

**Table VI.A.1., continued. List of Investigators of Study MD-03**

<i>Center No.</i>	<i>Investigator</i>	<i>Center Address</i>
112	Robert Golden, MD	Department of Psychiatry The University of North Carolina at Chapel Hill School of Medicine/Medical School Building, Wing B 101 Manning Drive, Room 224 Chapel Hill, NC 27599-7160
113	Peter Holland, MD	Boca Raton Medical Research, Inc. 7284 West Palmetto Park Road Suite 205 Boca Raton, FL 33433
114	Lorin Koran, MD	Stratford Medical Center Department of Psychiatry OCD Clinic- Room 2363 401 Quarry Road Stanford, CA 94305
115	Susan Kornstein, MD	Virginia Commonwealth University Mood Disorder Institute 700 West Grace Street - Suite 303 Richmond, VA 23220
116	Michael Lesem, MD	Claghorn-Lesem Research 6750 West Loop South Suite 1050 Bellaire, TX 77401
117	Michael Liebowitz, MD	The Medical Research Network LLC 123 West 79th Street New York, NY 10024
118	Mark Rapaport, MD	University of California, San Diego Department of Psychiatry - Suite 2243 8950 Villa La Jolla Drive La Jolla, CA 92037
119	Jeffrey Rausch, MD	Medical College of Georgia Outpatients Psychiatry 1515 Pope Avenue Augusta, GA 30912
120	Robert Riesenber, MD	Atlanta Center for Medical Research 811 Juniper Street Decatur, GA 30308
121	Stephen Stahl, MD	Clinical Neuroscience Research Center 8899 University Center Lane (closed on Fridays) Suite 130 San Diego, CA 92122
122	Kathleen Toups, MD	3704 Mt. Diablo Boulevard Suite 200 Lafayette, CA 94549
123	Lynn Crismon, PharmD	Center for Clinical Research-Austin 12221 North MoPac Expressway Austin, TX 78758

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**Table VI.A.1., continued. List of Investigators of Study MD-03**

<i>Center No.</i>	<i>Investigator</i>	<i>Center Address</i>
124	Bijan Bastani, MD	North Coast Clinical Trials One Commerce Park Square 23210 Chagrin Boulevard, Suite-300 Beachwood, OH 44122
126	Alan Jacobson, PhD	Administrative Office, Contracts: Allied Clinical Trials, Inc. 1385 NW 15th Street Miami, FL 33125
127	Dan Zimbroff, MD	Pacific Clinical Research Suite 150 560 E. Hospitality Lane San Bernardino, CA 92408
128	Charles Merideth, MD	Affiliated Research Institute 8880 Rio San Diego Drive Suite 1090 San Diego, CA 92108
129	John P. Docherty, MD	Comprehensive NeuroScience, Inc. 21 Bloomingdale Road White Plains, NY 10605
130	Jeffrey Danziger, MD	ICSL - Clinical Studies 597 Maitland Avenue Altamonte Springs, FL 32701
131	Louis Kirby, MD	Pivotal Research Centers 13128 N. 94th Drive Suite 200 Peoria, AZ 85381
132	Howard Hassman, DO	Comprehensive Clinical Research 160 S. White Horse Pike 2nd Floor Berlin, NJ 08009  130 White Horse Pike (as of 3/1/01) Clementon, NJ 08021
133	Evangelos Coskinas, MD	Affiliated Research Institute 801 N. Tustin Avenue Suite 600 Santa Ana, CA 92705
134	Mohammed Bari, MD	Synergy Clinical Research 450 Fourth Avenue Suite 409 Chula Vista, CA 91910
135	Martin Scharf, PhD	Center for Research in Sleep Disorders 1275 East Kemper Road Cincinnati, OH 45246
201	Jay Amsterdam, MD	University of Pennsylvania Depression Research Unit - 8th Floor 3600 Market Street Philadelphia, PA 19104-2649

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**Table VI.A.1., continued. List of Investigators of Study MD-03**

<i>Center No.</i>	<i>Investigator</i>	<i>Center Address</i>
202	James Barbee, MD	LSU Touro Anxiety Clinic & Mood Disorders Clinic/R-115 1401 Foucher Street Gumble Building, Room 312 New Orleans, LA 70115
203	Robert J. Bielski, MD	Summitt Research Network, Inc./Michigan Division Institute for Health Studies 4084 Okemos Road, Suite A Okemos, MI 48864
204	Joseph Calabrese, MD	University Hopsitals of Cleveland Mood Disorders Program 11400 Euclid Avenue, Suite 200 Cleveland, OH 44106
206	William S. Gilmer, MD	Northwestern University Department of Psychiatry 675 North St. Claire, Suite 20-250 Chicago, IL 60611
207	Susanna Goldstein, MD	Medical & Behavioral Health Research, P.C. 65 Central Park West, 1BR New York, NY 10023
209	Anita Kablinger, MD	Attention: Barbara Rogerro LSU Medical Center Shreveport Psychopharmacology Research Clinic Department of Psychiatry, Room 3-412/1501 Kings Highway Shreveport, LA 71130
210	Peter Londborg, MD	Seattle Clinical Research Center, Inc. 901 Boren Avenue Cabrini Medical Tower - Suite 1800 Seattle, WA 98104
211	Bruce Lydiard, MD	Medical University of South Carolina Department of Psychiatry - P.O. Box 250861 67 President Street Charleston, SC 29425
212	Jeffrey E. Kelsey, MD, PhD	Emory University Department of Psychiatry & Behavioral Sciences 1841 Clifton Road NE, 4th Floor Atlanta, GA 30329
213	William Patterson, MD	Birmingham Research Group, Inc. 2120 Lynngate Drive Birmingham, AL 35216
214	Nunzio Pomara, MD	Nathan S. Kline Institute Division of Geriatric Psychiatry 140 Old Orangeburg Road, Building 35 Orangeburg, NY 10962

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**Table VI.A.1., List of Investigators of Study MD-03**

<i>Center No.</i>	<i>Investigator</i>	<i>Center Address</i>
216	David R. Serota, MD	Jefferson Medical College Department of Psychiatry & Human Behavior 833 Chestnut Street Suite 210-E Philadelphia, PA 19107-4415
217	Jeffrey Simon, MD	Northbrooke Research Center 9275 North 49th Street Suite 200 Brown Deer, WI 53223
218	Ward Smith, MD	Summit Research Oregon Division 1849 N.W. Kearney Suite 201 Portland, OR 97209
219	Madhukar Trivedi, MD	University of Texas Southwestern Medical School St. Paul Professional Building #1, Suite 520 5959 Harry Hines Boulevard Dallas, TX 75235-9101
220	Ken Weiss, MD	Delaware Valley Research Associates, Inc. 922 Fayette Street Conshohocken, PA 19428
221	John Franklin Heiser, MD	Pharmaceutical Research Institute 1000 Dove Street, Suite 200 Newport Beach, CA 92660-2814
222	John Carman, MD	4015 S. Cobb Drive Suite 245 Smyrna, GA 30080
136 and 215*	Murray H. Rosenthal, DO	Behavioral and Medical Research, LLC 3625 Ruffin Road Suite 100 San Diego, CA 92123

\* Two center numbers assigned because patients from both studies participated:  
1 patient from Study SCT-MD-01 and 17 patients from SCT-MD-02.

