rates of 1% and 1%) and placed in Table 2 under Urogenital System, with rates of 1% and 0%, respectively.

DOSAGE AND ADMINISTRATION/Panic Disorder

The proposed language is acceptable.

10.0 Conclusions

This application presents adequate data to support the sponsor's claim of the effectiveness of paroxetine CR in the treatment of panic disorder. While the clinical experience with Paxil CR is too limited to rule out infrequently or rarely occurring safety problems, the safety record of Paxil (IR) is reassuring and the clinical trials data with Paxil CR in depression and panic disorder do not suggest any problems unique to this formulation. Thus, paroxetine CR is expected to be reasonably safe for use as labeled.

11.0 Recommendations

From a clinical perspective, it is recommended that Paxil CR be approved for the treatment of panic disorder after agreement is reached on the labeling issues raised in section 9.0.

/S/

Gregory M. Dubitsky, M.D.
February 1, 1999

3-2-99
I agree that this NDA is approvable. See memo to file for more detailed comments.

/S/

TL, PDP

cc: NDA 20-982
HFD-120/Division File
HFD-120/TLaughren
/GDubitsky
/MShin

APPENDIX 5.0

CLINICAL DATA SOURCES

Table 5.1.1.1: Table of Studies	
Phase 1 Studies (Healthy Volunteers)	
569 (Germany)	Open-label, randomized, single dose, two treatment, replicate, four period crossover study of the bioequivalence of paroxetine CR tablets manufactured at two sites (Cidra and Crawley) in 80 healthy volunteers, ages 20-55; dose= 2x12.5 mg (25mg total).
Phase 3 Studies (Panic Disorder)	
494 (U.S.)	Randomized, double-blind, placebo-controlled, flexible dose study in 283 outpatients; dose=12.5 to 75mg once daily; 10 weeks duration.
495 (U.S.)	Randomized, double-blind, placebo-controlled, flexible dose study in 321 outpatients; dose=12.5 to 75mg once daily; 10 weeks duration.
497 (U.S./Canada)	Randomized, double-blind, placebo-controlled, flexible dose study in 285 outpatients; dose=12.5 to 75mg once daily; 10 weeks duration.

TABLE 5.1.1.2		
	Paroxetine CR	**Placebo**
Phase 1		
Single Dose	80	0
Phase 3		
494, 495, 497	444	445
Phase 1 + Phase 3 Combined		
Grand Total	524	445

TABLE 5.1.2.1 DEMOGRAPHIC CHARACTERISTICS: PHASE 3 STUDIES		
	Paroxetine CR (n=444)	**Placebo (n=445)**
Enumeration (%) by Age Group		
18-24	40 (9%)	54 (12%)
25-34	148 (33%)	129 (29%)
35-44	138 (31%)	137 (31%)
45-54	88 (20%)	92 (21%)
55-65	30 (7%)	32 (7%)
>65	0 (0%)	1 (<1%)
Age (yrs)		
Mean	37.57	37.82
Range	19-65	19-72
Gender		
Male	162 (36%)	194 (44%)
Female	282 (64%)	251 (56%)
Race		
White	380 (86%)	389 (87%)
Non-White	64 (14%)	56 (13%)
Weight (lbs)		
Mean	170	175
Range	93-435	98-383

Table 5.1.3.1: Number (Percentage) of Patients by Daily Dosage Level and Duration of Exposure to Each Level (Phase 3 Studies)

Days Exposure:	1-7		8-14		15-21		22-28		29-35		36-42		43-56		57-70		>70		Total	
Daily Dose Level (mg/d)	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Paroxetine CR																				
Dose Level																				
1 (12.5mg)	308	69.4	119	26.8	3	0.7	1	0.2	2	0.5	2	0.5	1	0.2	8	1.8	0	0	444	100.0
2 (25.0mg)	180	43.2	109	26.1	33	7.9	8	1.9	10	2.4	7	1.7	17	4.1	50	12.0	3	0.7	417	93.9
3 (37.5mg)	118	38.1	83	26.8	35	11.3	14	4.5	9	2.9	10	3.2	27	8.7	14	4.5	0	0	310	69.8
4 (50.0mg)	80	35.6	56	24.9	24	10.7	18	8.0	15	6.7	15	6.7	17	7.6	0	0	0	0	225	50.7
5 (62.5mg)	51	35.4	35	24.3	16	11.1	20	13.9	9	6.3	8	5.6	5	3.5	0	0	0	0	144	32.4
6 (75.0mg)	8	9.4	10	11.8	8	9.4	10	11.8	34	40.0	12	14.1	3	3.5	0	0	0	0	85	19.1
Placebo																				
1	311	69.9	127	28.5	4	0.9	0	0	0	0	1	0.2	0	0	2	0.4	0	0	445	100.0
2	221	51.0	112	25.9	36	8.3	14	3.2	5	1.2	8	1.8	8	1.8	28	6.5	1	0.2	433	97.3
3	171	45.1	106	28.0	36	9.5	13	3.4	13	3.4	13	3.4	21	5.5	6	1.6	0	0	379	85.2
4	123	41.1	88	29.4	30	10.0	17	5.7	20	6.7	12	4.0	9	3.0	0	0	0	0	299	67.2
5	94	41.4	72	31.7	23	10.1	11	4.8	10	4.4	15	6.6	2	0.9	0	0	0	0	227	51.0
6	7	4.5	31	19.7	12	7.6	13	8.3	60	38.2	32	20.4	2	1.3	0	0	0	0	157	35.3

Data Source: ISS Table 4.3.1 in Section 21.1

APPENDIX 7.2.1

STUDY 494: EFFICACY

Table 7.2.1.1
Study 494 Investigators

Investigator	Site	Institution	Location
Jeffrey T. Apter, MD	001	Princeton Biomedical Research	Princeton, NJ
Robert J. Bielski, MD	002	Institute for Health Studies	Okemos, MI
James D. Brenner, MD	003	Brenner Research Institute	Olympia, WA
Alexander Bystritsky, MD	004	University of California, Los Angeles	Los Angeles, CA
John S. Carman, MD	005	Carman Research	Atlanta, GA
Mahesh R. Dave, MD	006	Scripps Biomedical Research	Bryan, TX
Alan D. Feiger, MD	007	Peiger Health Research Center	Wheat Ridge, CO
Saul H. Helfing, MD	008	Hill Top Research, Inc.	Portland, OR
Eric Hollander, MD	009	Mt. Sinai School of Medicine	New York, NY
Carl A. Houck, MD	010	University of Alabama at Birmingham, School of Medicine	Birmingham, AL
James W. Jefferson, MD	011	Dean Foundation for Health, Research and Education	Madison, WI
Barbara L. Kennedy, MD, PhD	012	University of Louisville School of Medicine	Louisville, KY
Peter D. Lundborg, MD	013	Seattle Clinical Research Center, Inc.	Seattle, WA
Kevin B. Miller, MD Joan Busner, PhD Jeff Gill, PhD	014	St. Louis University, Health Sciences Center	St. Louis, MO
Dennis M. Pavlinac, MD	015	Private Practice	Oceanside, CA
William S. Rea, MD	016	Clinical Studies	Ft. Lauderdale, FL
Eric M. Reiman, MD	017	Good Samaritan Regional Medical Center, Samaritan Behavioral Health	Phoenix, AZ
Edward Sewiezer, MD [a]	018	University PA Science Center	Philadelphia, PA
David V. Sheehan, MD, MBA	019	University of South Florida, College of Medicine	Tampa, FL
Richard C. Shelton, MD	020	Vanderbilt University	Nashville, TN
Ward T. Smith, MD	021	Pacific Northwest Clinical Research	Portland, OR
Murray B. Stein, MD, BSc (Med)	022	Univ. California San Diego Dept of Psychiatry	La Jolla, CA
Steven D. Targum, MD	023	Delaware Valley Clinical Studies Center	Philadelphia, PA
Peter M. Thompson, MD, MS	024	University of New Mexico Health Sciences Center	Albuquerque, NM
Madhukar H. Trivedi, MD	025	University of Texas, Southwestern Medical Center	Dallas, TX
Karen L. Weiks, MD	026	George Washington University Medical Center	Washington, DC
Charles H. Meredith, MD	027	Affiliated Research Institute	San Diego, CA
Patrick J. Donley, MD	028	Puget Sound Medical Research, a Subsidiary of Hill Top Research, Inc.	Tacoma, WA
Jeffrey S. Simon, MD	029	Northbrooke Research Center	Brown Deer, WI
Barnett M. Kaplan, MD	030	Private Practice	Renton, WA
Madelon Hartford, MD	031	Hartford Research Group	Cincinnati, OH
Jeffrey Mattes, MD	032	Psychopharmacology Research Associates of Princeton	Princeton, NJ
Larry M. Davis, MD	033	The Davis Psychiatric Clinic, Inc.	Indianapolis, IN

