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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Applicant:	Forest Research Institute
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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Study SCT-MD-32

In the primary analysis of CDRS-R Total score, adolescent patients (12 to 17 years of age) with Major Depressive Disorder on escitalopram 10-20mg/d were observed to show statistically significant improvement over patients in the placebo treatment group.

Escitalopram group also showed statistically significant improvement relative to placebo in the CGI-I score. Whether the magnitude of the observed treatment difference is clinically relevant is deferred to the clinical review team.

Study SCT-MD-32a

In this reviewer's opinion, this trial does not provide interpretable evidence for the long-term efficacy (maintenance) claim.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The sponsor submitted results of two efficacy and safety studies: Study SCT-MD-32 and Study SCT-MD-32a (extension of Study SCT-MD-32).

Study SCT-MD-32 was an 8-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study of the safety and efficacy of escitalopram in the treatment of adolescent patients (12-17 years of age) with Major Depressive Disorder. The escitalopram dosage was 10 mg/d for the first three weeks of double-blind treatment. The dosage could be increased to 20 mg/d by the investigator at the end of Treatment Week 3 (Visit 6) or Treatment Week 4 (Visit 7). Patients who completed the 8-week double-blind treatment period of Study SCT-MD-32 were eligible to enter the extension study, SCT-MD-32A, for an additional 16-24 weeks of treatment. During double-blind treatment in Study SCT-MD-32A, patients were to receive the same daily dosage of the blinded study drug they were receiving at Week 4 (Visit 7) of Study SCT-MD-32.

A total of 316 patients were randomized to receive double-blind study drug in Study SCT-MD-32; 312 patients received at least one dose of double-blind study drug (Safety Population); and 311 patients had at least one postbaseline CDRS-R assessment (ITT Population). A total of 133 (84.2%) placebo patients and 126 (79.7%) escitalopram patients completed 8 weeks of double-blind treatment, and 165 patients (82 placebo, 83 escitalopram) continued into the double-blind treatment of the extension study, SCT-MD-32A. Overall, 40 (25.3%) patients in the placebo group and 37 (23.4%) patients in the double-blind escitalopram group completed both studies SCT-MD-32 and SCT-MD-32A.

1.3 STATISTICAL ISSUES AND FINDINGS

Study SCT-MD-32

Escitalopram treatment group (10mg/d to 20mg/d) was statistically superior to placebo in mean change from baseline to Week 8 in CDRS-R Total score. The p-value of pairwise comparison with placebo obtained from LOCF ANCOVA model with treatment group and study center as factors, and the baseline CDRS-R total score as a covariate was 0.022.

Escitalopram group also showed statistically significant improvement relative to placebo in the CGI-I score at Week 8. The p-value of the ANCOVA LOCF analysis was 0.008. Whether the magnitude of the observed treatment difference (LSMD=-0.3) is clinically relevant is deferred to the clinical review team.

No statistical issues were found.

Study SCT-MD-32a

The primary efficacy endpoint was change from the baseline of Study 32 to the endpoint visit of Study 32a. Note that when the data of acute phase are combined with long-term phase, then the maintenance effect is confounded with acute effect.

Study SCT-MD-32A was initially an open-label extension but subsequently amended to a 24-week double-blind extension, and as the study progressed was further changed to a 16-week double-blind extension. Thus, patients enrolled in the double-blind extension had different exposure times.

Also, the patient population for study 32a consisted of completers of Study 32 who chose to continue into the extension study. Of the 259 patients who completed Study SCT-MD-32, 202 chose to enroll in Study SCT-MD-32A; 165 of these patients continued into the double –blind treatment and received the same blinded study drug they were receiving in Study SCT-MD-32. Thus, treatment groups in Study 32a do not represent random samples of the screened patient population. Typically, to assess maintenance effect patients should be stabilized on the studied medication and then randomized to placebo and drug treatment groups before entering into maintenance phase.

Of the 202 patients who entered the extension study (165 double-blind, 37 open-label), approximately 50% (103/202) prematurely discontinued. The most common reason for premature discontinuation during the extension study was insufficient therapeutic response (35 patients [18 placebo, 16 escitalopram, 1 open-label escitalopram]). Overall, only 25.3% of patients in the placebo group and 23.4% of patients in the double-blind escitalopram group completed both studies SCT-MD-32 and SCT-MD-32A. For any trial with a very high dropout rate, it is always questionable whether the data can be interpretable.

