3455 is provided for each investigator.

Although some investigators participating in study (b) (6) had disclosable financial arrangements, the sponsor feels the potential of these financial arrangements to bias the study is minimized by the following elements of the design and conduct of Study (b) (6) The study was:

(b) (6)

## IV. Review of Studies

I will review the safety sections of the two pharmacokinetic studies.

. CIT -PK-07 "An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Patients with Depression."

. CIT -PK-13 "An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Patients with Depression."

I will review the two clinical studies below in detail.

. 94 404 "A Double-blind Study Comparing Citalopram Tablets and Placebo in the Treatment of Major Depression in Adolescents."

. CIT-MD-18 "A Randomized Double-Blind, Placebo-controlled Evaluation of the Safety and Efficacy of Citalopram in Children and Adolescents."

**CIT-MD-18**

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). 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, for a total study duration of 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 of double-blind treatment. The diagnosis of MDD was based on the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (K-SADS-PL) administered at screening. The primary efficacy evaluation (Children's Depression Rating Scale-Revised) was conducted at each clinic visit. Patients who completed the study were eligible to participate in a separate 24-week open-label extension study.

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.

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 tablets.

Dosage groups: Citalopram 20 mg/day or citalopram 40 mg/day; placebo.

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 1. Dosing Regimen**

| | | ***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 | 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 |

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 (CGI-S);
Clinical Global Impression – Improvement (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. Comparisons 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 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 effiacacy parameters, using both the LOCF and observed cases (OC) approach.

Patient Disposition:
A total of 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. Thus, the safety population and the efficacy population were identical (N=174). 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:
Demographic characteristics were similar between the treatment groups. In the placebo group, 38 patients were 7-11 years of age and 47 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. The majority of subjects in both treatment groups were female (53% for citalopram and 54% for placebo) and Caucasian (81% and 73%, respectively).

Pharmacokinetics:

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=-0.059; p=0.650) or escitalopram concentration (r=0.048; p=0.714). Body weight also appeared to be uncorrelated with either citalopram concentration (r=-0.218; p=0.089) or escitalopram concentration (r=-0.119; p=0.357). Improvement on the CDRS-R also showed no significant relationship to

plasma levels of either citalopram (r=0.123; p=0.341) or its active enantiomer escitalopram (r=0.104; p=0.422).

Efficacy results:
On the primary efficacy parameter, the change from baseline in CDRS-R at Week 8, citalopram produced significantly greater improvement than placebo.

| **LOCF Change from Baseline to Week 8 in CDRS-R [Mean ± SEM]** | | | |
|---|---|---|---|
| | *Placebo (N=85)* | *Citalopram (N=89)* | *p-value* |
| Mean ± SEM | -16.5 ± 1.6 | -21.7 ± 1.6 | 0.038 |

The citalopram group exhibited significantly greater improvement than the placebo group beginning at Week 1 and at all subsequent clinic visits. Analysis of the response rate on the CDRS-R also revealed a significantly higher percentage of responders (CDRS-R ≤ 28 at study endpoint) in the citalopram group (36.0%) as compared to the placebo group (23.5%) (p=0.041).

Because of a drug packaging error, the citalopram or placebo tablets initially dispensed to 9 patients at 3 study centers were distinguishable in color, although otherwise blinded. The sponsor presents the results from the LOCF analysis for the change from baseline to Week 8 excluding data from the 9 patients for whom the study blind was potentially compromised. The results from the Week 8 LOCF analysis comparing the mean change from baseline in CDRS-R in the citalopram and placebo groups was affected by the exclusion of those patients; the LSM difference decreased from 4.6 to 4.3 and the p-value increased from 0.038 to 0.052.

Significant differences (p<0.05), indicative of greater improvement in citalopram patients than placebo patients, were also observed on the CGI-I, CGI-S, and CGAS. Statistically significant effects were not found as consistently across study timepoints for the secondary efficacy parameters as for the primary efficacy parameter, but numerically greater improvement in the citalopram group was observed on every efficacy parameter at every clinic visit in both the LOCF and OC analyses.