**Notes:**

Center numbers starting with "1" signify patients who participated in SCT-MD-01; center numbers starting with "2" signify patients who participated in SCT-MD-02.

Centers 125 and 208 did not participate in this study.

Highlight indicates site received study drug but enrolled no patients

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**Table VI.E.1. Study Flow Chart**

Visit Name	Baseline*	Open-Label: End of Week						Double-Blind Treatment: End of Week									
		1	2	4	6	8	10	12	16	20	24	28	32	36	40	44**	
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Assessment																	
Informed Consent	x																
Inclusion/Exclusion	x																
Physical Exam	x															x	
Laboratory Tests	x				x					x						x	
Urine Drug Screen	x				x											x	
Pregnancy Test	x				x											x	
ECG	x				x											x	
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
MADRS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
HAMD	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
CGI	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
HAMA	x			x		x	x									x	
CES-D	x					x										x	
DSM-IV Checklist						x										x	
Quality of Life Questionnaire	x					x										x	
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x***	
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Drug Dispensed/Returned	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Final Evaluation																x	

\* Final visit of the lead-in study.  
 \*\* Or when the patient discontinued prior to Week 44.  
 \*\*\* Clinical findings upon termination were followed until the condition returned to pretrial status or could be explained as unrelated to study drug.

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**Table VI.G.1. (as provided by the sponsor)**

Reasons for Discontinuation at the End of Week 8  
Open-Label Phase  
Safety Population

	Treatment Group in the Lead-in Studies			Total (N=504) n (%)
	Placebo (N=146) n (%)	Escitalopram (N=220) n (%)	Citalopram (N=138) n (%)	
Completed* Open-Label Phase	102 ( 69.9)	176 ( 80.0)	99 ( 71.7)	377 ( 74.8)
Randomized to Double-Blind Phase	77 ( 52.7)	127 ( 57.7)	72 ( 52.2)	276 ( 54.8)
Withdrawn at End of Week 8	25 ( 17.1)	49 ( 22.3)	27 ( 19.6)	101 ( 20.0)
Reason for Withdrawal				
Adverse event	1 ( 0.7)	2 ( 0.9)	1 ( 0.7)	4 ( 0.8)
Insufficient therapeutic response	0	0	0	0
Protocol violation	0	1 ( 0.5)	1 ( 0.7)	2 ( 0.4)
Withdrawal of consent	1 ( 0.7)	5 ( 2.3)	3 ( 2.2)	9 ( 1.8)
Lost to follow-up	1 ( 0.7)	0	0	1 ( 0.2)
Other reasons	0	1 ( 0.5)	1 ( 0.7)	2 ( 0.4)
Ineligible to continue	22 ( 15.1)	40 ( 18.2)	21 ( 15.2)	83 ( 16.5)

Note: N = Number of treated patients.  
n = Number of patients within a specific category.  
\* Patients who completed 8 weeks of treatment and had an end of week 8 assessment.

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Supporting Listing(s): Listing 1

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**Table VI.H.1.**

**Panel 9. Demographic Characteristics**

<i>Characteristic</i>		<i>Open-Label</i>	<i>Double-Blind</i>		<i>Long-Term</i>	
		<i>Escitalopram (N = 504)</i>	<i>Placebo (N = 93)</i>	<i>Escitalopram (N = 181)</i>	<i>Escitalopram &gt; 8 Weeks (N = 181)</i>	<i>Escitalopram &gt; 16 Weeks (N = 76)</i>
<b>Age (years)</b>	Mean (SD)	42 (11.9)	42 (11.9)	43 (11.6)	43 (11.6)	43 (12.7)
	Min, Max	18, 76	18, 69	18, 73	18, 73	19, 73
<b>Sex n (%)</b>	Female	312 (61.9%)	58 (62.4%)	109 (60.2%)	109 (60.2%)	46 (60.5%)
	Male	192 (38.1%)	35 (37.6%)	72 (39.8%)	72 (39.8%)	30 (39.5%)
<b>Race n (%)</b>	Caucasian	429 (85.1%)	79 (84.9%)	157 (86.7%)	157 (86.7%)	70 (92.1%)
	Noncaucasian	75 (14.9%)	14 (15.1%)	24 (13.3%)	24 (13.3%)	6 (7.9%)
<b>Weight (lbs)</b>	Mean (SD)	179.8 (46.6)	184.2 (43.1)	180.2 (48.6)	180.2 (48.6)	173.2 (37.5)
	Min, Max	95.0, 415.0	106.0, 309.0	95.0, 415.0	95.0, 415.0	109.0, 296.5

Percentages are relative to number of patients (N) in the safety population for each phase.  
 Cross-reference: Tables 2.1A, 2.1B and 2.1C, and Appendix IX, Listing 2.

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**Table VI.H.2. (as provided by the sponsor)**

**Panel 10. Efficacy Variables at Baseline by Lead-In Study Treatment Group, Open-Label Phase (Mean ± SEM)**

<i>Efficacy Parameter</i>	<i>Lead-In Study Treatment Group</i>			<i>Total (N=502)</i>
	<i>Placebo (N=145)</i>	<i>Escitalopram (N=219)</i>	<i>Citalopram (N=138)</i>	
MADRS	17.4 ± 0.8	13.8 ± 0.6	14.0 ± 0.9	14.9 ± 0.4
HAMD	15.7 ± 0.7	12.9 ± 0.5	12.8 ± 0.7	13.7 ± 0.4
CGI-S	3.2 ± 0.1	2.7 ± 0.1	2.7 ± 0.1	2.8 ± 0.1

Open-Label ITT population

Cross-reference: Tables 2.3A and Appendix IX, Listings 8 and 9.

**Panel 12. Efficacy Variables at Baseline, Double-Blind Phase (Mean ± SEM)**

<i>Efficacy Parameter</i>	<i>Placebo (N=93)</i>	<i>Escitalopram (N=181)</i>
MADRS	6.2 ± 0.4	7.2 ± 0.3
HAMD	6.6 ± 0.5	7.7 ± 0.3
CGI-S	1.7 ± 0.1	1.8 ± 0.1

Double-Blind ITT population

Cross-reference: Table 2.3B and Appendix IX, Listings 8 and 9.

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**Table VI.H.3. (as provided by the sponsor)**

**Panel 11. Change From Baseline at Endpoint, Open-Label Phase  
(Mean ±SEM)**

<i>Efficacy Parameter</i>	<i>Lead-In Study Treatment Group</i>			<i>Total (N=502)</i>
	<i>Placebo (N=145)</i>	<i>Escitalopram (N=219)</i>	<i>Citalopram (N=138)</i>	
MADRS	-5.5 ± 0.9	-3.2 ± 0.6	-2.9 ± 0.7	-3.8 ± 0.4
HAMD	-4.6 ± 0.8	-2.7 ± 0.5	-2.3 ± 0.7	-3.1 ± 0.4
CGI-S	-0.7 ± 0.1	-0.4 ± 0.1	-0.4 ± 0.1	-0.5 ± 0.1

Open-Label ITT population; LOCF values

Cross-reference: Table 4.8A, 4.9A, and 4.11A, and Appendix IX, Listings 8 and 9.

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Table VI.I.1.