2 INTRODUCTION

2.1 OVERVIEW

The sponsor intends to claim for acute treatment based on one placebo-controlled study with escitalopram in adolescents, 12 to 17 years (Study SCT-MD-32), and one placebo-controlled study with citalopram (Study CIT-MD-18, submitted earlier) in children and adolescents, 7 to 17 years (in accordance with agreements with the FDA). The primary efficacy parameter in these two studies was the change from baseline to the end of Week 8 in the Children's Depression Rating Scale–Revised (CDRS-R) score using the last-observation-carried-forward (LOCF) approach. Based on the sponsor's overview of clinical efficacy, in a previous double-blind acute treatment 8-week study (SCT-MD-15) in pediatric patients (6-17 years old) with MDD, escitalopram 10-20 mg/d did not demonstrate statistically significantly greater improvement than placebo in the primary efficacy parameter, the Children's Depression Rating Scale–Revised (CDRS-R) at Week 8, last observation carried forward (LOCF) analysis.

The sponsor intends to claim long-term treatment effect of escitalopram in adolescents with MDD based on one 24-week double-blind extension study (Study SCT-MD-32A) along with the lead-in study (Study SCT-MD-32). The change from baseline in the lead-in study to the end of Week 24 in CDRS-R score (using the LOCF approach) was proposed by the sponsor as the primary efficacy parameter.

This reviewer evaluated results of Study SCT-MD-32 and Study SCT-MD-32a.

2.2 DATA SOURCES

Data used for review are from the electronic submissions received on May 22, 2008 and December 11, 2008. The network paths are \\CDSESUB1\EVSPROD\NDA021323\0000 , \\CDSESUB1\EVSPROD\NDA021323\00007 , and \\CDSESUB1\EVSPROD\NDA021323\0010

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY SCT-MD-32

3.1.1.1 Objective

The objective of this study was to compare the safety and efficacy of escitalopram relative to placebo at a flexible dose of 10 mg/day or 20 mg/day relative to placebo in the treatment of major depressive disorder in pediatric patients as measured by change from baseline in CDRS-R total score at Week 8.

3.1.1.2 Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose (10-20 mg/day) study of the safety and efficacy of escitalopram in the treatment of adolescent patients (12-17 years of age) who have MDD.

As shown in Table 1, the study consisted of a 2-week screening period, including single-blind placebo lead-in during the second week, followed by 8 weeks of double-blind treatment. At the end of the single-blind period, patients meeting the entry criteria for this study were randomized 1:1 to one of two double-blind treatment groups (escitalopram or placebo). The escitalopram dosage was 10 mg/d for the first three weeks of double-blind treatment. The dosage could be increased to 20 mg/d by the investigator at the end of Treatment Week 3 (Visit 6) or Treatment Week 4 (Visit 7). Patients who completed the 8-week double-blind treatment period were eligible to enter a 1-week double-blind down-taper period or to continue in an extension study (Study SCT MD-32A). Patients who prematurely discontinued during Study SCT-MD-32 were also eligible to enter a 1-week double-blind down-taper period.

Table 1. Study SCT-MD-32 Flow Chart

Period	**Screening**		**Double-Blind Treatment**							**Down Taper**
		Single-Blind Placebo	Eslitalopram 10mg/day or Placebo			Eslitalopram 10mg/day, 20mg/day or Placebo				
Visit	1	2	3	4	5	6	7	8	9	10
Study Day/ Week (W)	W -2	W -1	Day 0 / Baseline	W 1	W 2	W 3	W 4	W 6	W 8	W 9

Source: Corresponds to Figure 9.1-1.(pg 24), Clinical Study Report SCT-MD-32.

3.1.1.3 Patient Disposition, Demographic and Baseline Characteristics

This study was conducted at 40 study centers in the United States (US). Of these study centers 38 centers randomized patients. For inclusion in the study, among other criteria, patients had to have CDRS-R score of ≥45 at Visits 1 and 3 and CGI-S score ≥4 at Visit 3.

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

A total of 133 (84.2%) placebo patients and 126 (79.7%) escitalopram patients completed 8 weeks of double-blind treatment, and 202 patients (100 placebo, 102 escitalopram) continued into the extension study, SCT-MD-32A. Of the 57 patients who did not continue into the extension study, 33 (23 placebo, 10 escitalopram) entered the double-blind down-taper period. All of these patients, with the exception of placebo Patient 0163201, completed Study SCT-MD-32 before entering down-taper.

Table 2. Study SCT-MD-32 Patient Population and Disposition

Patients	Escitalopram	Placebo
Randomized	158 (100%)	158 (100%)
Received Study Drug	155 (98.1%)	157 (99.4%)
ITT Population	154 (97.5%)	157 (99.4%)
Discontinued Study	52 (37.1%)	42 (30.0%)
Adverse Event	4 (2.5%)	1 (0.6%)
Lack of therapeutic response	5 (3.2%)	5 (3.2%)
Protocol violation, including lack of compliance	3 (1.9%)	0 (0.0%)
Withdrawal of consent	8 (5.1%)	9 (5.7%)
Lost to Follow-up	8 (5.1%)	6 (3.8%)
Other	1 (0.6%)	3 (1.9%)
Completed study	126 (79.7%)	133 (84.2%)
Enrolled in SCT-MD-32A	102 (64.6%)	100 (63.3%)

