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Study Report for Protocol No. SCT-MD-15

Title:	A Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Escitalopram in Pediatric Depression
Name of Study Drug:	Escitalopram
Indication:	Major Depressive Disorder
Study Phase:	III
Initiation Date:	December 09, 2002
Completion Date:	February 06, 2004

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

Report Date: December 03, 2004

FINAL

4.0 STUDY OBJECTIVE

The objective of this study was to evaluate the safety and efficacy of escitalopram in pediatric outpatients (6-17 years) diagnosed with major depressive disorder.

The CGAS was administered after 4 and 8 weeks of double-blind treatment. The following additional assessments were conducted at the final visit (end of Week 8 or early termination): a complete physical examination, comprehensive laboratory tests, and 12-lead ECG.

At each visit, patients returned previously dispensed bottles of double-blind study medication, and (except for the final visit) were dispensed new bottle(s) of double-blind study medication.

5.4.4 Premature Discontinuation

A premature discontinuation occurred when an enrolled patient ceased participation in the study, regardless of circumstances, prior to completion of the protocol. Drug treatment could be terminated for any of the following reasons, one of which was identified in the CRF as the primary reason for discontinuation.

- An adverse event
- An insufficient therapeutic response
- A protocol violation, including lack of compliance
- Withdrawal of consent
- The patient was "lost to follow-up"
- Other reasons, such as administrative reasons or pregnancy

All patients who prematurely discontinued from the study were to be seen for a final evaluation. Final evaluation was defined as completion of the evaluations scheduled for the final visit (end of Week 8). Patients who refused to appear for a final visit were requested in writing to return for a visit and to return all study medication.

5.5 EFFICACY MEASUREMENTS

The Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime (KSADS-PL), a semi-structured diagnostic interview, was performed at the screening visit only. The following efficacy evaluations were performed at the designated visits (see Panel 3).

Efficacy ratings were not to be administered if the patient was not accompanied by the identified parent or caregiver.

5.5.1 Children's Depression Rating Scale - Revised (CDRS-R)

The primary efficacy instrument was the Children's Depression Rating Scale – Revised (CDRS-R). The CDRS-R is a semi-structured, clinician-rated instrument designed for use with children and adolescents between the ages of 6 and 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 of ≥ 40 is consistent with a diagnosis of MDD (range: 17-113). The CDRS-R was assessed at each visit, and administered separately to the patient and to the identified parent or caregiver.

5.5.2 Clinical Global Impressions (CGI)

The CGI-Severity scale (CGI-S) was administered at baseline and all subsequent visits, including early termination. This scale rated the severity of the patient's current state of mental illness based on the Investigator's clinical opinion with regard to the pediatric patient population with MDD. The patient was rated on a scale from 1 to 7, with 1 being normal and 7 being a patient who was among the most severely ill.

The CGI-Improvement scale (CGI-I) was performed at all visits after the baseline visit, including early termination. Based on the Investigator's clinical opinion, this scale rated the total improvement or worsening in the patient's mental illness relative to his/her baseline condition, regardless of whether the Investigator considered it due to drug treatment or not. The patient was rated on a scale from 1 to 7 anchored at a score of 4 (no change), with 1 being very much improved and 7 being very much worse.

5.5.3 Children's Global Assessment Scale (CGAS)

The CGAS was completed at Baseline, at the end of Week 4, and at the end of Week 8 (or study termination) to evaluate overall functioning. This 100-point rating scale measured the psychological, social, and school functioning for children 6-17 years of age. The patient was rated from 1-100 on the basis of his/her general level of functioning over the previous 14 days, with 1-10 being "Needs Constant Supervision" and 91-100 being "Superior Functioning." It was adapted from the Adult Global Assessment Scale and is a valid and reliable tool for rating a child's general level of functioning on a health-illness continuum.

5.6 SAFETY MEASUREMENTS

Patients were seen by a physician at every visit and the evaluations documented. Evaluations of adverse events, laboratory tests, vital sign measurements and body weight, electrocardiograms, physical examinations, and concomitant medications were performed at the designated visits (see Panel 3).