**Safety results:**

No deaths occurred during the conduct of the study. The rate of discontinuation for adverse events was 5.6% in the citalopram group and 5.9% in the placebo group. There was one serious adverse event, in a placebo treated patient, and one clinically significant ECG abnormality, also in a placebo treated patient.

Patient 137, a 10-year-old male who had been discontinued from double-blind placebo because of the adverse event of personality disorder, showed serious impulsive behavior 24 days after discontinuation. The event was considered by the investigator to be moderate in severity and not related to study drug treatment. The impulsive behavior resolved spontaneously after seven days.

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 2. List of Patients who Discontinued due to Adverse Events**

| *Treatment Group/ Patient Number* | *Age (yrs)* | *Sex* | *AE Start Day** | *AE (Preferred Term)* |
|---|---|---|---|---|
| PLACEBO | | | | |
| 137 | 10 | Male | 31 | Personality Disorder |
| 507 | 13 | Female | 30 | Rash |
| 519 | 12 | Female | 41 | Suicidal Tendency |
| 550 | 13 | Male | 29 | Depression Aggravated |
| 574 | 15 | Female | 5 | Depression Aggravated |
| CITALOPRAM | | | | |

**Panel 2. List of Patients who Discontinued due to Adverse Events**

| *Treatment Group/ Patient Number* | *Age (yrs)* | *Sex* | *AE Start Day** | *AE (Preferred Term)* |
|---|---|---|---|---|
| 144 | 10 | Male | 47 | Hypomania |
| | | | 53 | Headache |
| | | | 53 | Abdominal Pain |
| 193 | 9 | Male | 36 | Agitation |
| 229 | 7 | Male | 15 | Agitation |
| | | | 15 | Concentration Impaired |
| 534 | 16 | Female | 24 | Akathisia |
| 561 | 16 | Female | 8 | Fatigue |
| | | | 8 | Appetite Decreased |
| | | | 8 | Weight Decreased |

* AE Start Day = AE Start Date – Date of First Dose +1.
Cross-reference: Table 7.3.

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 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), influenza-like symptoms (6.7% citalopram, 0% placebo), fatigue (5.6% citalopram, 1.2% placebo), and diarrhea (5.6% citalopram, 1.2% 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).

There were few cases of PCS values for blood pressure or pulse rate, and none of them continued to meet PCS criteria at the final visit. 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 a PCS increase in diastolic blood pressure. One (1.1%) adolescent in the citalopram group and 2 (2.4%) adolescents in the placebo group had PCS 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 in the citalopram group had a PCS decrease in pulse rate. The mean change in pulse rate from baseline to endpoint was an increase of 1.4 bpm for both treatment groups.

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.

**Weight**

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 mean change in body weight for patients in the citalopram group at endpoint; the mean change in the placebo group was an increase of 1.4 lb.

**Vital Signs**

One child in the placebo group and 2 children in the citalopram group had post-baseline 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 post-baseline diastolic blood pressure readings between 40 and 50 mmHg that met the adolescent PCS criteria. One child in the citalopram group exhibited a weight increase ≥7% and two children in the citalopram group exhibited weight decreases ≥7%.

## laboratory values

Four patients in the citalopram group and 2 patients in the placebo group had PCS clinical laboratory values. One adolescent patient receiving citalopram exhibited elevations of ALT and AST to 117 IU/L and 197 IU/L, respectively. These values had returned to normal after 13 days of continued citalopram treatment in the extension study. The mean change from screening to endpoint in ALT was -1.1 IU/L in the placebo group and 0.6 IU/L in the citalopram group; the mean change in AST was -0.4 IU/L in the placebo group and 1.6 IU/L in the citalopram group. 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.

