For reasons discussed previously, I consider study 448 to be failed.

Results from all three studies are summarized below in Table 7.4. The timepoint considered as primary is the week 12 visit since, in studies 449 and 487, at least 70% of the paroxetine CR and placebo patients completed this visit. In study 448, less than 70% completed the week 12 visit, with over 70% completing the week 8 visit; however, as discussed in the above review of that study, consideration of week 8 results does not change the overall efficacy conclusions from that trial.

Table 7.4: Summary of Efficacy Results (statistical significance of drug/placebo differences in adjusted mean change from baseline to week 12)

Study	Study Drug	HAM-D total		HAM-D item 1		CGI-severity	
		LOCF	OC	LOCF	OC	LOCF	OC
448[1]	Par CR	ns	ns	*	*	tr	*
	Par IR	ns	ns	ns	*	ns	ns
449	Par CR	**	**	**	*	*	ns
	Par IR	tr	ns	*	ns	ns	ns
487	Par CR	**	**	**	**	*	**
	Par IR	**	**	**	**	*	**

Codes: ns= not significant ($p>0.10$)
tr= trend ($0.05<p\leq0.10$)
* = significant ($0.01<p\leq0.05$)
**= highly significant ($p\leq0.01$)

In summary, these data are felt to be adequate to support the effectiveness claim for paroxetine CR in the treatment of depression in the dosage ranges of 25 to 62.5 mg/day for non-elderly adults and 12.5 to 50 mg/day for elderly patients.

[1] Results are based on the exclusion of center group 2/4.

8.0 Integrated Review of Safety

8.1 Methods and Findings for Safety Review

Paroxetine CR is a formulation of paroxetine with controlled release and delayed absorption characteristics compared to the approved immediate release product (Paxil). In view of the fact that extensive pre- and post-marketing safety experience has accumulated for paroxetine as the IR product, this safety review is more limited in scope than would be the case for an unapproved, new chemical entity.

This review will not explore safety findings from these studies associated with paroxetine IR given its extensive safety database to date and the strong likelihood that findings from this small database would not contribute substantially to already accumulated information.

Accordingly, this review will focus on the more significant adverse events (i.e., events associated with death, non-fatal events classified as serious, and events associated with premature termination) as well as any changes in laboratory, vital sign, and ECG parameters of potential clinical concern. Also, the common adverse event profile will be examined to discern any important differences between paroxetine CR and the marketed product, Paxil.

The ten Phase 1 and three Phase 3 depression studies comprise the safety database for this NDA.

8.1.1 Deaths

The sponsor reported all deaths occurring during study or within 30 days of last study medication dose.

No deaths occurred in the ten Phase 1 studies.

There were two deaths in Phase 3 trials:

Patient 448.021.00280 was a 19 year old male with recurrent major depression who received paroxetine IR in this study. Thirty-three days after randomization, his body was found. An autopsy revealed the cause of death to be severe myocarditis, with the time of death judged to be six days prior to discovery of his body. Pathology examination revealed chronic interstitial inflammation, predominantly in the right ventricle, and focal myocyte necrosis. No cardiac symptoms or abnormal laboratory, vital sign, or ECG findings were reported.

Patient 487.002.01373 was a 69 year old male randomized to paroxetine CR. He had completed 83 days of blinded treatment and finished a taper of study medication on day 91. Two days after completing the study, he died. No autopsy was performed. He had a long-standing history of hypertension and obesity and, according to the medical examiner, it appeared that the cause of death was cardiac failure.

Given the possibility of alternative etiologies in both cases and the lack of any known cardiac risk with paroxetine to date, neither case can be reasonably attributed to paroxetine, in my opinion. Nonetheless, the Division of Pharmacovigilance and Epidemiology was consulted on 6/1/98 to assess the risk of myocarditis with paroxetine based on available postmarketing data.

8.1.2 Other Serious Adverse Events

A serious non-fatal adverse event was defined as any event which was life-threatening, permanently or temporarily disabling or incapacitating, resulted in hospitalization, prolonged a hospital stay, or was associated with a congenital abnormality, cancer, or overdose. Additionally, this definition was expanded to include any experience which the investigator regarded as serious or which would suggest a significant hazard, contraindication, side effect, or precaution that may be associated with the study drug.