The baseline score of efficacy parameters was summarized by treatment group for the ITT Population. Descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum) were presented for continuous variables and frequency distributions (count and percent) were presented for categorical variables.

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

6.3 EFFICACY ANALYSES

All efficacy analyses were based on the ITT Population. All statistical tests were two-sided hypothesis tests performed at the 5% level of significance. All confidence intervals were two-sided 95% confidence intervals.

Primary analyses were performed using the Last Observation Carried Forward (LOCF) approach. In these analyses, missing assessments at post-baseline visits were imputed using the last observed non-missing value immediately prior to the missing value. If the missing value occurred at Week 1, the baseline value was carried forward for Week 1, provided that at least one subsequent post-baseline assessment was available. The observed cases (OC) approach was used for supportive analyses, where only observed values were analyzed.

6.3.1 Primary Efficacy Analysis

The primary efficacy parameter was the change from Baseline (Visit 2) to Week 8 in CDRS-R score. Comparison between-treatment groups was performed using a two-way analysis of covariance (ANCOVA) model with treatment group and study center as factors and baseline score as the covariate.

6.3.2 Secondary Efficacy Analyses

The secondary efficacy parameters were:

- CGI-I score at Week 8,
- Change from Baseline (Visit 2) to Week 8 in the CGI-S score, and
- Change from Baseline (Visit 2) to Week 8 in the CGAS score.

The secondary efficacy parameters were analyzed using the same ANCOVA model as described for the primary efficacy parameter. For CGI-I, which records improvement relative to Baseline, the baseline CGI-S score was used as the covariate.

6.3.3 Additional Efficacy Analyses

Additional efficacy parameters were:

- CDRS-R response rate (CDRS-R $\leq$ 28) at Week 8, and
- CGI-I response rate (CGI-I $\leq$ 2) at Week 8.

The response rates were analyzed using logistic regression with treatment group as an explanatory variable. For CDRS-R responder analysis, Baseline (Visit 2) CDRS-R score was also included as an explanatory variable. For CGI-I responder analysis, Baseline (Visit 2) CGI-S score was also included as an explanatory variable. By visit analyses were also performed using the LOCF and observed case (OC) approaches.

6.3.4 Descriptive Statistics

Descriptive statistics (n, mean, SD, SEM, median, minimum, and maximum) were presented for all efficacy parameters by treatment group, age group, and visit. Changes from baseline were also summarized. CGI-I and CDRS-R were summarized both as categorical and continuous variables.

6.4 SAFETY

The safety analysis was performed using the Safety Population.

6.4.1 Extent of Exposure

Extent of exposure to double-blind study medication was presented in terms of treatment duration (days), mean daily dose, dose distribution, and patient years. Mean daily dose and duration of treatment were summarized by treatment group and age group.

6.4.2 Adverse Events

All adverse events were coded using the World Health Organization Adverse Reaction Terminology (WHOART) Dictionary, Version 1998/04.

13.0 CONCLUSIONS

This study failed to demonstrate the effectiveness of escitalopram 10-20 mg/day relative to placebo with respect to the primary endpoint, change from Baseline to Week 8 in CDRS-R score using the LOCF approach. However, a trend toward significance was noted in two secondary efficacy parameters, CGI-S and CGAS. Escitalopram (10-20 mg/day) was well tolerated in pediatric patients (6-17 years).

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Table 3.1
Primary Efficacy
Change from Baseline in CDRS-R at Week 8 - LOCF
ITT Population

	Placebo (N=132)	Escitalopram (N=129)	LSMD [95% CI]	P-value
Baseline				
Mean	56.6	54.5		
SD	10.14	10.67		
SEM	0.88	0.94		
Median	55.0	53.1		
Min, Max	40.0, 82.0	40.0, 86.0		
n	132	129		
Week 8				
Mean	36.4	33.6		
SD	14.81	14.44		
SEM	1.29	1.27		
Median	34.0	31.0		
Min, Max	17.0, 81.0	17.0, 81.0		
n	132	129		
Week 8 - Baseline				
Mean	-20.3	-20.9	-1.73 [-5.08, 1.62]	0.310
SD	15.35	14.70		
SEM	1.34	1.29		
Median	-21.5	-21.0		
Min, Max	-54.0, 21.0	-57.0, 38.0		
n	132	129		

Note: P-value is from ANCOVA model with treatment group and study center as factors and baseline score as covariate.
'LSMD' indicates the difference in least squares mean. CI = Confidence Interval.
n = Number of patients within a specific category.