Relapse Rate by visit (LOCF)  
 Double-Blind Phase  
 Intent-to-Treat Population

	Placebo (N=93) n (%)	Escitalopram (N=181) n (%)	Escitalopram vs. Placebo P-value
<b>Week 10</b>			
Relapse	12 ( 11.8)	10 ( 5.5)	0.064
No Relapse	82 ( 88.2)	171 ( 94.5)	
<b>Week 12</b>			
Relapse	19 ( 20.4)	15 ( 8.3)	0.004
No Relapse	74 ( 79.6)	166 ( 91.7)	
<b>Week 16</b>			
Relapse	23 ( 24.7)	25 ( 13.8)	0.025
No Relapse	70 ( 75.3)	156 ( 86.2)	
<b>Week 20</b>			
Relapse	27 ( 29.0)	28 ( 15.5)	0.008
No Relapse	66 ( 71.0)	153 ( 84.5)	
<b>Week 24</b>			
Relapse	28 ( 30.1)	32 ( 17.7)	0.019
No Relapse	65 ( 69.9)	149 ( 82.3)	
<b>Week 28</b>			
Relapse	28 ( 30.1)	35 ( 19.3)	0.045
No Relapse	65 ( 69.9)	146 ( 80.7)	
<b>Week 32</b>			
Relapse	29 ( 31.2)	37 ( 20.4)	0.049
No Relapse	64 ( 68.8)	144 ( 79.6)	

Note: P-values are based on Mantel-Haenszel Chi-Square test.

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 Supporting listing(s): Listing 1 and Listing 6

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Table VI.I.1., continued.

Relapse Rate by visit (LOCF) Double-Blind Phase Intent-to-Treat Population			
	Placebo (N=93) n (%)	Escitalopram (N=181) n (%)	Escitalopram vs. Placebo P-value
Week 16			
Relapse	31 ( 33.3)	41 ( 22.7)	0.058
No Relapse	62 ( 66.7)	140 ( 77.3)	
Week 40			
Relapse	31 ( 33.3)	41 ( 22.7)	0.058
No Relapse	62 ( 66.7)	140 ( 77.3)	
Week 44			
Relapse	31 ( 33.3)	41 ( 22.7)	0.058
No Relapse	62 ( 66.7)	140 ( 77.3)	

Note: P-values are based on Mantel-Haenszel Chi-Square test.

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Supporting Listing(s): Listing 1 and Listing 8

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Table VII.2.

Relapse Rate by visit (OC)  
Double-Blind Phase  
Intent-to-Treat Population

	Placebo (N=93) n (%)	Escitalopram (N=181) n (%)	Escitalopram vs. Placebo P-value
Week 10			
Relapse	11 ( 11.8)	10 ( 5.5)	0.064
No Relapse	82 ( 88.2)	171 ( 94.5)	
Week 12			
Relapse	8 ( 10.4)	5 ( 3.1)	0.022
No Relapse	69 ( 89.6)	155 ( 96.9)	
Week 16			
Relapse	4 ( 6.6)	10 ( 6.6)	0.995
No Relapse	57 ( 93.4)	142 ( 93.4)	
Week 20			
Relapse	4 ( 8.3)	3 ( 2.2)	0.060
No Relapse	44 ( 91.7)	131 ( 97.8)	
Week 24			
Relapse	1 ( 2.3)	4 ( 3.3)	0.739
No Relapse	43 ( 97.7)	118 ( 96.7)	
Week 28			
Relapse	0	3 ( 2.7)	0.306
No Relapse	39 (100.0)	110 ( 97.3)	
Week 32			
Relapse	1 ( 2.6)	2 ( 1.9)	0.777
No Relapse	37 ( 97.4)	105 ( 98.1)	
Week 36			
Relapse	2 ( 5.7)	4 ( 3.9)	0.656
No Relapse	33 ( 94.3)	98 ( 96.1)	
Week 40			
Relapse	0	0	
No Relapse	32 (100.0)	95 (100.0)	
Week 44			
Relapse	0	0	
No Relapse	32 (100.0)	91 (100.0)	

Note: P-values are based on Mantel-Haenszel Chi-Square test.

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Supporting listing(s): Listing 1 and Listing 8

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**Table VI.L3.**

**Panel 14. Change from Baseline at Endpoint, Double-Blind Phase  
(Mean ± SEM)**

		<i>Placebo</i>		<i>Escitalopram</i>	
		<i>N</i>	<i>Mean Change</i>	<i>N</i>	<i>Mean Change</i>
MADRS	LOCF	92	6.7 ± 1.0	181	3.2 ± 0.7 *
	OC	32	0.7 ± 0.7	92	- 1.4 ± 0.5 *
HAMD	LOCF	92	5.7 ± 0.9	181	2.8 ± 0.6 *
	OC	32	0.8 ± 0.7	92	- 1.6 ± 0.5 *
CGI-S	LOCF	92	0.8 ± 0.1	181	0.4 ± 0.1
	OC	32	0.1 ± 0.1	92	- 0.3 ± 0.1*

\*p<0.05; p-value is based on the ANCOVA (additive model) with treatment and center as effects and baseline score as covariate.

\*Values at endpoint.

Double-Blind ITT population

Cross-reference: Tables 4.1A, 4.1B, 4.2A, 4.2B, 4.4A and 4.4B, and Appendix IX, Listings 8 and 9.

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**Table VII.E.1**

**Panel 15. List of Patients with Serious Adverse Events**

<i>Treatment/ Patient Number</i>	<i>Age (yrs)</i>	<i>Sex</i>	<i>SAE Start Day<sup>a</sup></i>	<i>Preferred Term</i>
<b>OPEN-LABEL PHASE: ESCITALOPRAM TREATMENT</b>				
1125	60	F	126	Breast Neoplasm
1306	26	F	15 15	Migraine* Paresthesia*
2172	33	F	12 15 15 16	Alcohol Abuse Depression* Suicide Attempt* Anxiety
2325	69	F	24	Bladder Carcinoma*
2374	53	M	46 46 46	Gastric Ulcer Syncope Inflicted Injury
<b>DOUBLE-BLIND PHASE: PLACEBO TREATMENT</b>				
2229	22	M	232	Pharyngitis
<b>DOUBLE-BLIND PHASE: ESCITALOPRAM TREATMENT</b>				
1234	44	F	190 190	Abdominal Pain Appendicitis
2101	24	M	228	Tonsillitis
2307	44	F	70	Uterine Hemorrhage

a: SAE Start Day = SAE Start Date – Date of First Dose of Study Medication in Respective Phase + 1.

\*Study drug discontinued because of this event.

Cross-reference: Table 7.1. Patient 1125 is not included in Table 7.1, as the SAE was reported approximately 2 months after the last dose of study medication, and is not included in the clinical database.

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**Table VII.F.1.**

**Panel 16. List of Patients who Discontinued due to Adverse Events**

<i>Treatment/ Patient Number</i>	<i>Age (yrs)</i>	<i>Sex</i>	<i>AE Start Day<sup>a</sup></i>	<i>AE (Preferred Term)</i>
<b>OPEN-LABEL PHASE: ESCITALOPRAM TREATMENT</b>				
1018	44	F	-28	Libido Decreased
1065	33	F	2	Headache
			28	Chest Tightness
			28	Agitation
			28	Insomnia
1094	40	F	-8	Fatigue
			7	Somnolence
			10	Weight Increase
			17	Restlessness Aggravated
			45	Palpitation
			45	Arthralgia
1106	52	F	1	Insomnia
			2	Decreased Appetite
			2	Urinary Frequency
			3	Palpitation
			4	Vasodilation
			4	Jitteriness
1108	38	F	10	Chest Pain
1122	57	M	10	Increased Sweating
			10	Faintness
			10	Paresthesia
			10	Anxiety
1138	45	M	42	ECG Abnormal
1140	51	M	14	Sleep Disorder

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Table VII.F.1., continued.