Source: Appendix A, Investigator CV
a Screening only patients

TABLE 7.2.1.2: STUDY 494 PATIENT DEMOGRAPHICS (ALL CENTERS)							
Treatment	ITT	Age (years)		Gender [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-white
Paroxetine CR	139	38.1	19-63	58(42%)	81(58%)	117(84%)	22(16%)
Placebo	144	37.0	20-61	64(44%)	80(56%)	135(94%)	9(6%)

TABLE 7.2.1.3: STUDY 494 NUMBER OF ITT PATIENTS IN-STUDY OVER TIME						
	Baseline	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10
Paroxetine CR	139	118	113	108	104	103
Placebo	144	128	117	112	109	109

Table 7.2.1.4: Study 494
Full Panic Attacks
Response Rate Reduced to Zero Attacks
Adjusting for the Effect of Center Only
Excluding Center 033
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons
	Paroxetine CR			Placebo			Paroxetine CR vs Placebo
	n	%	N	n	%	N	Odds Ratio (95% C.I.) p-value
Weeks 1 and 2	24	20.2%	119	34	26.8%	127	0.665 (0.363, 1.219) 0.187
Weeks 3 and 4	53	48.2%	110	42	36.5%	115	1.617 (0.944, 2.771) 0.080
Weeks 5 and 6	63	63.6%	99	52	49.1%	106	1.827 (1.040, 3.210) 0.036
Weeks 7 and 8	71	75.5%	94	57	55.3%	103	2.582 (1.393, 4.785) 0.003
Weeks 9 and 10	69	78.4%	88	61	59.2%	103	2.542 (1.332, 4.851) 0.005
Week 10 End Point	84	68.9%	122	66	50.4%	131	2.182 (1.303, 3.654) 0.003

Table 7.2.1.5: Study 494
Baseline and Change from Baseline in Total Number of Full Panic Attacks
Excluding Center 033
Intention to Treat Population

	Treatment Groups				Pairwise Comparisons		
	Paroxetine CR		Placebo		Paroxetine CR vs Placebo		
	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)		p-value
Baseline	5 (,)	122	5 (,)	128			
Weeks 1 and 2	-3 (,)	119	-2 (,)	124			
Weeks 3 and 4	-4 (,)	110	-3 (,)	113			
Weeks 5 and 6	-4 (,)	99	-3 (,)	105			
Weeks 7 and 8	-5 (,)	94	-3 (,)	102			
Weeks 9 and 10	-5 (,)	88	-3 (,)	102	-1 (-2, 0)		0.072
Week 10 End Point	-4 (,)	122	-3 (,)	128	-1 (-2, 0)		0.080

Table 7.2.1.6: Study 494
Baseline and Change from Baseline in CGI Severity of Illness Score
Excluding Center 033
Intention to Treat Population

	Treatment Groups					Pairwise Comparisons	
	Paroxetine CR			Placebo		Paroxetine CR vs Placebo	
	Median	(Min,Max)	N	Median	(Min,Max) N	Median (95% C.I.)	p-value
Baseline	4	( )	132	4	( ) 138		
Week 1	0	( )	128	0	( ) 136		
Week 2	0	( )	116	-1	( ) 125		
Week 3	-1	( )	109	-1	( ) 120		
Week 4	-1	( )	112	-1	( ) 116		
Week 5	-1	( )	106	-1	( ) 108		
Week 6	-1	( )	101	-1	( ) 110		
Week 8	-1	( )	101	-1	( ) 109		
Week 10	-2	( )	93	-1	( ) 104	0 (-1,0.0)	0.007
Week 10 End Point	-1		132	-1	( ) 138	0 (-1,0.0)	0.032

Table 7.2.1.7: Study 494
Summary Statistics for Baseline and Change from Baseline in Percentage of Time per Day with Anticipatory Anxiety
Adjusting for the Effect of Center Group Only
Excluding Center 033
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups			Pairwise Comparisons	
	Paroxetine CR	Placebo		Paroxetine CR vs Placebo	
	Mean (s.e.) N	Mean (s.e.) N		Mean (95% C.I.)	p-value
Baseline	26.2 (2.01) 122	26.0 (2.03) 128			
Weeks 1 and 2	-3.5 (0.97) 119	-3.5 (0.95) 124		-0.0 (-2.67, 2.61)	0.980
Weeks 3 and 4	-9.2 (1.35) 109	-6.8 (1.34) 113		-2.4 (-6.09, 1.30)	0.202
Weeks 5 and 6	-11.5 (1.57) 99	-8.6 (1.54) 105		-3.0 (-7.19, 1.28)	0.170
Weeks 7 and 8	-12.6 (1.86) 94	-10.3 (1.82) 102		-2.2 (-7.20, 2.74)	0.377
Weeks 9 and 10	-14.9 (1.92) 88	-11.1 (1.80) 102		-3.9 (-8.96, 1.21)	0.135
Week 10 End Point	-13.7 (1.62) 122	-9.8 (1.59) 128		-4.0 (-8.35, 0.44)	0.078

Table 7.2.1.8: Study 494
Marks Sheehan Phobia Scale (MSPS)
Summary Statistics for Baseline and Change from Baseline in Total Fear Score
Adjusting for the Effect of Center Group Only
Statistical Analysis presented at all Time Points
Excluding Center 033
Intention to Treat Population

	Treatment Groups		Pairwise Comparisons
	Paroxetine CR	Placebo	Paroxetine CR vs Placebo
	Mean (s.e.) N	Mean (s.e.) N	Mean (95% C.I.) p-value
Baseline	43.0 (2.24) 114	43.5 (2.04) 126	
Week 6	-16.8 (2.21) 91	-13.6 (2.19) 97	-3.2 (-9.16, 2.68) 0.282
Week 10	-21.5 (2.34) 89	-17.8 (2.21) 101	-3.8 (-10.00, 2.48) 0.235
Week 10 End Point	-20.7 (2.03) 114	-15.0 (1.93) 126	-5.7 (-11.11, -0.26) 0.040