### EKG

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 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. Only one patient had a clinically significant ECG abnormality, a child (Patient 203) treated with placebo who had a normal ECG at screening (PR=172 msec, QT=388 msec, and QTc=445 msec) and an ECG judged by the investigator as abnormal clinically significant at the end of Week 8 visit (PR=144 msec, QT=412 msec, QTc=467 msec). An ECG recorded one day later was judged abnormal not clinically significant (PR=118 msec, QT=428 msec, QTc=488 msec).

## Safety Summary

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. 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.

## CONCLUSION

I view this study as positive without significant safety issues.

## 94404 A double-blind study comparing citalopram tablets (Lu 10-171, 10-40 mg per day) and placebo in the treatment of major depression in adolescents

This was a multinational, multicentre, randomised, double-blind, parallel-group, placebo-controlled, flexible-dose study.

Study Centres
31 recruiting centres in 7 countries: 3 in Denmark, 2 in Estonia, 12 in Finland, 2 in Germany, 3 in Norway, 7 in Sweden, and 2 in Switzerland.

Objectives
• Primary objective – to study the efficacy and tolerability of citalopram compared to placebo in adolescent patients suffering from major depression
• Secondary objective – to investigate the Expressed Emotions (EE)

Methodology
• Multicentre, randomised, double-blind, parallel-group, placebo-controlled, flexible-dose study in adolescents with major depression
• At screening, patients were randomly assigned to 12 weeks of double-blind treatment with either citalopram 10mg daily or placebo. Based on the investigator's clinical evaluation, there was a possibility of a 10mg dose increase for patients in the citalopram group at the end of Week 1 (to a maximum of 20mg), Week 2 (to a maximum of 30mg), Week 5 (to a maximum of 40mg), or Week 9 (to a maximum of 40mg).

Diagnosis and Main Inclusion Criteria
Inpatients or outpatients who fulfilled the criteria for major depression according to DSM-IV, who had a Beck's Depression Inventory (BDI) score $\geq$21 (girls) or $\geq$16 (boys) and a Global Assessment of Functioning (GAF)

score  60 for any of the four items assessed, who were 13-18 years of age (extremes included), and whose puberty had commenced (Tanner Stage III). The duration of the current depressive episode was at least 4 weeks and up to one year.

Investigational Product, Dose and Mode of Administration, Batch Number- -Citalopram (Lu 10-171) – 10, 20, 30, or 40mg once daily; tablets, orally

Duration of Treatment
12 weeks of double-blind treatment

Criteria for Evaluation – Serum Concentrations/ Pharmacodynamics-
-Serum concentrations of citalopram and it’s metabolites, demethylcitalopram (DCT) and didemethylcitalopram (DDCT); correlation between serum concentrations and response on primary efficacy variable

Criteria for Evaluation – Efficacy
• Primary efficacy endpoint
- change from baseline in the Schedule for Affective Disorders and Schizophrenia for School Aged Children (Kiddie-SADS-P) total score over time
• Secondary efficacy endpoints
- change from baseline to each visit and to final assessment in Kiddie-SADS-P total score
- response on the Kiddie-SADS-P scale (items “depression” and “anhedonia” score $\leq$2) at each visit and at final assessment
- change from baseline in MADRS total score over time
- change from baseline to each visit and to final assessment in MADRS total score
- MADRS remission (total score $\leq$12) at each visit and at final assessment
- MADRS response (at least a 50% reduction of the baseline MADRS total score) at each visit and at final assessment
analyses of scores on the Kiddie-SADS-P single items, BDI, GAF, and Life Event Scales

Criteria for Evaluation – Safety
Adverse events (AEs), Utvalg for Kliniske Undersøgelser (UKU) symptom checklist, clinical laboratory tests, electrocardiograms (ECGs), weight, vital signs, and physical examination

Number of Patients Planned and Analysed
• A total of 220 patients were planned (110 patients in each treatment arm).
• Patient disposition is tabulated below.