Source: Corresponds to Figure 10.1-1.(pg. 51), and Table 10.2-1.(pg. 52) Clinical Study Report SCT-MD-32

The demographic characteristics and the baseline efficacy values of the ITT Population are presented in Table 3 . The average patient age was approximately 15 years, and approximately three quarters of the patients in each treatment group were Caucasian. Females comprised 59% of the Safety Population. There were no statistically significant differences between the two treatment groups with respect to demographic characteristics. The sponsor stated that at baseline there were statistically significant differences in CDRS-R total score and CGI-S between the two treatment groups (at nominal significance level of 0.05), with higher depression severity at baseline in the escitalopram group. The two treatment groups did not have different baseline CGAS scores.

Table 3. Study SCT-MD-32 Demographic and Baseline Characteristics (ITT analysis set)

Variable	Placebo N=157	Escitalopram N=154
Gender, n (%)		
Male	65 (41.4%)	62 (40.3%)
Female	92 (58.6%)	92 (59.7%)
Race		
Caucasian	123 (78.3%)	112 (72.7%)
Black	24 (15.3%)	30 (19.5%)
Asian	0 (0%)	3 (1.9%)
Other	10 (6.4 %)	9 (5.8%)
Age (years)		
Mean (SD)	14.52 (1.48)	14.73 (1.64)
Weight (lbs)		
Mean (SD)	157.4 (47.6)	159.0 (49.8)
Height (in)		
Mean (SD)	65.2 (3.7)	65.1 (3.8)
CDRS-R Total Score		
Mean (SD)	56.0 (8.3)	57.6 (8.3)
CGI-S Total Score		
Mean (SD)	4.4 (0.5)	4.6 (0.6)

Source: Table 14.2.2. (pg. 118), Table 10.3-3. (pg. 54) Clinical Study Report SCT-MD-32.

3.1.1.4 Statistical Methodologies

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

Primary Efficacy Parameter

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

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

Key Secondary Analysis

The key secondary efficacy parameter was the CGI-I score at Week 8. The between–treatment group analysis was performed using an ANCOVA model with treatment group and study center as factors and the baseline CGI-S score as covariate.

3.1.1.5 Results of Efficacy Analysis

Primary Efficacy Analysis

This reviewer confirmed sponsor's primary efficacy analysis. The primary efficacy parameter was the change from baseline to Week 8 in CDRS-R total score. Table 4 presents the results of the ANCOVA analysis for this primary endpoint, using the LOCF approach. The change from baseline to Week 8 in the escitalopram group was clinically and statistically significant and greater than that in the placebo group (LSMD = –3.4, p = .022).

Table 4. CDRS-R Total Score LS Mean Change from Baseline to Week 8 (ITT Population)

		Placebo	Escitalopram
No patients	N=311	157	154
Baseline	Mean (SEM)	56.0 (0.7)	57.6 (0.7)
Change from Baseline	Mean (SEM)	-18.4 (1.1)	-22.4 (1.1)
Placebo-adjusted difference	LS Mean Difference	NA	-3.4
	95% CI	NA	(-6.2, -0.5)
	P-value	NA	0.022

Source: Table 11.1.1.1–1. (pg. 58) Clinical Study Report SCT-MD-32
Remark: SEM stands for Standard Error of the Mean

As seen from Table 5, the observed treatment difference was numerically in favor of escitalopram at Weeks 2, 4, and 6.

Table 5. CDRS-R Total score mean change from baseline by visit with missing values imputed by LOCF method (ITT Population).

	Placebo	Escitalopram	Treatment Difference: Escitalopram - Placebo	
Week	**LS Mean (SE)**	**LS Mean (SE)**	**LS Mean**	**95% CI**
2	-11.3 (1.03)	-12.8 (1.00)	-1.48	(-3.83, 0.86)
4	-15.4 (1.06)	-18.8 (1.03)	-3.37	(-5.784, -0.958)
6	-18.6 (1.17)	-21.8 (1.13)	-3.22	(-5.86, -0.57)
8	-18.8 (1.27)	-22.1 (1.22)	-3.36	(-6.23, -0.49)

Source: Table 14.4.3.1A (pg. 162-163) Clinical Study Report SCT-MD-32
Note: The reported 95% CIs are nominal CIs and are not adjusted for multiplicity.

Sensitivity Analysis

The reviewer confirmed sponsor's sensitivity analysis on the primary endpoint. Change from baseline in CDRS-R Total score was analyzed by mixed effect repeated measures model. The model included study center, treatment group, visit, and treatment group-by-visit interaction as factors and baseline CDRS-R total score as covariate. The findings support the primary analysis results.