Table 7.2.1.9: Study 494
Marks Sheehan Phobia Scale (MSPS)
Summary Statistics for Baseline and Change from Baseline in Total Avoidance Score
Adjusting for the Effect of Center Group Only
Excluding Center 033
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups		Pairwise Comparisons
	Paroxetine CR	Placebo	Paroxetine CR vs Placebo
	Mean (s.e.) N	Mean (s.e.) N	Mean (95% C.I.) p-value
Baseline	15.1 (0.87) 114	15.3 (0.81) 125	
Week 6	-4.6 (0.90) 91	-4.8 (0.90) 96	0.1 (-2.29, 2.56) 0.910
Week 10	-6.9 (0.86) 89	-6.3 (0.81) 100	-0.7 (-2.98, 1.61) 0.557
Week 10 End Point	-6.8 (0.75) 114	-5.3 (0.72) 125	-1.5 (-3.52, 0.49) 0.139

APPENDIX 7.2.2

STUDY 495: EFFICACY

Table 7.2.2.1:
Study 495 Investigators

Investigator	Site	Institution	Location
Lawrence W. Adler, M.D.	001	Clinical Insights, Inc.	Glen Burnie, MD
Bernard D. Beitman, M.D.	002	University of Missouri	Columbia, MO
Jon Andrew Bell, M.D.	003	University of Colorado, School	Denver, CO
William J. Burke, M.D.	004	University of Nebraska	Omaha, NE
Larry M. Davis, M.D.	005	Davis Psychiatric Clinic, Inc.	Indianapolis, IN
Robert L. DuPont, M.D.	006	Institute for Behavior and	Rockville, MD
Donald LinkLater England, M.D.	007	Peace Health Medical Group	Eugene, OR
James M. Ferguson, M.D.	008	Pharmacology Research Corp.	Las Vegas, NV
Jack Matthew Gorman, M.D.	009	Phobia Clinic, Hillside	Glen Oaks, NY
James T. Hartford, M.D.	010	Hartford Research Group	Dayton, OH
Jon Franklin Heiser, M.D.	011	Pharmacology Research	Newport Beach,
Amir H. Kalali, M.D.	012	UC-Irvine College of	Irvine, CA
Jeffrey A. Matles, M.D.	013	Psychopharmacology Research	Princeton, NJ
Charles B. Nemeroff, M.D.,	014	Emory University, Department	Atlanta, GA
William M. Patterson, M.D.	016	Birmingham Research Group	Birmingham, AL
Mark H. Pollack, M.D.	017	Massachusetts General	Boston, MA
Harvey Resnick, M.D.	018	R/D Clinical Research Inc.	Lake Jackson, TX
Murray Hal Rosenthal, D.O.	019	Behavioral and Medical	San Diego, CA
Steven K. Strawn, M.D.	020	Freedom Research	College Station,
Nicholas William Telew, M.D.	021	Oregon Center for Clinical	Eugene, OR
Richard Templeton, M.D.	022	Psychiatric Research Group	Annapolis, MD
Phebe Tucker, M.D.	023	University of Oklahoma	Oklahoma City,
Richard H. Weisler, M.D.	024	900 Ridgefield Drive, Suite	Raleigh, NC
Kenneth J. Weiss, M.D.,	025	Delaware Valley Research	King of Prussia,
Lorna P. Charles, M.D.	026	Southern NJ Medical Institute	Stratford, NJ
Lynn A. Cunningham, M.D.	027	Vine St. Clinical Research	Springfield, IL
Jack M. Stack, M.D.	028	Gratiot Community Hospital	Alma, MI
Susanna Goldstein, M.D.	030	Center for Psychobiology	New York, NY
Randall R. Stoltz, M.D.	031	GFI Pharmaceutical Services,	Evansville, IN

Source: Curriculum Vitae, Appendix A

APPEARS THIS WAY
ON ORIGINAL

TABLE 7.2.2.2: STUDY 495 PATIENT DEMOGRAPHICS (ALL CENTERS)							
Treatment	ITT	Age (years)		Gender [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-white
Paroxetine CR	158	37	19-62	53(34%)	105(66%)	146(92%)	12(8%)
Placebo	163	37	19-72	60(37%)	103(63%)	146(90%)	17(10%)

TABLE 7.2.2.3: STUDY 495 NUMBER OF ITT PATIENTS IN-STUDY OVER TIME						
	Baseline	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10
Paroxetine CR	158	135	124	114	107	106
Placebo	163	152	148	134	126	124

APPEARS THIS WAY
ON ORIGINAL

Table 7.2.2.4: Study 495
Full Panic Attacks
Response Rate Reduced to Zero Attacks
Adjusting for the Effect of Center Group Only
Excluding Center 005
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons	
	Paroxetine CR			Placebo			Paroxetine CR vs Placebo	
	n	%	N	n	%	N	Odds Ratio (95% C.I.)	p-value
Weeks 1 and 2	14	11.8%	119	22	16.3%	135	0.693 (0.334, 1.441)	0.327
Weeks 3 and 4	41	40.6%	101	49	38.6%	127	1.084 (0.633, 1.856)	0.768
Weeks 5 and 6	55	59.8%	92	48	44.4%	108	1.985 (1.104, 3.570)	0.022
Weeks 7 and 8	58	64.4%	90	60	56.1%	107	1.458 (0.811, 2.623)	0.208
Weeks 9 and 10	60	71.4%	84	55	55.6%	99	2.022 (1.084, 3.774)	0.027
70% End Point	68	53.1%	128	69	49.3%	140	1.177 (0.727, 1.907)	0.507
Week 10 End Point	73	57.0%	128	70	50.0%	140	1.325 (0.816, 2.149)	0.255

Table 7.2.2.5: Study 495
Baseline and Change from Baseline in Total Number of Full Panic Attacks
Excluding Center 005
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons Paroxetine CR vs Placebo			
	Paroxetine CR			Placebo						
	Median	(Min,Max)	N	Median	(Min,Max)	N	Median	(95% C.I.)		p-value
Baseline	7	[illegible]	123	5	[illegible]	136				
Weeks 1 and 2	-2	[illegible]	116	-2	[illegible]	132				
Weeks 3 and 4	-5	[illegible]	96	-3	[illegible]	124				
Weeks 5 and 6	-5	[illegible]	87	-3	[illegible]	105				
Weeks 7 and 8	-6	[illegible]	86	-3	[illegible]	106				
Weeks 9 and 10	-6	[illegible]	80	-3	[illegible]	98	-3	(-5,	-1)	<0.001
70% End Point	-5	[illegible]	123	-3	[illegible]	136	-2	(-3,	-1)	<0.001
Week 10 End Point	-5	[illegible]	123	-3	[illegible]	136	-2	(-4,	-1)	<0.001

Table 7.2.2.6: Study 495
Baseline and Change from Baseline in CGI Severity of Illness Score
Excluding Center 005
Intention to Treat Population