| | Placebo N (%) | Citalopram N (%) | All N (%) |
|---|---|---|---|
| Patients randomised | 120 | 124 | 244 |
| Patients treated | 112 | 121 | 233 |
| Patients completed | 74 (66%) | 79 (65%) | 153 (66%) |
| Patients withdrawn from APTS | 38 (34%) | 42 (35%) | 80 (34%) |
| **Primary reason for withdrawal:** | | | |
| Adverse Event(s) | 9 (8%) | 13 (11%) | 22 (9%) |
| Lack of efficacy | 18 (16%) | 11 (9%) | 29 (12%) |
| **Patient data sets:** | | | |
| All Patients Treated Set (APTS) | 112 | 121 | 233 |
| Full Analysis Set (FAS) | 108 | 115 | 223 |

Statistical Methods
• The following analysis sets were used:
- all-patients-randomised set (APRS) – all patients randomised in the study
- all-patients-treated set (APTS) – all randomised patients who took at least one dose of double-blind study product
- full-analysis set (FAS) – all randomised patients who took at least one dose of double-blind study product and who had at least one post-baseline assessment of the Kiddie-SADS-P total score
• All efficacy analyses were conducted for the FAS. All safety analyses were conducted for the APTS.
• The primary efficacy endpoint was analysed using the principle of observed cases (OC) for each visit. The primary efficacy analysis was based on a repeated measures analysis using an unstructured variance covariance matrix and with factors for: treatment, centre, time, time squared, treatment by time, treatment by centre, and treatment by time by centre.
• The secondary efficacy endpoints were analysed using the principle of OC, and for analysis of final assessment data the principle of last observation carried forward (LOCF) at Week 12 was used. The secondary efficacy analyses were based on repeated measures analysis, ANCOVA, and Fisher’s exact test.
• The distribution of the FMSS scores (high or low) were tabulated. The FMSS score was included as an additional explanatory variable in the primary efficacy analysis.

• Withdrawals were compared between treatment groups using a X2 test.
• The incidences of all treatment-emergent adverse events (TEAEs) were tabulated by system organ class and preferred term for each treatment group.
• For each of the TEAEs with a frequency ≥5% in either treatment group, the incidence in the citalopram group versus that in the placebo group was tested using Fisher's exact test.
• Absolute values and changes in clinical laboratory tests, ECG parameters, vital signs, and weight / BMI were summarised using descriptive techniques. The QT c values were categorised in accordance with the CPMP recommendations. Values outside normal range and potentially clinically significant (PCS) values were flagged and tabulated. Treatment differences in baseline adjusted changes in ECG parameters were analysed by ANCOVA.

Demography of Study Population
• The treatment groups were comparable with respect to age, sex, race, BMI, and baseline efficacy parameters.
• There was a 3 to 1 ratio of females to males and almost all patients were Caucasian.
• At baseline, the mean Kiddie-SADS-P and MADRS total scores were 32 and 30, respectively.

Pharmacokinetic/ Efficacy Results of Sponsor
• The mean citalopram serum concentrations at Week 12 were 130, 217, and 288nmol / L after treatment with 20, 30, or 40mg,, respectively. No consistent pattern in serum levels in males as compared to females was observed.
• The primary analysis of efficacy could not detect a statistically significantly different response profile on the Kiddie-SADS-P scale over time between placebo and citalopram treatment. In both treatment groups, the mean Kiddie-SADS-P total score decreased as a function of time. In the citalopram group, the adjusted mean reduction in Kiddie-SADS-P total score from baseline to Week 12 (OC) was 12.4 points, a reduction that was not statistically significantly different from that observed in the placebo group (12.7 points).
• The proportion of responders on the Kiddie-SADS-P scale, defined as patients with score ≤2 on the "depression" and "anhedonia" items, increased during the study. A remarkably

high placebo response was observed (61% at Week 12) and the response rate in the citalopram group was similar.