Table 6. CDRS-R Total Score Change from Baseline Visitwise LS means, Mixed Effects Repeated Measures model (ITT Population).

Week	Study Treatment	Number of patients	LS Mean (SE)	Treatment difference : Escitalopram – Placebo	
				LS Mean (SE)	95 % CI
2	Placebo	145	-12.14 (1.02)		
2	Escitalopram	141	-13.30 (0.99)	-1.16 (1.24)	(-3.61, 1.29)
4	Placebo	144	-16.65 (1.01)		
4	Escitalopram	139	-19.93 (0.98)	-3.28 (1.22)	(-5.69, -0.87)
6	Placebo	135	-19.29(1.09)		
6	Escitalopram	135	-22.53 (1.06)	-3.24 (1.35)	(-5.90, -0.57)
8	Placebo	135	-19.58 (1.16)		
8	Escitalopram	129	-22.71 (1.14)	-3.13 (1.47)	(-6.03, -0.23)

Source: Table 16.1.9.3.1. (pg. 1792-1795), Clinical Study Report SCT-MD-32
Note: The reported 95% CIs are nominal CIs and are not adjusted for multiplicity.

Key Secondary Endpoint

Table 7 presents sponsor's results for the CGI-I score at Week 8, the secondary efficacy endpoint. At Week 8, statistically significant improvement was seen in the escitalopram group relative to the placebo group in the ANCOVA LOCF (LSMD = –0.3, p = .008) analysis with treatment group and study centers as factors and baseline CGI-S score as covariate. This reviewer verified sponsor's results. Whether the magnitude of observed difference is clinically relevant is deferred to the clinical review team.

Table 7. CGI-I Score at Week 8 (ITT Population)

		Placebo	**Escitalopram**
No patients	N=311	157	154
CGI-I at Week 8	Mean (SEM)	2.5 (0.1)	2.2 (0.1)
Placebo-adjusted difference	LS Mean Difference	NA	-0.3
	95% CI	NA	(-0.6, -0.1)
	P-value	NA	0.008

Source: Table 11.1.1.2–1. (pg. 61) Clinical Study Report SCT-MD-32
Remark: SEM stands for Standard Error of the Mean

3.1.1.6 Reviewer's Comments.

Escitalopram treatment group (10mg/d to 20mg/d) was statistically superior to placebo in mean change from baseline to Week 8 in CDRS-R Total score. The p-value of pairwise comparison with placebo obtained from LOCF ANCOVA model with treatment group and study center as factors, and the baseline CDRS-R total score as a covariate was 0.022.

Escitalopram group also showed statistically significant improvement relative to placebo in the CGI-I score at Week 8. The p-value of the ANCOVA LOCF analysis was 0.008. Whether the magnitude of the observed treatment difference (LSMD=-0.3) is clinically relevant is deferred to the clinical review team.

3.1.2 STUDY SCT-MD-32A

3.1.2.1 Objective

The objective of this study was to evaluate the **long-term** safety, efficacy, and tolerability of escitalopram at a flexible dose of 10 mg/day or 20 mg/day relative to placebo in the treatment of major depressive disorder in pediatric patients as measured by change from baseline to the endpoint in CDRS-R total score.

3.1.2.2 Study Design

Patients who completed the 8-week double-blind treatment period of Study SCT-MD-32 were eligible to enter the extension study, SCT-MD-32A, for an additional 16-24 weeks of treatment. The final visit of Study SCT-MD-32 double-blind treatment period, Visit 9, was therefore also Visit 1 of Study SCT-MD-32A. Study SCT-MD-32A was initially an open-label extension but

subsequently amended to a double-blind design. Protocol Amendment #2, September 30, 2005, changed the design to a 24-week double-blind extension. Protocol Amendment #3, February 8, 2007, changed the length of the extension to 16 weeks. The study was initiated on June 16, 2005 and completed on September 24, 2007.

During double-blind treatment in Study SCT-MD-32A, patients were to receive the same daily dosage of the blinded study drug they were receiving at Visit 7 of Study SCT-MD-32. The minimum and maximum dosages allowed were 10 mg/d and 20 mg/d. During Study SCT-MD-32A, visits occurred biweekly. Accordingly, patients were given bottles containing 20 tablets of escitalopram 10 mg, escitalopram 20 mg, or matching placebo. Patients who did not enter the extension study entered a 1-week double-blind down-taper period.

Patients who completed the open-label or double-blind treatment period of Study SCT-MD-32A and patients who prematurely discontinued during Study SCT-MD-32A were eligible to enter a 2-week down-taper period, which was open-label or double-blind in correspondence with the patient's treatment group assignment. Patients who prematurely discontinued from Study SCT-MD-32A for insufficient therapeutic response were eligible to receive 6 months of aftercare, provided at the discretion of the investigator.