	Treatment Groups				Pairwise Comparisons	
	Paroxetine CR		Placebo		Paroxetine CR vs Placebo	
	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value
Baseline	4 ( )	137	4 ( )	147		
Week 1	0 ( )	134	0 ( )	144		
Week 2	0 ( )	121	0 ( )	135		
Week 3	-1 ( )	119	-1 ( )	130		
Week 4	-1 ( )	101	-1 ( )	128		
Week 5	-1 ( )	101	-1 ( )	123		
Week 6	-2 ( )	91	-1 ( )	110		
Week 8	-2 ( )	95	-1 ( )	119		
Week 10	-2 ( )	85	-1 ( )	101	-1 (-1, -1)	<0.001
70% End Point	-1 ( )	137	-1 ( )	147	0 (-1,0.0)	0.007
Week 10 End Point	-2 ( )	137	-1 ( )	147	0 (-1,0.0)	0.004

Table 7.2.2.7: Study 495

Summary Statistics for Baseline and Change from Baseline in Percentage of Time per Day with Anticipatory Anxiety
Adjusting for the Effect of Center Group Only
Excluding Center 005
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups				Pairwise Comparisons	
	Paroxetine CR		Placebo		Paroxetine CR vs Placebo	
	Mean (s.e.)	N	Mean (s.e.)	N	Mean (95% C.I.)	p-value
Baseline	29.0 (2.10)	122	24.5 (1.79)	136		
Weeks 1 and 2	-2.9 (1.09)	115	-1.8 (1.01)	132	-1.1 (-3.97, 1.79)	0.457
Weeks 3 and 4	-9.9 (1.52)	96	-5.4 (1.33)	124	-4.5 (-8.43, -0.58)	0.025
Weeks 5 and 6	-14.5 (1.77)	87	-8.1 (1.60)	105	-6.3 (-10.93, -1.73)	0.007
Weeks 7 and 8	-15.9 (1.93)	86	-9.5 (1.71)	106	-6.4 (-11.36, -1.52)	0.011
Weeks 9 and 10	-17.4 (1.84)	80	-8.3 (1.64)	98	-9.0 (-13.78, -4.31)	<0.001
70% End Point	-13.1 (1.53)	122	-7.6 (1.45)	136	-5.5 (-9.60, -1.43)	0.008
Week 10 End Point	-14.1 (1.59)	122	-7.9 (1.51)	136	-6.1 (-10.38, -1.87)	0.005

Table 7.2.2.8: Study 495
Marks Sheehan Phobia Scale (MSPS)
Summary Statistics for Baseline and Change from Baseline in Total Fear Score
Adjusting for the Effect of Center Group Only
Statistical Analysis presented at all Time Points
Excluding Center 005
Intention to Treat Population

	Treatment Groups		Pairwise Comparisons	
	Paroxetine CR	Placebo	Paroxetine CR vs Placebo	
	Mean (s.e.) N	Mean (s.e.) N	Mean (95% C.I.)	p-value
Baseline	45.9 (2.19) 118	44.3 (2.00) 132		
Week 6	-15.0 (1.90) 80	-10.2 (1.75) 93	-4.8 (-9.75, 0.22)	0.061
Week 10	-22.9 (2.37) 82	-12.8 (2.16) 97	-10.1 (-16.32, -3.86)	0.002
Week 10 End Point	-19.3 (1.95) 118	-11.7 (1.84) 132	-7.7 (-12.87, -2.49)	0.004

Table 7.2.2.9: Study 495
Marks Sheehan Phobia Scale (MSPS)
Summary Statistics for Baseline and Change from Baseline in Total Avoidance Score
Adjusting for the Effect of Center Group Only
Excluding Center 005
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups		Pairwise Comparisons
	Paroxetine CR	Placebo	Paroxetine CR vs Placebo
	Mean (s.e.) N	Mean (s.e.) N	Mean (95% C.I.) p-value
Baseline	16.4 (0.83) 118	15.3 (0.83) 132	
Week 6	-5.0 (0.77) 80	-2.8 (0.71) 93	-2.2 (-4.23, -0.19) 0.032
Week 10	-7.9 (0.87) 81	-4.0 (0.79) 97	-3.9 (-6.18, -1.61) <0.001
Week 10 End Point	-6.8 (0.71) 118	-3.8 (0.67) 132	-3.1 (-4.98, -1.18) 0.002

APPENDIX 7.2.3

STUDY 497: EFFICACY

Table 7.2.3.1:
Study 497 Investigators

Investigator	Site	Institution	Location
Ryan Easton, M.D.	001	North East Ohio Health Services	Beachwood, OH
David Brown, M.D.	002	Community Clinical Research	Austin, TX
Joseph Baugher Beyer, M.D.	003	Clary Research Associates	New Castle, DE
Cal K. Cohn, M.D.	004	Hauser Clinic	Houston, TX
Alan Gelenberg, M.D. Pedro L. Delgado, M.D.	005	University of Arizona Health Science Center	Tucson, AZ
Eugene A. DuBoff, M.D.	006	Center for Behavioral Medicine	Denver, CO
James Meeham Ferguson, M.D.	007	Pharmacology Research Corporation	Salt Lake City, UT
Gregory Hanner, M.D.	008	Miami Sinai Medical Center	Miami Beach, FL
Peter J. Heiland, M.D., F.A.C.O.E.M., F.A.P.A.	009	Private Practice	*Boca Raton, FL*
Richard J. Kavoussi, M.D.	010	Allegheny University of the Health Sciences	Philadelphia, PA
Arifulla Khan, M.D.	011	Northwest Psychiatric Institute, Inc. PC	Kirkland, WA
Ronald P. Landbloom, M.D.	012	St. Paul Ramsey Medical Center	St. Paul, MN
Randall H. Leefelda, M.D.	013	Sutter Institute for Medical Research	Sacramento, CA
Robert Bruce Lydiard, Ph.D., M.D	014	Medical University of South Carolina	Charleston, SC
Dennis J. Murjack, M.D. John J. Murphy, M.D.	015	Southwestern Research Institute	Beverly Hills, CA
Frederick W. Reichert, M.D.	016	University of Utah Health Sciences Center	Salt Lake City, UT
Robert A. Rheaberg, M.D.	017	BioBehavioral Research Center	Decatur, GA
Peter C. Schram, M.D.	018	Menninger Clinic	Topeka, KS
JoAnne Santa, Ph.D. Leslie Seiden, M.D.	019	Center for Research in Anxiety, Inc.	New York, NY
George M. Simpson, M.D.	020	LAC - USC Medical Center	Los Angeles, CA
Harold David Udelman, M.D., F.A.P.A., F.A.P.M.	022	Psychiatric Research Network	Phoenix, AZ
Dan L. Zinbrolf, M.D.	023	Behavioral Medicine Center	Upland, CA
Pedro Melchor, M.D.	029	PharmResearch, Inc.	Pinecrest, FL
Kenneth Neil Sokolski, M.D. M.S.	031	Affiliated Research Institute	Santa Ana, CA
Shirvan Kutchi Mahmud, M.B., Ch.B., F.R.C.P., L.M.C.C.	024	Private Practice	Saskatoon, Saskatchewan
Dr. Charles Henri Rapnar Lefrancoise	025	Samson Lejeunesse Assoc.	Sillery, Quebec
Paul Stanley Morris, M.D.	026	Private Practice	Etobicoke, Ontario
Dr. Pierre Savard, Ph.D.	027	Private Practice	Montreal, Quebec
Peter G. Turner, M.B., Ch.B., F.R.C.P.C.	028	Private Practice	Burlington, Ontario