• The analyses of scores on the MADRS scale showed similar results. The response profile over time did not differ between treatment groups. The adjusted mean reduction in MADRS total score from baseline to Week 12 (OC) was 16 points in both treatment groups.
• The proportion of responders on the MADRS scale, defined as patients with at least a 50% reduction from baseline, increased during the study period. At Week 12, 59% and 61% of the patients treated with placebo and citalopram, respectively, were responders. With respect to frequency of remission, defined as MADRS total score $\leq$12, no difference between treatments was detected.
• The results of the analyses of the BDI and GAF scales did not reveal any additional information regarding the therapeutic effect of citalopram versus placebo.
• The baseline Kiddie-SADS-P and MADRS total scores had a statistically significant impact on the response profiles over time. This means that patients with higher baseline scores were likely to show a greater improvement than patients with lower scores.
• Expressed emotions did not have a statistically significant impact on the response profile over time.
• An apparent relationship between the citalopram serum concentrations and response at last assessment on the Kiddie-SADS-P scale was not detected.
• Overall, the proportion of patients withdrawn from the study did not differ between treatment groups. Approximately one-third of the patients withdrew from the study. However, withdrawals due to lack of efficacy were more frequent in the placebo group than in the citalopram group (16% versus 9%), whereas withdrawals due to adverse events were slightly more common in the citalopram group (8% in the placebo group and 11% in the citalopram group). The differences were not statistically significant.

## Safety Results

• The AE incidence is summarized below:

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| | Placebo N (%) | Citalopram N (%) |
|---|---|---|
| Patients with serious AEs | 16 (16%) | 18 (15%) |
| Patients with treatment-emergent AEs | 70 (71%) | 91 (75%) |
| Total number of treatment-emergent AEs | 275 | 344 |

N = number of patients; % = percentage of patients within treatment group

• Citalopram was safe and well tolerated. No deaths occurred during the study. After start of double-blind treatment, SAEs were reported by 16 patients in the placebo group and by 18 patients in the citalopram group. The majority of the patients with SAEs reported hospitalisations due to psychiatric disorders (9 patients in the placebo group and 14 patients in the citalopram group). In the placebo group, the other SAEs were surgical interventions (3 patients), epileptic fit, head trauma, medication error, and hospitalisation for social reasons. In the citalopram group, the other SAEs were dyspnoea, non-suicidal overdose, hospitalisation for social reasons, and abortion.
• Withdrawal due to AEs occurred for 9% of the patients and were similarly distributed among treatment groups.
• Treatment emergent adverse events (TEAEs) were reported by 71% of patients in the placebo group and 75% of patients in the citalopram group. The majority of the TEAEs were considered by the investigator to be mild or moderate for both treatment groups.

• The TEAEs that occurred in ≥5% of patients and were more common in the citalopram group than in the placebo group were (in descending order): headache, nausea, insomnia, suicide attempt, rhinitis, abdominal pain, dizziness, pharyngitis, diarrhoea, fatigue, and influenza-like symptoms. Fatigue was the only TEAE that was statistically significantly more common in citalopram-treated patients (6%) than in placebo-treated patients (1%).
• There were no discernible trends within treatment groups or between treatment groups with regard to laboratory tests, vital signs, weight changes, or ECGs.

## Conclusions

In this 12-week study, a better therapeutic effect of citalopram in the treatment of adolescent depression as compared to placebo could not be established. The patients showed improvement on the efficacy scales as a function of time, but the placebo response was high and not different from that of citalopram.

Treatment with citalopram was safe and well tolerated. Safety findings were similar to the safety profile known from adults.

**CIT -PK-07** "An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Patients with Depression."

The primary objective of this study was to evaluate the pharmacokinetics of citalopram, DCT, and DDCT and their enantiomers in pediatric patients with depression (compared to adult patients with depression), following titration to a dose of 40 mg daily from a starting dose of 20 mg daily. The secondary objectives were to assess the safety and efficacy of citalopram in pediatric patients.