3.1.2.3 Patient Disposition, Demographic and Baseline Characteristic

As seen from Table 8, of the 259 patients who completed Study SCT-MD-32, 202 enrolled in Study SCT-MD-32A; 165 of these patients were assigned to double-blind escitalopram (N = 83) or placebo (N = 82), and 37 enrolled in the open-label extension. The remaining 57 patients (33 placebo, 24 escitalopram) chose not to continue in the extension study.

Of the 202 patients who entered the extension study (165 double-blind, 37 open-label), approximately 50% (103/202) prematurely discontinued. The most common reason for premature discontinuation during the extension study was insufficient therapeutic response (35 patients [18 placebo, 16 escitalopram, 1 open-label escitalopram]). Overall, 25.3% of patients in the placebo group and 23.4% of patients in the double-blind escitalopram group completed both studies SCT-MD-32 and SCT-MD-32A. Per the sponsor's study report, more escitalopram-treated patients relative to placebo-treated patients prematurely discontinued during the combined double-blind treatment periods because of AEs (2.5% vs. 0.0%,) and protocol violations (3.8% vs. 1.3%).

Table 8. Study SCT-MD-32/ SCT-MD-32a Patient Population and Disposition

	Escitalopram	Placebo
Patients		
Randomized	158 (100%)	158 (100%)
Received Study Drug	155 (98.1%)	157 (99.4%)
ITT Population	154 (97.5%)	157 (99.4%)
Completed Study SCT-MD-32	126 (79.7%)	133 (84.2%)
Did not continue into Extension	24 (15.2%)	33 (20.9%)
Enrolled in Open Label Extension	19 (12.0%)	18 (11.4%)
Enrolled in Double-Blind (DB) Extension	83 (52.5%)	82 (51.9%)
Discontinued DB Extension	46 (29.1%)	42 (26.6%)
Adverse Event	4 (2.5%)	0 (0%)
Insuffic. therapeutic response	16 (10.1%)	18 (11.4%)
Protocol violation	6 (3.8%)	2 (1.3%)
Withdrawal of consent	10 (6.3%)	8 (5.1%)
Lost to Follow-up	6 (3.8%)	12 (7.6%)
Other	4 (2.5%)	2 (1.3%)
Completed DB Extension	37 (23.4%)	40 (25.3%)

Source: Corresponds to Figure 10.1-1.(pg. 56), and Table 10.2-1.(pg. 58) Clinical Study Report SCT-MD-32a

3.1.2.4 Statistical Methodologies and Endpoints

All efficacy analyses were performed on the combined double-blind treatment periods of Studies SCT-MD-32 and SCT-MD-32A. Baseline for these analyses was defined as the Visit 3 assessment in the lead-in study (SCT-MD-32). All efficacy analyses were performed on the ITT Population.

The change from baseline to the end of study in CDRS-R total score was the primary efficacy parameter. The primary analysis was performed using the LOCF approach. The between-treatment group comparison for the primary efficacy parameter was performed using an analysis of covariance (ANCOVA) model with treatment group and study center as factors and baseline CDRS-R total score as the covariate.

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

The secondary efficacy parameter was the CGI-I score at the end of study. The between–treatment group comparison for the secondary efficacy parameter was performed using an ANCOVA model with treatment group and study center as factors and baseline CGI-S score as the covariate.

3.1.2.5 Results of Efficacy Analysis

Primary Efficacy Analysis

The primary efficacy parameter was the change from baseline (Visit 3 of SCT-MD-32) to Week 24 in the CDRS-R total score using the LOCF approach. As shown in Table 9, at the end of the 24-week double-blind treatment period, patients in the escitalopram treatment group had significantly greater improvement relative to placebo-treated patients in the CDRS-R total score using the LOCF approach (least squares mean difference [LSMD] = – 4.5, p = .005). This reviewer confirmed the sponsor's results. However, please see the next section for reviewer's comments.

Table 9. CDRS-R Total Score LS Mean Change from Baseline to Week 24 (ITT population)

		Placebo	**Escitalopram**
No patients	N=311	157	154
Baseline	Mean (SEM)	56.0 (0.7)	56.7 (0.7)
Change from Baseline	Mean (SEM)	-18.2 (1.1)	-23.1 (1.2)
Placebo-adjusted difference	LS Mean Difference	NA	-4.5
	95% CI	NA	(-7.6, -1.3)
	P-value	NA	0.005

Source: Table 11.1.1.1–1. (pg. 66) Clinical Study Report SCT-MD-32a
Remark: SEM stands for Standard Error of the Mean

Key Secondary Endpoint

The secondary efficacy parameter was the CGI-I score at Week 24. At the end of 24 weeks of double-blind treatment, patients receiving escitalopram showed significantly greater improvement relative to placebo-treated patients in the CGI-I score using the LOCF approach (LSMD = – 0.4, p = .003; Table 11.1.1.2–1). These results were confirmed by the reviewer. However, please see the next section for reviewer's comments.