Panel 16. List of Patients who Discontinued due to Adverse Events

Treatment/ Patient Number	Age (yrs)	Sex	AE Start Day <sup>a</sup>	AE (Preferred Term)
1141	50	F	-2	Anorgasmia
1303	23	F	-63	Weight Increase
1306	26	F	15	Migraine*
			15	Paresthesia*
1311	57	M	43	Atrial Arrhythmia
1391	58	F	31	Fatigue
1408	45	F	10	Mitral Valve Prolapse
			11	Anxiety
			11	Insomnia
2029	41	F	-30	Weight Increase
2046	42	M	2	Palpitation
			2	Anxiety
			2	Bruxism
			2	Insomnia
			4	Tremulousness Nervous
2071	40	M	51	Hepatic Enzymes Increased
2083	35	F	41	Hypertension
2116	62	F	29	Diarrhea
2133	56	F	1	Weight Increase
2142	47	M	15	Rash
2172	33	F	15	Depression*
			15	Suicide Attempt*
2176	25	F	32	Nausea
2181	42	F	30	Somnolence

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Table VII.F.1., continued.

Panel 16. List of Patients who Discontinued due to Adverse Events

<i>Treatment/ Patient Number</i>	<i>Age (yrs)</i>	<i>Sex</i>	<i>AE Start Day<sup>a</sup></i>	<i>AE (Preferred Term)</i>
2184	45	M	1	Asthenia
			1	Headache
			1	Shaking
			1	Constipation
			1	Nausea
			1	Insomnia
			1	Visual Disturbance
2187	33	M	2	Headache
			2	Pain Neck / Shoulder
			2	Lethargy
			3	Chills
			3	Nausea
			4	Chest Pain
			6	Vomiting
2198	51	F	1	Fatigue
			1	Headache
			1	Nausea
			1	Jitteriness
2201	51	M	22	Somnolence
2254	48	F	-2	Nodal Arrhythmia
2299	44	M	41	Syncope
2306	24	F	4	Dizziness
			4	Somnolence
2345	24	F	1	Bradycardia
2374	53	M	30	Aggravated Depression

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Table VII.F.1., continued.

Panel 16. List of Patients who Discontinued due to Adverse Events

Treatment/ Patient Number	Age (yrs)	Sex	AE Start Day <sup>a</sup>	AE (Preferred Term)
<b>DOUBLE-BLIND PHASE: PLACEBO TREATMENT</b>				
1103	47	M	15	Anxiety
			15	Irritability
1233	62	F	-27	Headache
1559	34	F	2	Increased Appetite
			3	Fatigue
			3	Insomnia
			3	Irritability
2157	33	F	2	Dizziness
2217	38	M	-6	Light-Headed Feeling
			14	Tinnitus
2325	69	F	-35	Bladder Carcinoma*
<b>DOUBLE-BLIND PHASE: ESCITALOPRAM TREATMENT</b>				
1334	45	F	68	Edema
			68	Weight Increase
1542	57	F	19	Palpitation
			19	Abnormal Crying
			19	Insomnia
2005	44	F	-126	Weight Increase
			-119	Libido Decreased
2136	29	M	2	Abdominal Pain
2249	54	F	174	Dizziness
			174	Scotoma
2356	73	M	144	Libido Decreased
2425	40	F	52	Apathy

<sup>a</sup>AE Start Day = AE Start Date – Date of First Dose of Study Medication in Respective Phase + 1.

\* The event was classified as an SAE.

Cross-reference: Tables 7.3A and 7.3B.

## **Table VII.F.2.**

### **Selected Adverse Dropouts.**

**S1138 discontinued** open label SCT treatment (had received 58 days of citalopram in the lead-in study and 57 days of open label SCT) **due to an abnormal ECG** on 2/29/00 (the day the drug was discontinued) which was first detected on 2/14/00. ECG results of this 45 y.o. male showed **“abnormal left axis deviation and left anterior fascicular block.”** This result was also found on a repeat ECG at the terminal visit on 3/4/00 and was interpreted by the physician as being due to “high lateral or inferior myocardial or pericardial damage.” This information, as provided in the narrative is insufficient to determine if whether or not this event was drug-related. The gender and possibly the age of the S are associated with an increase risk for cardiac disease. The S was reported as having no concomitant medications, so otherwise he appeared to be in good health. There were no other signs or symptoms described in the narrative. The sponsor has added “abnormal ECG” as an infrequent event under the “Other Events Observed During the Premarketing Evaluation...” section of proposed labeling. Further information regarding this S is also being requested from the sponsor.

**S 1311 discontinued** open label SCT treatment (55 days on 10 mg/day SCT in the lead-in study, which was continued, as open label drug, for 44 days) **due to atrial arrhythmia revealed on ECG** (“multiple atrial premature complexes”) obtained on 6/26/00. His ECG on 5/15/00 was normal, when he started the open-label phase of MD-03 (note he had received 55 days of double-blind SCT in the lead-in study and treatment on the same dose was continued as open label drug without interruption between studies). His ECG was also normal in a follow-up ECG after cessation of treatment on 7/10/00 (his abnormal ECG was on 6/26/00 with the stop date of 6/27/00 of the study drug). It is not clear if whether or not this event was drug related since the abnormal ECG appeared to be intermittent in a 57 year old male (risk factors for cardiac disease) and the S was not reported in the narrative as having associated symptoms. Nevertheless, abnormal ECG is listed under the “Other Events...” section of proposed labeling.

**S 2254 discontinued** open label SCT treatment (69 days on 10 mg/day double-blind SCT in the lead-in study, and continued on open label SCT for two days) **due to a “moderate junctional escape rhythm”** on ECG when the S began the open-label treatment phase of MD-03. A follow-up ECG 2 days later (also 2 days post cessation of the study drug) was normal. This patient was reported as having an ongoing bradycardia. This 48 year old female S is also described in the 10/19/01 review of the original submission. The temporal relationship of ECG abnormalities with resolution of the arrhythmia suggests a possible role of SCT treatment. However, this subject was reported to have bradycardia at baseline, whereby she appeared to be at risk of a junctional nodal arrhythmia. The issue of bradycardia and conduction defect in Ss in the various clinical trials is discussed in the 10/19/01 review and briefly summarized in the Executive Summary of the 10/19/01 review which is also provided in the appendix of this Addendum 1 Review.

**S 2345 discontinued open label SCT due to bradycardia.** This 24 year old female had a ventricular rate of 38 bpm on 4/27/00 when she entered the open label phase of MD-03 (had completed 52 days of double blind SCT). A repeat ECG on 5/15/00 after 18 days of open label SCT showed a rate of 47 bpm. Treatment was discontinued due to sinus

Continued on the next page.

Table VII.F.2., continued.

bradycardia. It is not clear if this event is drug-related. However, bradycardia in a young healthy female is not uncommon and there were no associated symptoms reported in the narrative.

**S 2299 discontinued open label SCT due to syncope.** According to the narrative, this S was a 44 year old male who received 26 days double blind citalopram followed by 15 days of open label SCT. On Day 15 of open label treatment he experienced syncope resulting in cessation of treatment. The syncope resolved on the same day that it occurred. It is not clear if this drug related given the information provided in the narrative. This S was taking ibuprofen and naproxen at various times during the study for sinus headache or migraine. Syncope is listed in the "Other Events..." section of proposed labeling.