This study was a 4 week, open-label, parallel groups, multiple-dose, dose-escalating study. The study was initially designed to include three groups of 12 depressed patients each, aged 7-11 years (children), 12-17 years (adolescents), and 21-45 years (adults). Because of difficulty recruiting depressed children, the protocol was amended to define a single group of pediatric patients from 10-17 years of age for comparison with the adult patients.

The patients received citalopram at a starting dose of 20 mg daily for one week and then received citalopram 40 mg daily for 3 weeks.

Blood and urine samples for pharmacokinetic analysis were collected throughout the study. Efficacy assessments in adult patients were performed by use of Clinical Global Impressions Severity Scale (CGI-S) and Clinical Global Improvement Scale (CGI-I). In the pediatric patients, Kiddie and Young Adult-Schizophrenia and Affective Disorders Schedule-Present and Lifetime (K-SADS-PL) and Children’s Depression Rating Scale, Revised (CDRS-R) were used. Safety was assessed throughout the study by monitoring adverse events, laboratory tests, ECG’s, physical examinations, and vital signs. Efficacy assessments were administered prior to the first dose of citalopram (Baseline) and after four weeks of treatment with citalopram.

Thirteen (13) pediatric (10 - 17 years of age), and twelve (12) adult (21 - 45 years of age) patients with depression entered the study.

No patients discontinued from the study due to an adverse event.

There were no serious adverse events reported. Twenty-two (22) (88%) of the 25 patients reported a total of 27 adverse events. Sixty adverse events were mild, 23 were moderate, and 4 were severe in severity. The most common adverse events (i.e., occurring in 3 or more patients) were headache, nausea, fatigue, rhinitis, decreased appetite, dry mouth, insomnia, and lightheadedness. There were no apparent clinically relevant differences in adverse event type or frequency between the adult and pediatric patients. Only lightheadedness, occurring in three adults and no pediatric patients, occurred with an incidence that differed by more than 2 patients between age groups.

Table 8.1 Incidence of Treatment Emergent Adverse Events (≥3 patients)

| Preferred Term | Adult (N=12) n (%) | Pediatric (N=13) n (%) |
|---|---|---|
| Patients with at least one TEAE | 12 (100) | 10 (76.9) |
| Headache | 5 (41.7) | 3 (23.1) |
| Nausea | 2 (16.7) | 3 (23.1) |
| Fatigue | 1 (8.3) | 3 (23.1) |
| Rhinitis | 3 (25.0) | 1 (7.7) |
| Decreased Appetite | 1 (8.3) | 2 (15.4) |
| Dry Mouth | 2 (16.7) | 1 (7.7) |
| Insomnia | 1(8.3) | 2 (15.4) |
| Lightheaded feeling | 3 (25) | 0 (0) |

**Clinical Laboratory Tests**

None of the mean changes in laboratory values were considered medically important. PCS laboratory abnormalities were limited to patient #01126, (15 years old) who had a previous medical history for asthma who had a PCS value for eosinophils of 11.4% on Day 8 (screening value 6.68%) and patient #02130 (an adult) had a PCS value

for urine protein of 2+ at the end of the study (screening value = negative). Neither PCS value was considered medically significant nor was related to an adverse event report.

**Vital Signs**

There were no clinically relevant mean changes in vital sign values observed. PCS vital sign observances were infrequent. Two PCS values for low systolic blood pressure in two adults (patients #02104, #02108), one PCS value for high diastolic blood pressure (patient #01105), two PCS values for low diastolic blood in an adult pressure in (patients #02104, #02130) and one PCS value for low pulse (patient #02104) were observed in adult patients. There were no AEs reported related to these PCS values.

**Electrocardiograms**

There were no clinically important changes observed in the mean ECG interval or heart rate results. No potentially clinically significant ECG abnormalities were reported.