Table 10. CGI-I Score at Week 24 (ITT Population)

		Placebo	**Escitalopram**
No patients	N=311	157	154
CGI-I at Week 24	Mean (SEM)	2.5 (0.1)	2.2 (0.1)
Placebo-adjusted difference	LS Mean Difference	NA	-0.4
	95% CI	NA	(-0.7, -0.1)
	P-value	NA	0.003

Source: Table 11.1.1.2–1. (pg. 69) Clinical Study Report SCT-MD-32a
Remark: SEM stands for Standard Error of the Mean

3.1.2.6 Reviewer's Comments

The primary efficacy endpoint was change from the baseline of Study 32 to the endpoint visit of Study 32a. Note that when the data of acute phase are combined with long-term phase, then the maintenance effect is confounded with acute effect.

Study SCT-MD-32A was initially an open-label extension but subsequently amended to a 24-week double-blind extension, and as the study progressed was further changed to a 16-week double-blind extension. Thus, patients enrolled in the double-blind extension had different exposure times.

Also, the patient population for study 32a consisted of completers of Study 32 who chose to continue into the extension study. Of the 259 patients who completed Study SCT-MD-32, 202 chose to enroll in Study SCT-MD-32A; 165 of these patients continued into the double –blind treatment and received the same blinded study drug they were receiving in Study SCT-MD-32. Thus, treatment groups in Study 32a do not represent random samples of the screened patient population. Typically, to assess maintenance effect patients should be stabilized on the studied medication and then randomized to placebo and drug treatment groups before entering into maintenance phase.

Of the 202 patients who entered the extension study (165 double-blind, 37 open-label), approximately 50% (103/202) prematurely discontinued. The most common reason for premature discontinuation during the extension study was insufficient therapeutic response (35 patients [18 placebo, 16 escitalopram, 1 open-label escitalopram]). Overall, only 25.3% of patients in the placebo group and 23.4% of patients in the double-blind escitalopram group completed both studies SCT-MD-32 and SCT-MD-32A. For any trial with a very high dropout rate, it is always questionable whether the data can be interpretable.

3.2 EVALUATION OF SAFETY

Background

To assess growth during pediatric depression escitalopram studies, the medical division asked Forest Research Institute to provide analyses of weight (growth) data. Specifically, the medical division asked for analyses that examine changes in mean weight z-scores. For these analyses, the medical division asked the sponsor to assign a z-score to each study subject for baseline and end of study. The z-score is the number of standard deviations from the population mean for a specific subject's weight, given their age and sex. This analysis uses population data from CDC growth charts and allows a determination about whether study subjects are growing along their predicted growth curve. No change in mean z-score would indicate that subjects are growing as predicted by data from age adjusted peers. Decreases in mean z-score would indicate that subjects are lagging behind in growth.

Forest Research Institute responded with a series of tables summarizing the z-score analyses and an electronic data set with weight and z-score data.

Studies reviewed

The weight data analyses submitted by the sponsor came from: one placebo-controlled study with escitalopram in adolescents, 12 to 17 years, (Study SCT-MD-32); one placebo-controlled study with escitalopram (Study CIT-MD-15) in children and adolescents, 7 to 17 years; one placebo-controlled study with citalopram (Study CIT-MD-18) in children and adolescents, 7 to 17 years; and the double-blind extension study (Study SCT-MD-32A).

The three acute treatment controlled trials (Studies 15, 18 and 32) lasted eight weeks. Patients who completed the 8-week double-blind treatment period of Study SCT-MD-32 were eligible to enter the extension study, SCT-MD-32A, for an additional 16-24 weeks of treatment. Study SCT-MD-32A was initially an open-label extension but subsequently amended to a double-blind design.

The acute treatment controlled trials included 282 subjects exposed to escitalopram, 89 patients exposed to citalopram and 373 exposed to placebo. Of the 202 patients enrolled in the extension study, 165 patients entered the double-blind extension (83 escitalopram, 82 placebo), and 37 entered the open-label extension.

Results from individual Randomized Controlled Trials

The sponsor summarized the weight z-scores for individual studies SCT-MD-15, Study SCT-MD-18, and SCT-MD-32. Sponsor's analysis included output tables that provided the mean z-scores at baseline and end of study by treatment. This reviewer confirmed sponsor's results and conducted exploratory descriptive subgroup analysis by age (children, adolescents), and gender. See Tables 11, 12 and 13 below for details. In all three studies, for all treatment arms the mean change in z-score was in the range from 0.2 to 0.5, except the citalopram arm in study SCT-MD-18. The difference between the treatment arms in Study SCT-MD-18 appeared to be mainly driven by the female subgroup.