**S2071** is a 40 year old male with **elevated liver enzyme levels (up to about a 3-6 fold increase from baseline)** who had normal levels at baseline. This S was also described in the 10/19/01 review of this NDA but is also described in the following. These abnormal results led to cessation of treatment. Upon treatment cessation, this S had received 51 days of citalopram followed by 58 days of open label SCT treatment. Within 4 days after treatment was discontinued, the elevated levels returned to baseline levels (within normal limits). The elevation in enzyme levels from baseline to Day 51 of open label SCT (after completing 51 days of citalopram in a previous trial) were as follows:

- SGOT increased from 23 IU/l at baseline to 74 IU/l.
- SGPT increased from 26 to 149 IU/l.
- LDH increased from 163 to 492 IU/l.

Given the temporal relationship of elevated liver enzymes with treatment, as above and in the absence of any other information, it appears that this event could be drug-related. However, this event is listed in the "Other Events Observed..." section of Celexa®.

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**Table VII.H.1.**

**Panel 19. Most Frequent (Incidence > 5% in Any Period) Newly Emergent AEs Over Time**

Preferred Term	Number (%) of Patients			
	1 – 8 Weeks (N=181)	9 – 16 Weeks (N=181)	17 – 24 Weeks (N=157)	25 – 52 Weeks (N=125)
Patients with at least 1 TEAE	149 (82.3%)	107 (59.1%)	64 (40.8%)	70 (56.0%)
Headache	29 (16.0%)	12 (6.6%)	5 (3.2%)	1 (0.8%)
Diarrhea	24 (13.3%)	4 (2.2%)	2 (1.3%)	3 (2.4%)
Nausea	23 (12.7%)	3 (1.7%)	5 (3.2%)	4 (3.2%)
Dry Mouth	21 (11.6%)	4 (2.2%)	0	0
Ejaculation Disorder *	7 (9.7%)	5 (6.9%)	0	0
Insomnia	17 (9.4%)	10 (5.5%)	3 (1.9%)	2 (1.6%)
Rhinitis	17 (9.4%)	4 (2.2%)	6 (3.8%)	7 (5.6%)
Upper Respiratory Tract Infection	17 (9.4%)	5 (2.8%)	5 (3.2%)	7 (5.6%)
Indigestion	15 (8.3%)	1 (0.6%)	3 (1.9%)	2 (1.6%)
Somnolence	12 (6.6%)	5 (2.8%)	0	2 (1.6%)
Dizziness	11 (6.1%)	2 (1.1%)	2 (1.3%)	5 (4.0%)
Fatigue	10 (5.5%)	7 (3.9%)	0	3 (2.4%)
Pharyngitis	10 (5.5%)	2 (1.1%)	2 (1.3%)	5 (4.0%)
Influenza-Like Symptoms	8 (4.4%)	5 (2.8%)	1 (0.6%)	9 (7.2%)

Percentages are relative to number of patients (N) in respective time windows.

\*Percentage is relative to number of male patients (N= 72, 72, 61, and 53 in each successive period).

Cross-reference: Table 7.9, Appendix IX, Listings 18 and 21.

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**Table VII.I.1.**

**Panel 5. Criteria for Potentially Clinically Significant Laboratory Values**

<i>Laboratory Parameter</i>	<i>SI Units</i>	<i>US units</i>	<i>Conversion Factor<sup>a</sup></i>	<i>PCS Criteria Low Values</i>	<i>PCS Criteria High Values</i>
<b>HEMATOLOGY</b>					
Hemoglobin	mmol/L	g/dL	1.611	≤ 0.9*LNL	
Hematocrit	1.0	%	100	≤ 0.9*LNL	
Eosinophils	%	%	1		≥ 10
Neutrophils Segs	%	%	1	≤ 15	
Platelet Count	G/L	mm <sup>3</sup>	1000	≤ 75	≥ 700
White Cell Count	G/L	Thousand /μL	1	≤ 2.8	≥ 16
<b>CHEMISTRY</b>					
Alkaline Phosphatase	U/L	U/L	1	--	≥ 3*UNL
ALT (SGPT)	U/L	U/L	1	--	≥ 3*UNL
AST (SGOT)	U/L	U/L	1	--	≥ 3*UNL
Lactic dehydrogenase	U/L	U/L	1	--	≥ 3*UNL
Blood Urea Nitrogen	mmol/L	mg/dL	2.801	--	≥ 10.7
Calcium	mmol/L	mg/dL	4.008	≤ 1.75	≥ 3.0
Cholesterol	mmol/L	mg/dL	38.67	--	≥ 7.8
Creatinine	μmol/L	mg/dL	0.011	--	≥ 175
Potassium	mmol/L	mEq/L	1	≤ 3.0	≥ 5.5
Sodium	mmol/L	mEq/L	1	≤ 125	≥ 155
Total Bilirubin	μmol/L	mg/dL	0.058	--	≥ 34.2
<b>URINALYSIS</b>					
Protein				--	Increase of ≥ 2
Glucose				--	Increase of ≥ 2

LNL= Lower normal limit of laboratory reference range.

UNL= Upper normal limit of laboratory reference range.

a: Conversion factor to convert SI units into standard U.S. units.

**Table VII.J.1.**

**Panel 4. Criteria for Potentially Clinically Significant Vital Signs**

<i>Variable</i>	<i>Criterion Value</i>	<i>Change Relative to Baseline</i>
Systolic Blood Pressure	≥ 180 mmHg	Increase of ≥ 20
	≤ 90 mmHg	Decrease of ≥ 20
Diastolic Blood Pressure	≥ 105 mmHg	Increase of ≥ 15
	≤ 50 mmHg	Decrease of ≥ 15
Pulse	≥ 120 bpm	Increase of ≥ 15
	≤ 50 bpm	Decrease of ≥ 15
Weight		Increase of ≥ 7%
		Decrease of ≥ 7%

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

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## **ATTACHMENT 1**

### **A summary of a published article entitled "QTc Interval Prolongation Associated with Citalopram Overdose...", Catalano et al., 2001 (Clin. Neuropharm.; 24 (3): 158-62).**

These authors describe a review of the literature regarding a potential association of QTc interval prolongation with citalopram (CT) overdose and provide one new case report of this possible association. According to Catalano and colleagues, previous authors who conducted a review of the literature on this topic concluded that there is no evidence of QTc interval prolongation or cardiac conduction/repolarization effects of CT at therapeutic doses. One study of healthy young adult males receiving daily doses of 60 mg of CT is described as showing no evidence of QTc prolongation. Another study did not reveal tachycardia but showed a "small quinidine-like effect" in psychiatric patients treated with 20-60 mg/day of CT. Other ECG changes were observed.

According to Catalano and colleagues, fatalities have been reported in patients following pure CT overdoses, of which one of these deaths occurred after ingestion of 2.8 mg of CT. However, case reports of overdoses of up to 2 grams did not result in death. Five cases of overdoses of up to 5.2 g also had nonfatal outcomes. The most common symptoms observed in these patients included ECG changes (included QT prolongation, tachycardia, and inferolateral repolarization) in 100%, seizures in 80% and rhabdomyolysis in 40%.