Source: Submission Vol. Appendix A

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TABLE 7.2.3.2: STUDY 497 PATIENT DEMOGRAPHICS							
Treatment	ITT	Age (years)		Gender [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-white
Paroxetine CR	147	38	20-65	51(35%)	96(65%)	117(80%)	30(20%)
Placebo	138	40	19-64	70(51%)	68(49%)	108(78%)	30(22%)

TABLE 7.2.3.3: STUDY 497 NUMBER OF ITT PATIENTS IN-STUDY OVER TIME						
	Baseline	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10
Paroxetine CR	147	130	120	117	105	103
Placebo	138	128	119	106	99	96

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Table 7.2.3.4: Study 497
Full Panic Attacks
Response Rate Reduced to Zero Attacks
Adjusting for the Effect of Center Group Only
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons
	Paroxetine CR			Placebo			Paroxetine CR vs Placebo
	n	%	N	n	%	N	Odds Ratio (95% C.I.) p-value
Weeks 1 and 2	29	22.8%	127	31	25.2%	123	0.895 (0.491, 1.629) 0.716
Weeks 3 and 4	51	43.6%	117	44	38.6%	114	1.203 (0.697, 2.079) 0.507
Weeks 5 and 6	69	63.9%	108	63	58.3%	108	1.330 (0.745, 2.375) 0.334
Weeks 7 and 8	74	73.3%	101	52	56.5%	92	2.154 (1.150, 4.036) 0.017
Weeks 9 and 10	68	70.1%	97	63	65.6%	96	1.224 (0.651, 2.302) 0.530
Week 10 End Point	84	62.7%	134	73	56.2%	130	1.362 (0.822, 2.257) 0.230

Table 7.2.3.5: Study 497
Baseline and Change from Baseline in Total Number of Full Panic Attacks
Intention to Treat Population

	Treatment Groups				Pairwise Comparisons				
	Paroxetine CR			Placebo			Paroxetine CR vs Placebo		
	Median	(Min,Max)	N	Median	(Min,Max)	N	Median	(95% C.I.)	p-value
Baseline	5	(,)	132	4	(,)	130			
Weeks 1 and 2	-2	(,)	125	-2	(,)	123			
Weeks 3 and 4	-4	(,)	115	-2.5	(,)	114			
Weeks 5 and 6	-4	(,)	106	-3	(,)	108			
Weeks 7 and 8	-4	(,)	99	-3	(,)	92			
Weeks 9 and 10	-4	(,)	95	-3	(,)	96	-1	(-2, 0)	0.088
Week 10 End Point	-4	(,)	132	-3	(,)	130	-1	(-2, 0)	0.239

Table 7.2.3.6: Study 497
Baseline and Change from Baseline in CGI Severity of Illness Score
Intention to Treat Population

	Treatment Groups				Pairwise Comparisons	
	Paroxetine CR		Placebo		Paroxetine CR vs Placebo	
	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value
Baseline	4 ( )	144	4 ( )	136		
Week 1	0 ( )	142	0 ( )	136		
Week 2	0 ( )	128	0 ( )	122		
Week 3	-1 ( )	123	-1 ( )	120		
Week 4	-1 ( )	114	-1 ( )	116		
Week 5	-1 ( )	111	-1 ( )	110		
Week 6	-1 ( )	108	-1 ( )	110		
Week 8	-1 ( )	114	-1 ( )	101		
Week 10	-2 ( )	98	-1 ( )	96	0 (-1,0.0)	0.122
Week 10 End Point	-1 ( )	144	-1 ( )	136	0 (-1,0.0)	0.078

Table 7.2.3.7: Study 497

Summary Statistics for Baseline and Change from Baseline in Percentage of Time per Day with Anticipatory Anxiety
Adjusting for the Effect of Center Group Only
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups		Pairwise Comparisons	
	Paroxetine CR	Placebo	Paroxetine CR vs Placebo	
	Mean (s.e.) N	Mean (s.e.) N	Mean (95% C.I.)	p-value
Baseline	25.6 (1.94) 132	27.4 (2.12) 130		
Weeks 1 and 2	-3.0 (1.11) 125	-2.6 (1.12) 123	-0.3 (-3.38, 2.71)	0.831
Weeks 3 and 4	-8.1 (1.21) 114	-4.0 (1.20) 114	-4.0 (-7.34, -0.72)	0.017
Weeks 5 and 6	-11.1 (1.45) 106	-8.1 (1.44) 107	-3.0 (-6.99, 0.95)	0.135
Weeks 7 and 8	-13.2 (1.68) 99	-9.3 (1.76) 92	-3.8 (-8.59, 0.90)	0.112
Weeks 9 and 10	-13.8 (1.76) 95	-10.1 (1.76) 96	-3.6 (-8.49, 1.22)	0.142
Week 10 End Point	-12.4 (1.50) 132	-8.7 (1.50) 130	-3.7 (-7.80, 0.41)	0.078

Table 7.2.3.8: Study 497
Marks Sheehan Phobia Scale (MSPS)
Summary Statistics for Baseline and Change from Baseline in Total Fear Score
Adjusting for the Effect of Center Group Only
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups				Pairwise Comparisons	
	Paroxetine CR		Placebo		Paroxetine CR vs Placebo	
	Mean (s.e.)	N	Mean (s.e.)	N	Mean (95% C.I.)	p-value
Baseline	42.6 (2.25)	129	40.9 (1.94)	125		
Week 6	-14.9 (2.03)	87	-10.3 (2.11)	86	-4.6 (-10.32, 1.08)	0.112
Week 10	-19.1 (2.06)	89	-14.4 (2.07)	89	-4.7 (-10.38, 1.02)	0.107
Week 10 End Point	-19.6 (1.84)	129	-10.8 (1.86)	125	-8.7 (-13.81, -3.66)	<0.001

Table 7.2.3.9: Study 497
Marks Sheehan Phobia Scale (MSPS)
Summary Statistics for Baseline and Change from Baseline in Total Avoidance Score
Adjusting for the Effect of Center Group Only
Statistical Analysis presented at all Time Points
Intention to Treat Population

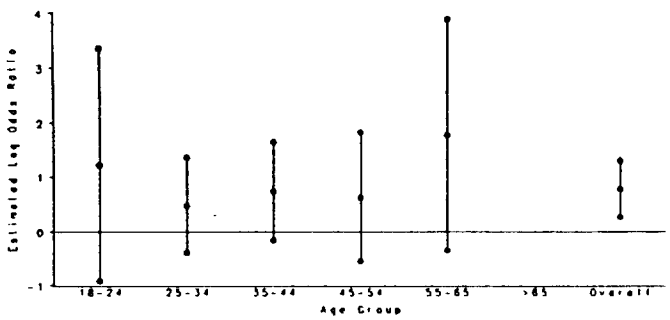
	Treatment Groups			Pairwise Comparisons	
	Paroxetine CR	Placebo		Paroxetine CR vs Placebo	
	Mean (s.e.) N	Mean (s.e.) N		Mean (95% C.I.)	p-value
Baseline	15.4 (0.86) 128	15.2 (0.80) 125			
Week 6	-4.7 (0.87) 87	-3.1 (0.91) 85		-1.6 (-4.03, 0.86)	0.203
Week 10	-6.2 (0.79) 89	-4.4 (0.80) 88		-1.8 (-3.99, 0.39)	0.107
Week 10 End Point	-6.0 (0.68) 128	-3.3 (0.69) 125		-2.7 (-4.55, -0.79)	0.006