Table 11. Mean change from baseline in weight z-scores for Study 15.

Study 15	**Placebo**		**Escitalopram**	
	N	**Mean (SD)**	**N**	**Mean (SD)**
Overall	132		129	
Baseline		1.25 (0.99)		1.06 (1.11)
Change		0.05 (0.13)		0.04 (0.13)
Children	52		52	
Baseline		1.46 (0.91)		1.08 (1.16)
Change		0.05 (0.14)		0.07 (0.13)
Adolescents	80		77	
Baseline		1.11 (1.02)		1.04 (1.08)
Change		0.05 (0.12)		0.02 (0.13)
Male	63		63	
Baseline		1.12 (0.92)		0.77 (1.14)
Change		0.06 (0.14)		0.05 (0.13)
Female	69		66	
Baseline		1.37 (1.05)		1.33 (1.01)
Change		0.04 (0.11)		0.03 (0.13)

Source: Sponsor's submission \\CDSESUB1\EVSPROD\NDA021323\00007 and reviewer's results

Table 12. Mean change from baseline in weight z-scores for Study18

Study 18	Placebo		Citalopram	
	N	Mean (SD)	N	Mean (SD)
Overall	85		89	
Baseline		1.07 (1.20)		1.11 (1.25)
Change		0.04 (0.13)		0.00 (0.17)
Children	38		45	
Baseline		1.16 (1.27)		1. 31 (1.28)
Change		0.06 (0.15)		0.01 (0.16)
Adolescents	47		44	
Baseline		0.99 (1.14)		0.92 (1.20)
Change		0.03 (0.10)		-0.02 (0.18)
Male	39		42	
Baseline		0.95 (1.21)		1.13 (1.28)
Change		0.04 (0.13)		0.03 (0.19)
Female	46		47	
Baseline		1.16 (1.19)		1.10 (1.23)
Change		0.05 (0.12)		-0.04 (0.15)

Source: Sponsor's submission \\CDSESUB1\EVSPROD\NDA021323\00007 and reviewer's results

Table 13. Mean change from baseline in weight z-scores for Study 32.

Study 32	Placebo		Escitalopram	
	N	Mean (SD)	N	Mean (SD)
Overall	156		153	
Baseline		1.24 (1.11)		1.20 (1.17)
Change		0.04 (0.12)		0.02 (0.13)
Male	64		61	
Baseline		1.33 (1.25)		1.33 (1.25)
Change		0.06 (0.14)		0.04 (0.12)
Female	92		92	
Baseline		1.17 (1.00)		1.12 (1.12)
Change		0.02 (0.10)		0.01 (0.13)

Source: Sponsor's submission \\CDSESUB1\EVSPROD\NDA021323\00007 and reviewer's results

Results from Pooled Data

Per medical officer's request, the sponsor pooled the escitalopram/citalopram exposure data from the randomized controlled trials (studies 15, 18, and 32) to calculate mean changes in z-score. This reviewer confirmed the sponsor's results and conducted additional exploratory descriptive subgroup analysis by gender (see Table 14). Numerically, the results appeared to be consistent among the treatment groups, except the female subgroup randomized to citalopram arm. For citalopram female subgroup the mean change in weight z-score was -0.04. For all other subgroups the mean change in z-score was in the range from 0.2 to 0.5.

Table 14. Pooled analysis: Mean change from baseline in weight z-scores.

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

Source: Sponsor's submission \\CDSESUB1\EVSPROD\NDA021323\00007 and reviewer's results

Results from Extension Study

Using the submitted electronic data sets, this reviewer conducted additional exploratory descriptive analysis of the weight z-scores using only the data for those subjects who continued into the extension treatment (Study SCT-MD-32A). For patients who participated in the double-blind extension, the mean z-score changes were numerically consistent between the treatment groups: change in mean z-score of 0.09 for escitalopram group and 0.08 for placebo group. The results were also consistent within gender subgroups and by visit (see Tables 15 and 16). This reviewer noticed that there were unusual fluctuations in the numbers of patients having z-score assessments after Week 12. This reviewer further determined that all patients with z-score assessments at Week 16 did not have any assessments at Week 14 or Week 18. One possible explanation of the fluctuations could be that some patients were scheduled for visits at different study weeks. Thus, the numerical results presented in Table 16 should be interpreted with caution.

For the open-label extension, the escitalopram/escitalopram subjects experienced an increase in mean z-score of 0.04 from the beginning of the double-blind phase. The subjects who received escitalopram for the first time during the open label phase experienced a mean decrease in z-score of -0.01 (see Table 15).

Table 15. Mean change from baseline in weight z-scores for Study 32/32A

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

Source: Sponsor's submission \\CDSESUB1\EVSPROD\NDA021323\00007 and reviewer's results

Table 16. Study 32/32A. Mean change from baseline in weight z-scores by week.