Catalano and colleagues also describe CT overdoses reported to The Swedish Poison Information Center in 1995 (citing Personne et al., 1997). 44 CT overdoses (ages 14-80 years) were reported at doses ranging from 70 mg to 3000 mg. Overdoses over 600 mg were associated with seizures and/or ECG changes (6 out of 18 of these patients had both events following the overdose). Seizures are reported to occur within a few hours after ingestion, while the appearance of QRS changes (widening) occurs later. Ventricular extra beats and nonspecific ST-T wave changes (NSST wave changes) were also described. When combining overdose cases reported in 1995 with those reported in 1996 in Sweden 25% of the cases were associated with widening of the QRS complex or NSST wave changes, including transient bundle branch block in 2 cases and ventricular fibrillation in one case (requiring multiple electroconversions). 47% of the overdoses of 1.9 g or greater were associated with seizures. It is not clear from the description of these cases whether or not there were other factors that may be associated, at least in part, with the development of these adverse events (e.g. concomitant medications, underlying cardiac conditions, or other possible factors).

One case report of CT overdose is described in the Catalano and colleagues article. The patient was a 21 year old female who was prescribed 30 mg/day of CT. As a suicidal attempt she ingested alcohol (121 mg/dl blood level), one 0.25 mg alprazolam tablet and 400 mg of CT. She was also taking an oral contraceptive agent, and over the previous month she was taking alprazolam and zolmitriptan, on an as needed basis. Urine drug screen was positive for benzodiazepines only. Laboratory parameters and arterial blood gases were within normal limits except for a carboxyhemoglobin of 4.5% (0-3% is within normal limits). She was treated with activated charcoal and gastric lavage (tablet fragments were retrieved). She developed QTc prolongation of up to a maximum of 457 msec at approximately 13 hours post ingestion compared to a QTc of 380 msec at approximately one hour post ingestion (obtained upon arrival in the emergency room). A QTc interval of 438 msec was observed at 2 hours post ingestion and QTc prolongation was also observed at other time-points post-ingestion. The QTc interval normalized by approximately 20 hours post dose (393 msec at 20 hours and 353 msec at 21

hours post ingestion). Her vital signs were within normal limits and oxygen saturation was 99% on room air. There were no apparent sequelae following this episode.

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**ATTACHMENT 2. A Copy of Labeling Recommendations from a Previous Clinical Review (Amendment 1 Clinical review of the 10/19/01 NDA 21-323 Amendment submission) of Safety Information from Study MD-03**

It is also noted that examination of common AEs ( $\geq 5\%$  in SCT Ss) the cumulative treatment emergent AE incidence summary table of 999 SCT exposed Ss from all completed depression trials (MD-01, MD-02, MD-03, 99001 and 99003, combined) revealed no new or unexpected common AEs.

The discussion below pertains to changes that the sponsor proposes in the Adverse Reactions section of labeling, based on the safety results of MD-03. This discussion also includes some recommendations regarding the sponsor's proposed labeling changes (refer to the 10/19/01 Clinical Review of this NDA regarding for other recommendations regarding this NDA).

The modification of the Adverse Reactions section of the sponsor's proposed labeling in this amendment submission (10/19/01 submission) shows the addition of the following AEs to AE listings under the "Other Events Observed..." section: hypertension, ECG abnormal, flushing, varicose vein. Since this section includes Ss from MD-03, the total number of SCT exposed Ss described in this section was changed from 715 Ss to 999 Ss. This section of proposed labeling also specifies that Ss were exposed to periods of up to one year in double-blind or open-label trials during premarketing evaluation of SCT.

When comparing the summary table of cumulative incidence rates of AEs in SCT Ss (on page 141 of volume 1 of the submission, cited in the annotated proposed labeling), a number of AEs (such as bradycardia, elevated liver enzymes, among others) meeting the incidence rate criterion of at least 1 in 1000 were excluded from the proposed labeling. It is not clear why these other AEs were excluded. It is suggested that these events are included in the "Others Events Observed..." section, unless there is clear and reasonable rationale as to why the sponsor excluded these events. One event was the elevation liver enzyme levels. While only one S had this event, the elevation was markedly high (up to 3-6 fold) resulting in discontinuation of study drug. This S had normal levels preceding drug exposure and the elevated levels resolved upon cessation of study drug (see description of S2071). The narrative on this S does not describe any other information, such as alcohol abuse or underlying liver disease in this S. Therefore, it appears from the limited information on this S that this event may be drug-related. Consequently, it is recommended that while, this event appears to be an isolated event, this event (elevated liver enzymes) should be listed under the "Other Events Observed ..." section of labeling for SCT.

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this page is the manifestation of the electronic signature.**  
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/s/  
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Karen Brugge  
3/8/02 04:50:13 PM  
MEDICAL OFFICER

Thomas Laughren  
7/21/02 12:54:52 PM  
MEDICAL OFFICER

I agree that this NDA is approvable, once a  
final action is taken on NDA 21-323 for  
the short-term depression claim for this product.--TPL

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**STATISTICAL REVIEW AND EVALUATION**

**NDA:** 21-440  
**DRUG NAME:** Escitalopram Oxalate 5 mg, 10 mg, and 20 mg Tablets  
**INDICATION:** Treatment of depression and prevention of relapse  
**SPONSOR:** Forest Laboratories, Inc  
**STATISTICAL REVIEWER:** Ohidul Siddiqui  
**DATE OF DOCUMENT:** October 26, 2001

**DISTRIBUTION:**

**HFD-120** Paul David, R. Ph., Project Manager  
Karen Brugge, M.D., Clinical Reviewer  
Thomas Laughren, M.D., Team Leader  
Russell Katz, M.D., Director  
**HFD-710** Kun Jin, Ph.D., Team Leader  
George Chi, Ph.D., Director  
**HFD-700** Charles Anello, Sc. D., Deputy Director

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## **EXECUTIVE SUMMARY OF STATISTICAL FINDINGS**

Results of a relapse prevention study were submitted to demonstrate the long-term maintained efficacy, safety and tolerability of escitalopram on patients with major depressive disorder. The results from the study clearly demonstrated the maintained efficacy of escitalopram in the prevention of relapse of major depressive disorder. The patients with major depressive disorder would be benefited by maintaining treatment with escitalopram for long term. This reviewer found sufficient evidence from the sponsor's reported efficacy findings and from the reviewer's own analyses to support the sponsor's claim.

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ON ORIGINAL**

## INTRODUCTION

Results of a multicenter relapse prevention study were submitted to demonstrate the long-term maintained efficacy, safety and tolerability of escitalopram on patients with major depressive disorder. The primary objective of the study was to compare the efficacy of escitalopram and placebo in the prevention of depression relapse. The secondary objective of the study was to evaluate the long-term safety and tolerability of escitalopram in the treatment of depression. The study was carried out in 53 US centers.

Before conducting this relapse prevention study, two 8-week randomized controlled studies were conducted to demonstrate short-term efficacy of escitalopram in the treatment of major depression (ref: NDA 21-323). Patients who had completed one of the two 8-week studies were administered for 8 weeks of open-label escitalopram treatment, starting at dose of 10 mg/day, with a dose increase of 20 mg/day allowed for nonresponders (MADRS score >12) at the end of weeks 4 and 6. At the end of week 8, patients classified as responders (MADRS score ≤ 12) were randomly assigned to 36 weeks of double-blind treatment with either escitalopram or placebo in a 2:1 ratio. Patients were dispensed one bottle containing 40 tablets of 10 mg escitalopram or placebo. They were instructed to continue taking the same number of tablets each day (one or two) that they were taking at the end of week 8. Patients taking one tablet per day received 10 mg/day escitalopram or placebo. Patients taking two tablets per day received 20 mg/day escitalopram or placebo. No adjustment of dosage was permitted during the double-blind phase.