APPENDIX 7.3.1

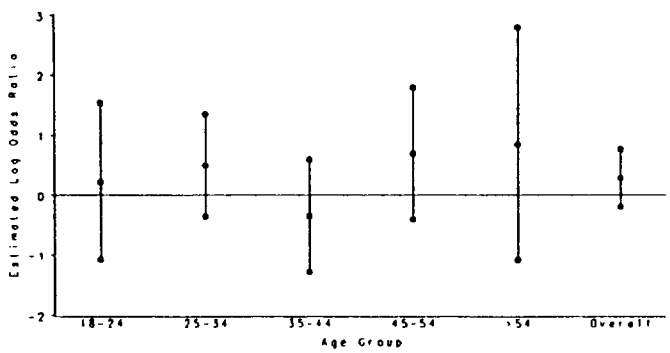
PREDICTORS OF RESPONSE

Figure 7.3.1.1 Natural Logarithm of Odds Ratio with 95% CI for Percentage Patients Free of Full Panic Attacks at Week 10 Endpoint by Age Group

Study 494 (excl. center 33)



Study 495 (excl. center 5)



Study 497

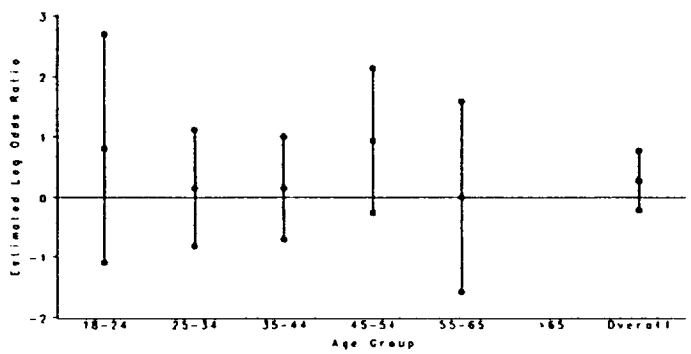
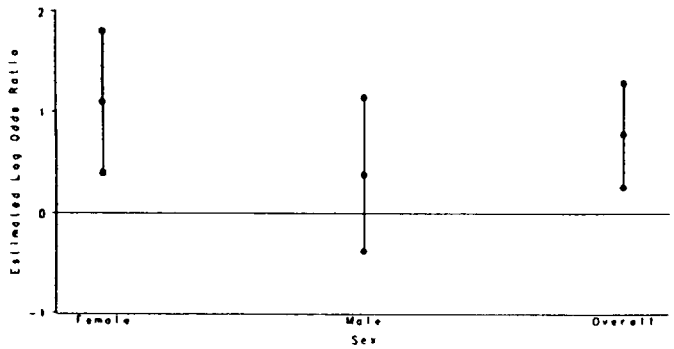
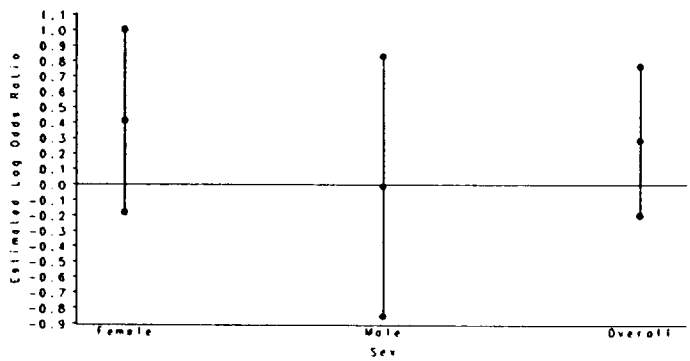


Figure 7.3.1.2 Natural Logarithm of Odds Ratio with 95% CI for Percentage Patients Free of Full Panic Attacks at Week 10 Endpoint by Gender

Study 494 (excl. center 33)



Study 495 (excl. center 5)



Study 497

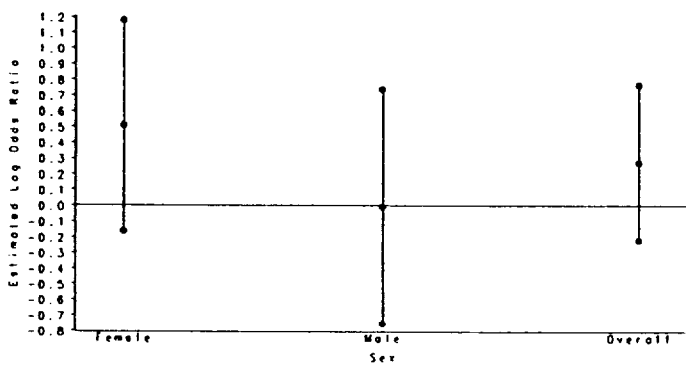
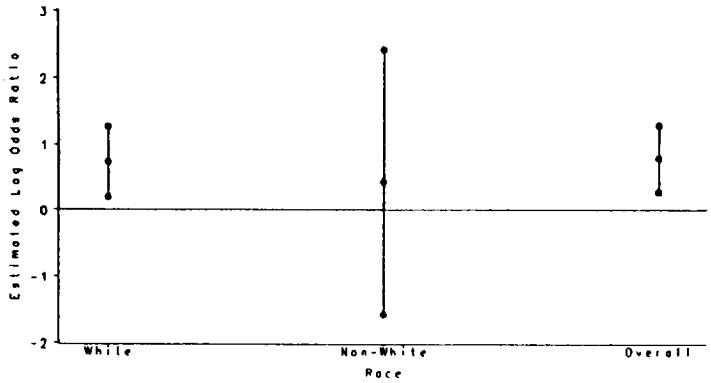
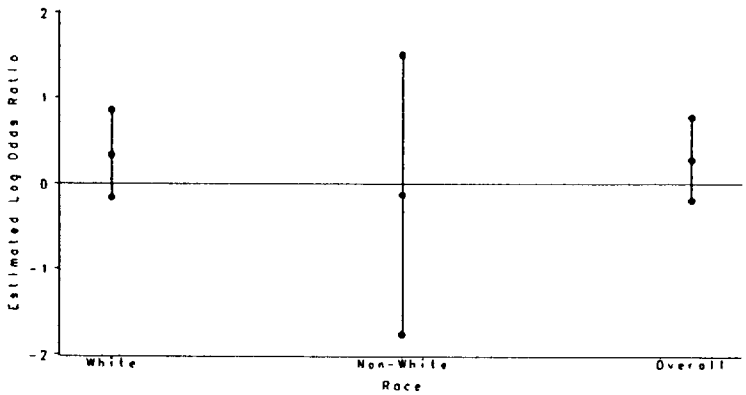


Figure 7.3.1.3 Natural Logarithm with 95% CI of Odds Ratio for Percentage Patients Free of Full Panic Attacks at Week 10 Endpoint by Race

Study 494 (excl. center 33)



Study 495 (excl. center 5)