## Safety summary:

There were no deaths or serious adverse events reported. No patients discontinued from the study due to an adverse event. There were no apparent clinically relevant differences in adverse event type or frequency between the adult and pediatric patients.

## Conclusions:

The sponsor concluded that pharmacokinetic parameters Cmax, Tmax and AUC0-24 after a single dose of 20 mg citalopram and Cmax, Tmax, AUCss, t1/2, CL/F, and Vz/F after multiple doses of 40 mg citalopram were unaffected by age. The only age effect observed was a 30 % increase in urinary excretion of the demethylcitalopram in pediatric patients relative to adult patients. Comparison of pharmacokinetic parameters between male and female patients revealed no gender effects except for 42 % decrease in demethylcitalopram Tmax at steady state in male patients relative to female patients. There is no correlation between pharmacokinetic parameters of citalopram and demethylcitalopram and age. The rate and extent of

absorption as well as the disposition of escitalopram and S-demethylcitalopram were similar in both adult and pediatric patients. In general, none of the patients had detectable concentrations of didemethylcitalopram during the 24 hour period after the initial dose of 20 mg citalopram and the concentrations for didemethylcitalopram in the steady state were too low to estimate the pharmacokinetic parameters. The pharmacokinetic parameters for didemethylcitalopram were not calculated.

**CIT -PK-13** "An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Patients with Depression."

This was an open-label, parallel, single dose study in 12 pediatric (7 -11 years old) and 12 adult (18 - 35 years old) healthy male and female subjects. Subjects were institutionalized for the entire study. The parent or guardian of the pediatric subject accompanied the institutionalized subject during the study.

Subjects received 20 mg of citalopram in a 10 mL oral solution at 0800 on Study Day 1. Multiple plasma samples were obtained on Study Day 1. On Study Days 2 through 8, subjects had a single blood draw at 0800 hours. Blood samples were collected for the measurement of plasma concentrations of each citalopram enantiomer and its respective metabolites.

Safety was assessed throughout the study by monitoring of adverse events and by laboratory and physical examinations and vital sign and ECG assessments.

Twelve (12) pediatric and twelve (12) adult subjects were required to complete the study.

Pediatric subjects had to be between 7 and 11 years of age inclusive. Adult subjects had to be between 18 and 35 years of age inclusive.

Twenty-four subjects, twelve adults (3 males and 9 females) and twelve children (6 males and 6 females) were enrolled and received citalopram.

There were no serious adverse events reported. Twelve (50%) of the twenty-four subjects reported a total of thirty-three adverse events. All adverse events were mild in severity. All were resolved by the time the study ended. The most common AEs (i.e., reported by 2 or more subjects) were nausea, headache, vomiting, and diarrhea.

Table 8.2 Incidence of Treatment Emergent Adverse Events

| Preferred Term | Adults (N=12) n (%) | Children (N=12) n (%) |
|---|---|---|
| Patients with at least one TEAE | 7 (58.3) | 5 (41.7) |
| Nausea | 5 (41.7) | 5 (41.7) |
| Headache | 5 (41.7) | 1 (8.3) |
| Diarrhea | 2 (16.7) | 2 (16.7) |
| Dizziness | 1 (8.3) | 0 (0) |
| Chills | 1 (8.3) | 0 (0) |
| Fever | 0 (0) | 1 (8.3) |
| Vomiting | 0 (0) | 4 (33.3) |

Cross Reference Table 2.3, Appendix E

**Clinical Laboratory Tests**

Subject 009 (pediatric) had high PCS values for eosinophils of 11.9 and 12% at screening and end of study, respectively. Adult subjects 022 and 027 had low PCS hemoglobin values at screening and end of study. Subject 010 (adult) had a PCS high serum potassium value of 5.6 at end of study. All PCS values were judged not clinically significant by the investigator. The observed mean changes in laboratory values were not medically important.