The primary endpoint was time to relapse defined as the period from the start of double-blind treatment until the time the patient met relapse criteria. Any patient who met relapse criteria (MADRS score ≥ 22) at any visit during the double-blind treatment phase was to be discontinued from the study. Patients who discontinued treatment because of an insufficient therapeutic response during double-blind treatment were also considered to have relapsed. Patients who completed the study or discontinued the study due to reasons other than relapse or insufficient therapeutic response were considered as censored at the time of completion or discontinuation, respectively.

Efficacy analyses in the double-blind phase were based on the double-blind ITT population. The ITT group will consist of all randomized patients at double-blind phase with at least one post-randomization efficacy assessment of the MADRS score. The log rank test was used to test the equality of relapse hazards of patients in the escitalopram group relative to those in the placebo group. All tests were two-sided with a 5% significance level. Kaplan-Meier survival curves were also estimated.

Exploratory analyses investigating the effect of sex, age, race (Caucasian vs. non-Caucasian), and depression history (single episode vs. recurrent) on the relapse rate were performed using Cox regression with these effects included as covariates in addition to the treatment effect.

The secondary efficacy parameters include: Change from baseline in MADRS score, Change from baseline in HAMD score, CGI-I score, Change from baseline in CGI-S score, Crude relapse rate, percent of patients meeting DSM-IV criteria for a major depressive episode, and Percent of patients with full relapse (meeting both relapse and DSM-IV criteria for a major depressive episode).

Comparisons between escitalopram and placebo with respect to crude relapse rate, percent of patients meeting DSM-IV criteria for a major depressive episode and percent of patients with full relapse (meeting both relapse criteria and DSM-IV criteria for a major depressive episode) were performed using the Mantel-Haenszel Chi-Square test. Comparisons between escitalopram and placebo with respect to the other secondary efficacy measures were performed using an additive ANCOVA model with treatment, and center as factors and the baseline score as a covariate. The baseline was defined as the last assessment prior to randomization to double-blind relapse prevention study medication. The analyses were carried out using both the LOCF approach and OC approach.

## SPONSOR'S RESULTS

A total 540 patients received open-label treatment with escitalopram, of whom 274 patients were randomized in the double-blind phase to receive escitalopram (181 patients) or placebo (93 patients). In the escitalopram treated group, 95 patients received 10 mg/day escitalopram and 86 patients received 20 mg/day escitalopram. In the double-blind phase, the patient population was 61% female and 86% Caucasian, with a mean age of 43 years. The treatment groups were well matched for all demographic parameters.

Table 1 lists the reasons for dropout at the double-blind phase. During the double-blind phase, 49.2% and 66.7% patients discontinued from escitalopram and placebo groups, respectively. The placebo treated patients had a higher percentage of patients who discontinued because of relapse (23.7% versus 16.6%), insufficient therapeutic response (7.5% versus 2.8%), withdrawal of consent (15.1% versus 10.5%), lost to follow-up (8.6% versus 5.5%), and adverse events (6.5% versus 3.9%).

Table 1: Reasons for patient Discontinuation during the double-blind Phase by Treatment Group

Reason	Double-Blind Phase (N=274)	
	Placebo (N=93)	Escitalopram (N=181)
Total Completers	31 (33.3%)	92 (50.8%)
Total Withdrawn for Any Reason	62 (66.7%)	89 (49.2%)
Reason for Withdrawal		
Adverse Event	6 (6.5%)	7 (3.9%)
Insufficient Therapeutic Response	7 (7.5%)	5 (2.8%)
Withdrawal of Consent	14 (15.1%)	19 (10.5%)
Lost to Follow-Up	8 (8.6%)	10 (5.5%)
Protocol Violation	2 (2.2%)	12 (6.6%)
Relapse (i.e., MADRS score $\geq 22$ )	22 (23.7%)	30 (16.6%)
Other	3 (3.2%)	6 (3.3%)

Table 2: Number of patients censored and relapsed over time in double-blind phase

Time interval (in days)	Placebo (N=93)		Escitalopram (N=181)	
	Number relapsed	Number Censored	Number relapsed	Number Censored
1-14	1	3	5	3
15-28	11	3	7	9
29-56	10	9	7	6
57-84	1	7	9	10
85-112	4	0	2	5
113-140	1	4	3	5
141-168	1	2	3	4
169-196	0	1	4	2
197-224	2	1	1	3
225-252*	0	14	0	34
253+		18		59
Total	31 (33.33%)	62 (66.67%)	41 (22.65%)	140 (77.35%)

\*End of double-blind phase

Note: The sponsor did not report this table. This reviewer has created this table from the submitted data set. Eight patients (2 from placebo and 6 from Escitalopram were recorded as relapsed patients in the data set. But in table 1, these patients were recorded as discontinued patients due to AEs (1 patient), Protocol violation (3 patients), withdrawn consent (3 patients), and one patient's reason is missing.

Table 2 lists the number of censored and relapsed patients during the double blind study period. The placebo-treated group had smaller percentages of censored patients (66.67%), as compared to the corresponding percentage (77.35%) for the Escitalopram-treated group. At the end of double-blind phase, Escitalopram-treated group had a higher percentage of censored patients. The time-to-censor analysis indicated that the two groups were not statistically different ( $p=0.309$ , log-rank test) with respect to the rates of censoring during the double-blind study period.

## PRIMARY PARAMETER

The primary efficacy parameter was time to relapse from the start of double-blind treatment, with relapse defined as MADRS $\geq$ 22 or discontinuation because of insufficient therapeutic response. Table 3 presents the hazard ratio for escitalopram relative to placebo and the p-value. Figure 1 presents the Kaplan-Meier curves for time to relapse.

Table 3: Time to Relapse during the Double-Blind Treatment Phase

	Hazard Ratio	95% CI	P-value
Escitalopram vs. Placebo	0.56	0.35, 0.89	0.013

Hazard ratio for escitalopram relative to placebo is based on Cox proportional hazards regression model with treatment as the covariate.