Study 497

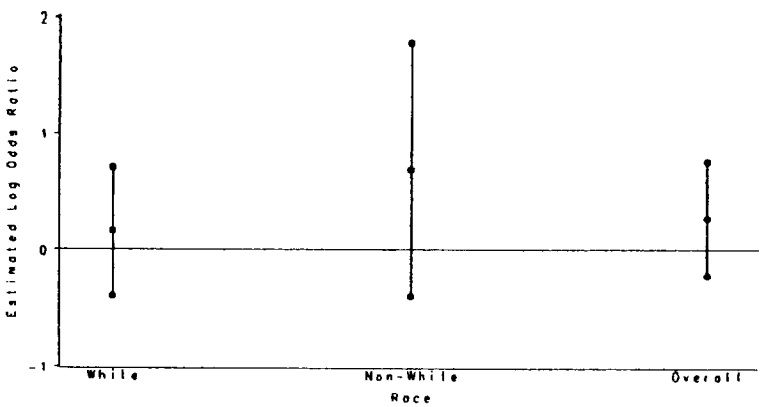
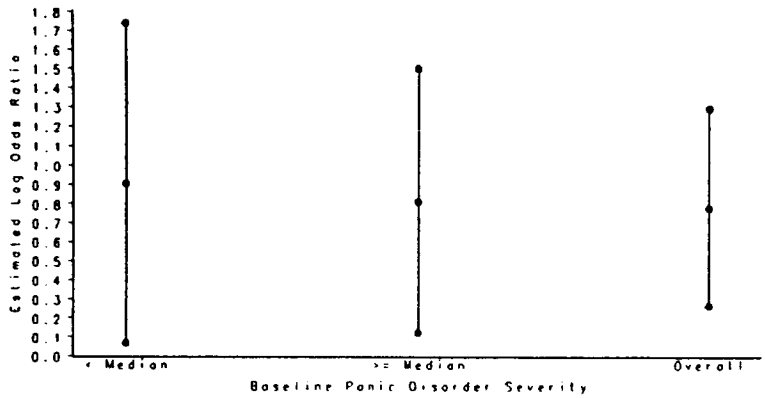
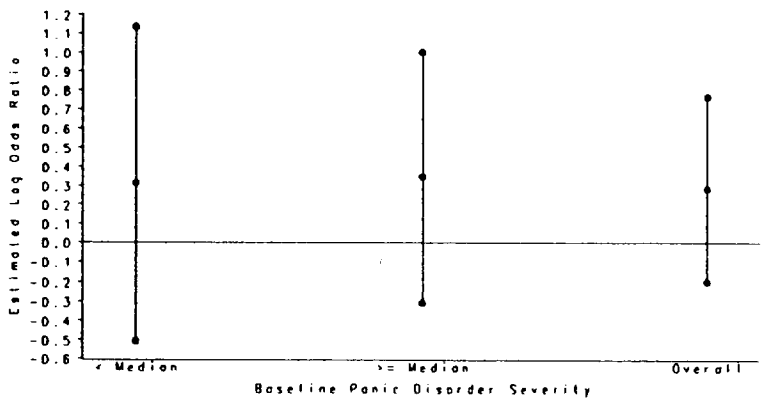


Figure 7.3.1.4 Natural Logarithm with 95% CI of Odds Ratio for Percentage Patients Free of Full Panic Attacks at Week 10 Endpoint by Severity of Panic Disorder at Baseline

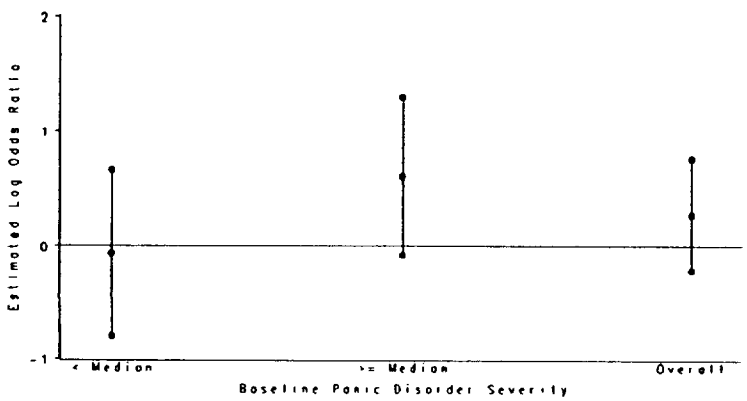
Study 494 (excl. center 33)



Study 495 (excl. center 5)



Study 497



APPENDIX 8.1

SAFETY FINDINGS

TABLE 8.1.2: Line Listing of Patients with Non-Fatal Serious Adverse Events (Studies 494, 495, and 497)					
Patient ID	**Age (yrs)**	**Sex**	**Dose at Onset (mg/day)**	**Day of Onset**	**Serious Event(s)**
Paroxetine CR					
494.021.00043	25	F	Unknown	Unknown	Ectopic pregnancy.
494.024.00345	48	F	Unknown	Unknown	Myoclonus.
494.027.00417	29	F	25	22	Acute anxiety reaction.
494.007.00024	29	F	Unknown	Unknown	Unintended pregnancy.
495.017.00934	22	F	Unknown	Unknown	Unintended pregnancy.
495.030.01095	33	M	37.5	37	Stab wound.
495.012.00994	33	M	25	43	Rhabdomyolysis.
495.028.01111	36	F	62.5	39	Depression.
497.004.01206	42	F	62.5	35	Unintended overdose.
497.002.02406	30	F	Unknown	Unknown	Unintended pregnancy.
Placebo					
494.022.00151	35	M	0	47	Agitation.
494.024.00518	21	F	0	Unknown	Unintended pregnancy.
494.025.00141	25	M	0	42	Arthritis.
495.009.00877	48	F	0	24	Traumatic bone fracture.
495.023.00968	42	F	0	37	Dyspepsia.
497.007.01428	21	F	0	~64	Unintended pregnancy.
494.027.00067	41	M	0	80	Kidney calculus (post-treatment).
497.004.01758	48	M	0	71	Pancreatitis (post-treatment)

TABLE 8.1.4.2: TREATMENT-EMERGENT ADVERSE EVENTS IN ≥1% OF PAROXETINE CR PATIENTS DURING THE TREATMENT PHASES OF STUDIES 494, 495, AND 497 [1,2]		
	% Reporting Event	
	Par CR (n=444)	Placebo (n=445)
Body as a Whole		
Asthenia	15%	10%
Abdominal Pain	6%	4%
Trauma[3]	5%	4%
Cardiovascular System		
Vasodilatation[4]	3%	2%
Digestive System		
Nausea	23%	17%
Dry Mouth	13%	9%
Diarrhea	12%	9%
Constipation	9%	6%
Decreased Appetite	8%	6%
Metabolic/Nutritional Disorders		
Weight Loss	1%	0%
Musculoskeletal System		
Myalgia	5%	3%
Nervous System		
Insomnia	20%	11%
Somnolence	20%	9%
Libido Decreased	9%	4%
Nervousness	8%	7%
Tremor	8%	2%
Anxiety	5%	4%
Agitation	3%	2%
Hypertonia[5]	2%	1%
Myoclonus	2%	1%

[1] Percentages are rounded to the nearest whole percent.
[2] Adverse events for which the paroxetine CR reporting rate was less than or equal to the placebo rate are not included. These events are: abnormal dreams, allergic reaction, back pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression, dizziness, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection, menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis, tachycardia, taste perversion, thinking abnormal, urinary tract infection, vomiting.
[3] Various physical injuries.
[4] Mostly flushing.
[5] Mostly muscle tightness or stiffness.