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Table 3.2
Secondary Efficacy
CGI Improvement at Week 8 - LOCF
ITT Population

	Placebo (N=132)	Escitalopram (N=129)	LSMD [95% CI]	P-value
Week 8				
Mean	2.6	2.3	-0.22 [-0.52, 0.09]	0.169
SD	1.27	1.26		
SEM	0.11	0.11		
Median	2.0	2.0		
Min, Max	1.0, 6.0	1.0, 6.0		
n	132	129		

Note: P-value is from ANCOVA model with treatment group and study center as factors and baseline CGI-S score as covariate.
'LSMD' indicates the difference in least squares mean. CI = Confidence Interval.
n = Number of patients within a specific category.

Table 3.3
Secondary Efficacy
Change from Baseline in CGI Severity at Week 8 - LOCF
ITT Population

	Placebo (N=132)	Escitalopram (N=129)	LSMD [95% CI]	P-value
Baseline				
Mean	4.4	4.2		
SD	0.63	0.57		
SEM	0.05	0.05		
Median	4.0	4.0		
Min, Max	3.0, 6.0	3.0, 6.0		
n	132	129		
Week 8				
Mean	3.0	2.7		
SD	1.31	1.23		
SEM	0.11	0.11		
Median	3.0	3.0		
Min, Max	1.0, 6.0	1.0, 6.0		
n	132	129		
Week 8 - Baseline				
Mean	-1.3	-1.5	-0.29 [-0.59, 0.01]	0.057
SD	1.26	1.27		
SEM	0.11	0.11		
Median	-1.0	-2.0		
Min, Max	-5.0, 2.0	-4.0, 2.0		
n	132	129		

Note: P-value is from ANCOVA model with treatment group and study center as factors and baseline score as covariate.
'LSMD' indicates the difference in least squares mean. CI = Confidence Interval.
n = Number of patients within a specific category.

Table 3.4
Secondary Efficacy
Change from Baseline in CGAS at Week 8 - LOCF
ITT Population

	Placebo (N=132)	Escitalopram (N=129)	LSMD [95% CI]	P-value
Baseline				
Mean	51.9	52.9		
SD	6.04	7.12		
SEM	0.53	0.63		
Median	51.0	52.0		
Min, Max	40.0, 70.0	31.0, 80.0		
n	132	129		
Week 8				
Mean	64.7	68.3		
SD	13.71	13.82		
SEM	1.23	1.26		
Median	65.0	70.0		
Min, Max	31.0, 90.0	31.0, 97.0		
n	125	120		
Week 8 - Baseline				
Mean	12.9	15.3	2.86 [-0.18, 5.90]	0.065
SD	12.91	12.56		
SEM	1.15	1.15		
Median	10.0	15.0		
Min, Max	-14.0, 42.0	-9.0, 44.0		
n	125	120		

Note: P-value is from ANCOVA model with treatment group and study center as factors and baseline score as covariate.
'LSMD' indicates the difference in least squares mean. CI = Confidence Interval.
n = Number of patients within a specific category.

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Table 3.5
Additional Efficacy
Analysis of CDRS-R Response Rate at Week 8 - LOCF
ITT Population

	Placebo (N=132)	Escitalopram (N=129)	P-value
Week 8			
Responder	50/132 (37.9)	59/129 (45.7)	0.317
Nonresponder	82/132 (62.1)	70/129 (54.3)	

Note: P-value is from logistic regression with treatment group as the factor and baseline CDRS-R as covariate.
The responder is defined as CDRS-R score <= 28.