**Vital Signs**

No PCS values for pulse or diastolic blood pressure were recorded; the only PCS values observed were for systolic blood pressure. Two adult subjects (subjects 022 and 029) had PCS values for low systolic blood pressure 4 hours post dose on day 1. In both instances no AEs related to decreased blood pressure were reported. Twenty-four hours after dosing systolic blood pressure returned to within 14 mm Hg (subject 022) and 2 mm Hg (subject 029) of predose values on day 1.

**Electrocardiograms**

There were no clinically important study related changes observed in these mean values. No potentially clinically significant ECG abnormalities were reported.

**Safety summary:**

There were no deaths or serious adverse events reported. No patients discontinued from the study due to an adverse event. There were no apparent clinically relevant differences in adverse event type or frequency between the adult and pediatric patients.

**Conclusions:**

The sponsor concluded that the rate of absorption of citalopram was faster and the extent of absorption was larger in children compared to adults. A shorter Tmax (24%) and t1/2 (24%), higher Cmax (114%), larger AUC0-t (38%) and AUC0-inf (33%), and smaller CL/F (28%) and Vz/F (43%) for citalopram were observed in children compared to adults. Similar conclusions were obtained when adjustments were made for differences in body weights between the subject populations. A higher Cmax (142%) and AUC0-t (114%) for demethylcitalopram was observed in children compared to adults. Tmax, t1/2 and AUC0-inf for demethylcitalopram were not significantly different in children relative to adults.

The rate and extent of absorption as well as the disposition of escitalopram and S-demethylcitalopram were similar in both adult and pediatric subjects. No gender effects on pharmacokinetic parameters (except citalopram Tmax) were found for citalopram and DCT in this study. Tmax (11%)

## V. Human Pharmacokinetic Studies

Vanitha J. Sekar, PhD reviewed the pharmacokinetic studies and her conclusions are listed below.

"In a single dose pharmacokinetic study (PK-13) of 20 mg citalopram oral solution in healthy children (aged 7-11 years) and adults, the rate of absorption of citalopram was faster and the extent of absorption was larger in children compared to adults. A shorter tmax (24%), higher Cmax (114%), larger AUC0- (33%), and smaller CL/F (28%) for citalopram were observed in children compared to adults. Similar conclusions were obtained when adjustments were made for differences in body weights between the subject populations. No gender effects on pharmacokinetic parameters (except citalopram Tmax) were found for citalopram in this study. Tmax (11%) for citalopram was shorter in females than in males.

In a multiple dose pharmacokinetic study (PK-07) in children (aged 10-17 years) and in adults given 20 mg citalopram once daily with forced titration to 40 mg once daily for a total of four weeks, pharmacokinetic parameters of citalopram after a single dose of 20mg citalopram and after multiple doses of 40 mg once daily were similar in depressed adolescents and adults. Comparison of pharmacokinetic parameters between male and female patients revealed no significant gender effects for citalopram.

Comparison of the pharmacokinetics of citalopram and demethylcitalopram following a single 20 mg dose across the above 2 studies (PK-13 and PK-07) suggests that younger children (aged 7-11 years) have higher AUC (approximately 30%) and Cmax (60-100%) than adolescents and adults following a single 20 mg dose of citalopram."

**VI.** (b) (4)

(b) (4)

## VII. CONCLUSIONS AND RECOMMENDATIONS

### A. Efficacy and Safety

Efficacy in this population was not established. There were no new safety patterns in these studies.

### B. Pharmacokinetics

Please see section V with conclusions of Vanitha Sekar,PhD.

**C.** (b) (4)

(b) (4)

**D. Exclusivity**

Exclusivity has been granted based on the completion of these studies.

Earl D. Hearst, MD
Medical reviewer
HFD-120

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/
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Earl Hearst
9/12/02 03:24:41 PM
MEDICAL OFFICER

Thomas Laughren
9/16/02 09:09:04 AM
MEDICAL OFFICER

(b) (4) see memo to file for more detailed comments.--TPL