TABLE 8.1.4.2: TREATMENT-EMERGENT ADVERSE EVENTS IN ≥1% OF PAROXETINE CR PATIENTS DURING THE TREATMENT PHASES OF STUDIES 494, 495, AND 497 [1,2]		
	% Reporting Event	
	Par CR (n=444)	Placebo (n=445)
Respiratory System		
Sinusitis	8%	5%
Yawning	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal Vision[6]	3%	1%
Urogenital System		
Abnormal Ejaculation[7]	27%	3%
Impotence[7]	10%	1%
Female Genital Disorders[8,9]	7%	1%
Vaginitis[8]	1%	0%
Urinary Frequency	2%	1%
Urination Impaired	2%	0%

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[6] Mostly blurred vision.
[7] Based on the number of male patients.
[8] Based on the number of female patients.
[9] Mostly anorgasmia or difficulty achieving orgasm.

Table 8.1.4.5: Other Events Observed During Premarketing Panic Studies (494, 495, 497) with Paroxetine CR[10,11,12]
Body as a Whole
Abnormal laboratory value (+alprazolam on drug screen), accidental overdose, anaphylactoid reaction, cellulitis, chills, flu syndrome, malaise.
Cardiovascular System
Bradycardia, hemorrhage, hypertension, hypotension, palpitation, syncope.
Digestive System
Bruxism, digestive system disorder, dysphagia, eructation, gastroenteritis, gastrointestinal disorder, gingivitis, gum hyperplasia, increased salivation, liver function tests abnormal, melena, tooth disorder, ulcerative stomatitis.
Endocrine System
Testes disorder (testicular pain).
Hemic and Lymphatic System
Lymphadenopathy, purpura, thrombocytopenia.
Metabolic and Nutritional Disorders
Bilirubinemia, dehydration, generalized edema, hyperglycemia, hypokalemia, SGOT increased, SGPT increased, thirst, weight gain.
Musculoskeletal System
Arthralgia, arthritis, arthrosis, myopathy, myositis, tendinous disorder.
Nervous System
Alcohol abuse, amnesia, ataxia, convulsion, depersonalization, drug dependence, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, incoordination, lack of emotion, neuropathy, nystagmus, paralysis (facial weakness), paranoid reaction, withdrawal syndrome.
Respiratory System
Dyspnea, epistaxis, larynx disorder, pneumonia.
Skin and Appendages
Acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, herpes simplex, photosensitivity, pruritis, rash, benign skin neoplasm, urticaria.

[10] Events listed in Table 8.1.4.2 are excluded.
[11] All events in this table were reported at a frequency between 1/100 and 1/1,000 within the pool of studies 494, 495, and 497 (N=444).
[12] Gender-specific event rates have been corrected for the number of males or females, as appropriate.

Special Senses
Ear pain, eye disorder, eye pain, keratoconjunctivitis, mydriasis, otitis externa, otitis media, photophobia, tinnitus, visual field defect.
Urogenital System
Albuminuria, amenorrhea, breast enlargement, breast pain, cystitis, dysuria, ectopic pregnancy, nocturia, pregnancy, prostate disorder, urinary retention, vaginal moniliasis.

Table 8.1.5.2 Predetermined Clinical Laboratory Values of Potential Clinical Concern

Hematology	
Hemoglobin - Male	≤ 115 gL
Hemoglobin - Female	≤ 95 gL
Hematocrit - Male	≤ 37%
Hematocrit - Female	≤ 32%
WBC	≤ 2.8 or ≥ 16.0 x109L
Lymphocytes	≥ 75%
Monocytes	≥ 15%
Basophils	≥ 10%
Eosinophils	≥ 10%
Platelets	≤ 75 or ≥ 700 x109L
Bands	≥ 10%
Segmented Neutrophils	≤ 15%
Blood Chemistry	
BUN (Blood Urea Nitrogen)	≥ 30 mgdL
Serum creatinine	≥ 2.3 mgdL
Total bilirubin	≥ 2.0 mgdL
SGOT (AST)	≥ 150 UL
SGPT (ALT)	≥ 165 UL
Alkaline phosphatase	≥ 390 UL
Chloride	≤ 90 or ≥118 mmolL
Potassium	≤ 3 or ≥ 6 mmolL
Sodium	≤ 126 or ≥ 156 mmolL

TABLE 8.1.5.3:
PROPORTIONS OF PATIENTS WITH LABORATORY VALUES OF POTENTIAL CLINICAL CONCERN
(STUDIES 494, 495, AND 497)

Test	Paroxetine CR			Placebo		
	N	n	%	N	n	%
↓Hemoglobin	444	1	<1%	445	0	0%
↓Hematocrit	444	2	<1%	445	2	<1%
↑Eosinophils	444	1	<1%	445	3	<1%
↓Platelets	444	1	<1%	445	1	<1%
↑Creatinine	444	0	0%	445	1	<1%
↑Bilirubin	444	1	<1%	445	1	<1%
↑AST	444	3	<1%	445	0	0%
↑ALT	444	4	<1%	445	0	0%
↓Chloride	444	1	<1%	445	0	0%

Key: N=total number of patients with test values.
n=number with values of potential clinical concern that emerged post-baseline.
%=(n/N)×100%.

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Table 8.1.6.2: Vital Sign Values of Potential Clinical Concern

Systolic Blood Pressure	
Significant Increase	Increase of >= 40 mmHg from baseline
Significant Decrease	Decrease of >= 30 mmHg from baseline
Diastolic Blood Pressure	
Significant Increase	Increase of >= 30 mmHg from baseline
Significant Decrease	Decrease of >= 20 mmHg from baseline
Heart Rate	
Significant Increase	Increase of >= 30 bpm from baseline
Significant Decrease	Decrease of >= 30 bpm from baseline
Body Weight	
Significant Increase	Increase of >= 7% from baseline
Significant Decrease	Decrease of >= 7% from baseline

TABLE 8.1.6.3:
PROPORTIONS OF PATIENTS WITH VITAL SIGN MEASUREMENTS OF POTENTIAL CLINICAL CONCERN (STUDIES 494, 495, AND 497)

Sitting Diastolic BP (mmHg)

Treatment Group	Paroxetine CR		Placebo	
	N	%	N	%
Significant Increase	0	0.0	4	0.9
Significant Decrease	39	8.9	43	9.7
Number with Assessment	444	100.0	445	100.0

Sitting Systolic BP (mmHg)

Treatment Group	Paroxetine CR		Placebo	
	N	%	N	%
Significant Increase	1	0.2	5	1.1
Significant Decrease	19	4.3	20	4.5
Number with Assessment	444	100.0	445	100.0

Pulse (bpm)

Treatment Group	Paroxetine CR		Placebo	
	N	%	N	%
Significant Increase	10	2.3	17	3.8
Significant Decrease	7	1.6	8	1.8
Number with Assessment	444	100.0	445	100.0

Weight (lbs)

Treatment Group	Paroxetine CR		Placebo	
	N	%	N	%
Significant Increase	12	2.7	7	1.6
Significant Decrease	12	2.7	6	1.4
Number with Assessment	444	100.0	445	100.0