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Table 3.6
Additional Efficacy
Analysis of CGI-I Response Rate at Week 8 - LOCF
ITT Population

	Placebo (N=132)	Escitalopram (N=129)	p-value
Week 8			
Responder	69/132 (52.3)	81/129 (62.8)	0.144
Nonresponder	63/132 (47.7)	48/129 (37.2)	

Note: P-value is from logistic regression with treatment group as the factor and baseline CGI-S as covariate.
The responder is defined as CGI-I score <= 2.

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Table VI.7A
Change from Baseline in CDRS-R by Age Group and Visit - LOCF
ITT Population

	Children (6-11 years)		Esc vs. Plb		Adolescents (12-17 years)		Esc vs. Plb	
	Placebo (N=52)	Escitalopram (N=52)	LSMD	p-value	Placebo (N=80)	Escitalopram (N=77)	LSMD	p-value
Baseline								
Mean	55.8	53.2			57.2	55.4		
SD	8.81	10.62			10.94	10.67		
SEM	1.22	1.47			1.22	1.22		
Median	53.5	50.0			55.5	54.0		
Min, Max	40.0, 76.0	40.0, 86.0			40.0, 82.0	40.0, 83.0		
n	52	52			80	77		
Week 1 - Baseline								
Mean	-11.1	-12.4	-2.04	0.301	-7.7	-9.4	-2.00	0.213
SD	11.64	10.65			8.23	10.43		
SEM	1.61	1.48			0.92	1.19		
Median	-10.0	-10.5			-7.0	-10.0		
Min, Max	-37.0, 23.0	-47.0, 3.0			-28.0, 14.0	-48.0, 16.0		
n	52	52			80	77		
Week 2 - Baseline								
Mean	-18.2	-16.6	0.392	0.861	-12.9	-16.0	-3.63	0.045
SD	12.91	11.35			10.51	13.28		
SEM	1.79	1.57			1.18	1.51		
Median	-17.0	-15.0			-12.5	-17.0		
Min, Max	-44.0, 10.7	-45.0, 5.0			-36.0, 12.0	-52.0, 14.0		
n	52	52			80	77		

Note: n = Number of patients within a specific category.
'LSMD' indicates the difference in least squares mean.
P-value is from ANCOVA model with treatment group, age type, and study center as factors and baseline score as covariate.

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Table VI.7A
Change from Baseline in CDRS-R by Age Group and Visit - LOCF
ITT Population

	Children (6-11 years)		Esc vs. Plb		Adolescents (12-17 years)		Esc vs. Plb	
	Placebo (N=52)	Escitalopram (N=52)	LSMD	p-value	Placebo (N=80)	Escitalopram (N=77)	LSMD	p-value
Week 4 - Baseline								
Mean	-19.9	-19.5	-0.78	0.744	-14.9	-16.0	-1.98	0.310
SD	14.06	12.08			12.65	14.93		
SEM	1.95	1.68			1.41	1.70		
Median	-19.0	-19.5			-14.0	-17.0		
Min, Max	-52.0, 15.0	-55.0, 0.0			-42.0, 27.0	-50.0, 38.0		
n	52	52			80	77		
Week 6 - Baseline								
Mean	-21.9	-20.3	0.100	0.968	-16.3	-18.4	-2.87	0.157
SD	13.38	13.37			13.44	15.32		
SEM	1.86	1.85			1.50	1.75		
Median	-22.5	-19.0			-15.5	-19.0		
Min, Max	-43.0, 7.0	-56.0, 20.0			-45.0, 13.0	-51.0, 38.0		
n	52	52			80	77		
Week 8 - Baseline								
Mean	-23.8	-22.3	-0.42	0.875	-18.0	-19.9	-2.63	0.233
SD	14.38	14.13			15.62	15.08		
SEM	1.99	1.96			1.75	1.72		
Median	-23.5	-21.0			-18.0	-22.0		
Min, Max	-49.0, 18.0	-57.0, 14.0			-54.0, 21.0	-51.0, 38.0		
n	52	52			80	77		

Note: n = Number of patients within a specific category.
'LSMD' indicates the difference in least squares mean.
P-value is from ANCOVA model with treatment group, age type, and study center as factors and baseline score as covariate.

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