Study 32/32A	Placebo		Escitalopram	
	N	Mean (SD)	N	Mean (SD)
Baseline	82	1.37 (1.17)	83	1.10 (1.20)
Week 1	80	-0.00 (0.06)	76	-0.01 (0.07)
Week 2	76	0.01 (0.07)	78	-0.01 (0.07)
Week 3	77	0.02 (0.09)	77	-0.02 (0.07)
Week 4	81	0.04 (0.08)	80	-0.01 (0.09)
Week 6	76	0.04 (0.09)	80	-0.01 (0.13)
Week 8	81	0.04 (0.12)	82	0.02 (0.12)
Week 10	72	0.05 (0.11)	72	0.04 (0.16)
Week 12	64	0.06 (0.11)	65	0.07 (0.18)
Week 14	13	0.04 (0.08)	18	0.04 (0.19)
Week 16	48	0.07 (0.13)	48	0.10 (0.17)
Week 18	8	0.04 (0.07)	4	0.06 (0.15)
Week 20	40	0.05 (0.15)	39	0.11 (0.21)
Week 22	10	0.04 (0.17)	8	0.10 (0.13)
Week 24	40	0.09 (0.17)	39	0.13 (0.24)

Source: Reviewer's Results

Statistical Comment

Numerically, the weight z-score changes appeared to be similar between the treatment groups for all studies.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

4.1.1 STUDY 32

This reviewer conducted exploratory subgroup analysis on the primary efficacy variable (change from baseline in CDRS-R Total score at week 8), using ANCOVA models, including the terms for treatment and the baseline score. The subgroups of interest included gender and race. For all subgroups except the black race the treatment effect appeared to be numerically in favor of escitalopram when compared with placebo.

Table 17. Subgroup Analysis: CDRS-RS Total score mean change from baseline with missing values imputed by LOCF method.

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

Source: Reviewer's Results
Note: the reported 95% CIs are nominal and are not adjusted for multiplicity.

4.1.2 STUDY 32A

Omitted, because the results on the overall population are not interpretable.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

Not available.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Study SCT-MD-32

Escitalopram treatment group (10mg/d to 20mg/d) was statistically superior to placebo in mean change from baseline to Week 8 in CDRS-R Total score. The p-value of pairwise comparison with placebo obtained from LOCF ANCOVA model with treatment group and study center as factors, and the baseline CDRS-R total score as a covariate was 0.022.

Escitalopram group also showed statistically significant improvement relative to placebo in the CGI-I score at Week 8. The p-value of the ANCOVA LOCF analysis was 0.008. Whether the magnitude of the observed treatment difference (LSMD=-0.3) is clinically relevant is deferred to the clinical review team.

No statistical issues were found.

Study SCT-MD-32a

The primary efficacy endpoint was change from the baseline of Study 32 to the endpoint visit of Study 32a. Note that when the data of acute phase are combined with long-term phase, then the maintenance effect is confounded with acute effect.

Study SCT-MD-32A was initially an open-label extension but subsequently amended to a 24-week double-blind extension, and as the study progressed was further changed to a 16-week double-blind extension. Thus, patients enrolled in the double-blind extension had different exposure times.

Also, the patient population for study 32a consisted of completers of Study 32 who chose to continue into the extension study. Of the 259 patients who completed Study SCT-MD-32, 202 chose to enroll in Study SCT-MD-32A; 165 of these patients continued into the double –blind treatment and received the same blinded study drug they were receiving in Study SCT-MD-32. Thus, treatment groups in Study 32a do not represent random samples of the screened patient population. Typically, to assess maintenance effect patients should be stabilized on the studied medication and then randomized to placebo and drug treatment groups before entering into maintenance phase.

Of the 202 patients who entered the extension study (165 double-blind, 37 open-label), approximately 50% (103/202) prematurely discontinued. The most common reason for premature discontinuation during the extension study was insufficient therapeutic response (35 patients [18 placebo, 16 escitalopram, 1 open-label escitalopram]). Overall, only 25.3% of patients in the placebo group and 23.4% of patients in the double-blind escitalopram group completed both studies SCT-MD-32 and SCT-MD-32A. For any trial with a very high dropout rate, it is always questionable whether the data can be interpretable.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Study SCD-MD-32

In the primary analysis of CDRS-R Total score, adolescent patients (12-17 years of age) with Major Depressive Disorder on escitalopram 10-20mg/d were observed to show statistically significant improvement over patients in the placebo treatment group.

Escitalopram group also showed statistically significant improvement relative to placebo in the CGI-I score. Whether the magnitude of the observed treatment difference is clinically relevant is deferred to the clinical review team.

Study SCD-MD-32a

In this reviewer's opinion, this trial does not provide interpretable evidence for the long-term efficacy (maintenance) claim.

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