P-value is based on the log-rank test

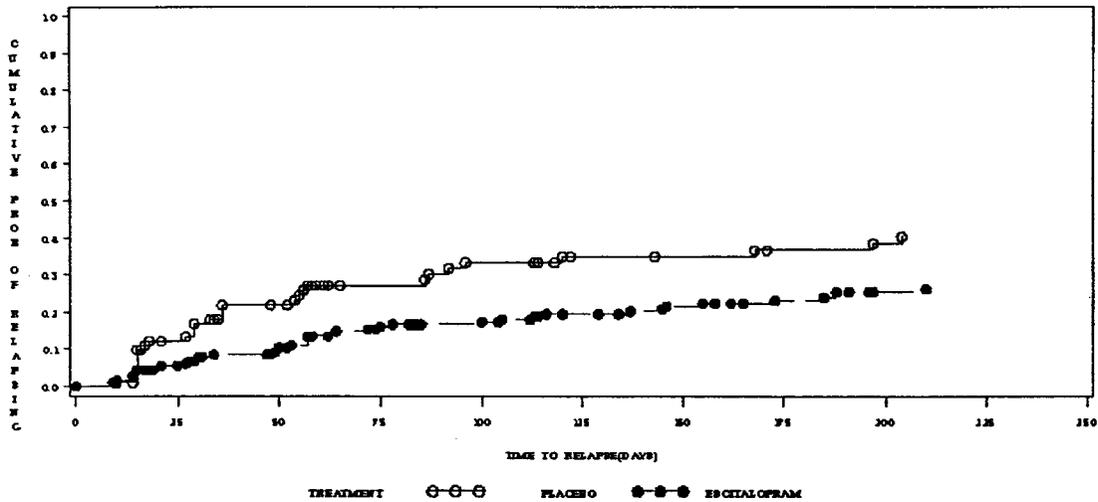


FIGURE 1: KAPLAN-MEIER CURVES OF TIME TO RELAPSE IN DOUBLE-BLIND PHASE

The time to relapse was significantly longer and the cumulative rate of relapse was significantly lower in the escitalopram treated patients than in the placebo treated patients (26% vs. 40%; p=0.013). The time associated with a 25% chance of relapse was 188 days in escitalopram treated patients compared with 56 days in placebo treated patients. The risk of relapse was 44% lower in escitalopram treated patients than in placebo treated patients (hazard ratio of escitalopram to placebo=0.56). The Kaplan-Meier curve of time to relapse during the double-blind treatment phase clearly demonstrates the increased risk of relapse for placebo treated patients compared with escitalopram treated patients.

**SECONDARY PARAMETERS**

Table 4 presents the crude rate of relapse, the rate of relapse as defined by DSM-IV depressive episode criteria and the rate of "full relapse" (defined as patients meeting both relapse and DSM-IV depressive episode criteria) by treatment group for the double-blind phase. The percentage of crude relapse and the percentage of patients with full relapse were lower in the escitalopram group relative to the placebo group (23% vs. 33%, and 20% vs. 29%, respectively), but the difference were not statistically significant based on Mantel-Haenszel Chi-Square test.

Table 4. Crude Rate of Relapse, DSM-IV Depression Criteria and Full Relapse in Double-Blind Phase.

	Placebo (N=93) n/N (%)	Escitalopram (N=181) n/N (%)	P-value
Crude Relapse	31/93 (33.3)	41/181 (22.7)	0.058
DSM-IV Relapse	28/79 (35.4)	37/164 (22.6)	0.034
Full Relapse	23/79 (29.1)	32/164 (19.5)	0.095

Percentages for DSM-IV Relapse and Full Relapse are relative to the number of patients with post-randomization DSM-IV assessment.

P-values are based on Mantel-Haenszel Chi-Square test.

Table 5. Change from baseline at endpoint, double-blind phase.

		Placebo		Escitalopram		P-value
		N	Mean Change	N	Mean Change	Escitalopram vs. Placebo
MADRS	LOCF	92	6.7	181	3.2	0.013
	OC	32	0.7	92	-1.4	0.047
HAMD	LOCF	92	5.7	181	2.8	0.019
	OC	32	0.8	92	-1.6	0.049
CGI-S	LOCF	92	0.8	181	0.4	0.076
	OC	32	0.1	92	-0.3	0.009

Table 5 lists the LOCF and OC analyses of the changes from baseline at endpoint at double-blind phase for MADRS, HAMD, and CGI-S scores. The baseline was defined as the last assessment prior to randomization (i.e., last assessment at open label, where all patients were treated with escitalopram) to double-blind relapse prevention study medication. In both the LOCF and OC analyses of MADRS, HAMD, and CGI-S scores, the worsening in depressive symptomatology observed at endpoint in the placebo treated group was significantly greater than that observed in the escitalopram treated group.

Exploratory analysis investigating the effect of age, sex, race, and depressive history indicates that time to relapse was not significantly affected by age, sex, race, or depression history.

## ADVERSE EVENTS

Table 6 lists the number and percentage of patients who experienced a TEAE by treatment groups in double-blind phase. TEAEs were reported in 56 of 93 (60.2%) placebo treated patients, and 124 of 181 (68.5%) escitalopram treated patients. Of the ten TEAEs with an incidence greater than 5% in either treatment group, 6 occurred at a greater incidence in the escitalopram treatment group than in the placebo treatment group: headache, rhinitis, sinusitis, back pain, influenza-like symptoms, and nausea. No deaths occurred during the study period.

Table 5: Number (%) of Patients with the Most Frequent (i.e., at least 5%) Reported Treatment Emergent AEs during the Double-Blind Phase

	Number (%) of Patients	
	Placebo (N=93)	Escitalopram (N=181)
Patients with at least 1 TEAE	56 (60.2%)	124 (68.5%)
Headache	8 (8.6%)	16 (8.8%)
Upper Respiratory Tract Infection	10 (10.8%)	16 (8.8%)
Rhinitis	1 (1.1%)	16 (8.8%)
Sinusitis	4 (4.3%)	13 (7.2%)
Back Pain	1 (1.1%)	11 (6.1%)
Influenza-Like Symptoms	1 (1.1%)	11 (6.1%)
Insomnia	7 (7.5%)	10 (5.5%)
Nausea	4 (4.3%)	10 (5.5%)
Dizziness	8 (8.6%)	8 (4.4%)
Pharyngitis	5 (5.4%)	8 (4.4%)

## **SPONSOR'S FINAL CONCLUSION**

The results of this study clearly demonstrate the maintained efficacy of escitalopram in the prevention of depression relapse, with the primary and all secondary efficacy variables showing statistically significant differences compared with placebo. As compared with placebo, escitalopram was well tolerated, with few and no unexpected findings regarding AEs, vital signs and laboratory values. The results from this study show that consistent evidence for long-term antidepressant efficacy of escitalopram and support the conclusion that escitalopram is effective in the prevention of depression relapse.

## **REVIEWER'S ANALYSIS AND COMMENTS**

This reviewer reanalyzed the data set according to the statistical analysis plan specified in the protocol. The findings were consistent with the sponsor's reported findings and were true for both primary and secondary outcome measures.

This reviewer did a Kaplan-Meier analysis considering all of the censored patients who were censored before the endpoint (i.e., end of week 36) as relapsed patients. The times-to-censoring of these patients were considered as their times-to-relapse in this analysis. The patients who were censored at the end of the study period were considered as censored. The Kaplan-Meier analysis of time-to-relapse resulted a statistically significant difference in favor of escitalopram when the survival curves for the two treatment groups were compared using log-rank ( $p=0.0023$ ) test.

This reviewer also compared the two treatment groups with respect to the time-to-censor of the censored patients. The Kaplan-Meier analysis of the censored patients indicated that the two treatment groups were not statistically different ( $p$ -value: 0.309 from Log-rank test) with respect to time-to-censoring of the patients during the study period.

## **REVIEWER'S OVERALL CONCLUSION**

The sponsor designed the trial and analyzed the dataset appropriately to assess the maintained efficacy of escitalopram in preventing relapse of major depressive disorder. The results from the study clearly demonstrated the maintained efficacy of escitalopram in the prevention of relapse of major depressive disorder. Patients with major depressive disorder would be benefited by maintaining treatment with escitalopram for long term. This reviewer found sufficient evidence from the sponsor's reported efficacy findings and from the reviewer's own analyses to support the sponsor's claim.

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