The sponsor reported all non-fatal serious adverse events occurring during study or within 30 days of last study medication dose for the ten Phase 1 and three Phase 3 studies.

In the ten Phase 1 studies, 5 volunteers experienced non-fatal serious adverse events (3 on paroxetine CR, 1 on a prototype formulation, and 1 on placebo).

In the pool of the three Phase 3 depression studies, a total of 40 patients had such events (11 on paroxetine CR, 18 on paroxetine IR, and 11 on placebo).

Data for these occurrences are summarized in a patient line listing, which can be found in Appendix 8.1, Table 8.1.2.2.

Narrative summaries for all patients treated with paroxetine CR who had a non-fatal serious event were examined to verify the characterization of adverse events in the above table.

Table 7.2.1.6 Study 448: HAM-D Depressed Mood Item (LOCF)

Baseline and Change from Baseline in HAMD Mood Item Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Mood Item Score and Duration of Current Episode of Depression
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.8	(0.06)	102	2.9	(0.06)	104	2.9	(0.06)	101						
Week 2 LOCF	-0.8	(0.14)	102	-0.6	(0.13)	104	-0.6	(0.13)	101	-0.2	(-0.45, 0.01)	0.062	-0.1	(-0.31, 0.15)	0.488
Week 4 LOCF	-1.4	(0.16)	102	-1.1	(0.16)	104	-1.0	(0.16)	101	-0.3	(-0.62, -0.07)	0.014	-0.1	(-0.35, 0.20)	0.608
Week 6 LOCF	-1.6	(0.17)	102	-1.4	(0.17)	104	-1.0	(0.16)	101	-0.6	(-0.88, -0.32)	<0.001	-0.4	(-0.69, -0.13)	0.005
Week 8 LOCF	-1.7	(0.19)	102	-1.5	(0.18)	104	-1.2	(0.18)	101	-0.5	(-0.82, -0.20)	0.001	-0.3	(-0.60, 0.03)	0.071
Week 12 LOCF	-1.8	(0.19)	102	-1.5	(0.19)	104	-1.2	(0.19)	101	-0.6	(-0.91, -0.26)	<0.001	-0.3	(-0.65, -0.00)	0.049

Table 7.2.1.7 Study 448: HAM-D Depressed Mood Item (OC)

Baseline and Change from Baseline in HAMD Depressed Mood Item Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Depressed Mood Item and Duration of Current Episode of Depression
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.8	(0.06)	102	2.9	(0.06)	104	2.9	(0.06)	101						
Week 1	-0.1	(0.10)	100	-0.1	(0.10)	103	-0.0	(0.10)	100	-0.1	(-0.29, 0.06)	0.188	-0.1	(-0.25, 0.10)	0.411
Week 2	-0.8	(0.14)	88	-0.6	(0.14)	84	-0.6	(0.14)	96	-0.3	(-0.52, -0.03)	0.026	-0.0	(-0.29, 0.21)	0.740
Week 3	-1.2	(0.15)	87	-1.0	(0.15)	87	-0.8	(0.15)	91	-0.5	(-0.74, -0.21)	<0.001	-0.2	(-0.48, 0.06)	0.130
Week 4	-1.5	(0.16)	86	-1.2	(0.16)	83	-1.1	(0.16)	93	-0.4	(-0.68, -0.12)	0.005	-0.1	(-0.41, 0.16)	0.405
Week 6	-1.9	(0.17)	78	-1.7	(0.16)	78	-1.1	(0.16)	87	-0.7	(-1.01, -0.43)	<0.001	-0.6	(-0.86, -0.27)	<0.001
Week 8	-1.9	(0.17)	80	-1.8	(0.17)	70	-1.3	(0.17)	79	-0.6	(-0.90, -0.28)	<0.001	-0.5	(-0.85, -0.20)	0.002
Week 12	-2.0	(0.19)	66	-1.9	(0.19)	57	-1.3	(0.18)	67	-0.7	(-1.04, -0.35)	<0.001	-0.6	(-0.94, -0.20)	0.002

Table 7.2.1.8 Study 448: CGI-severity (LOCF)

Baseline and Change from Baseline in CGI Severity of Illness Score
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons			
	Paroxetine CR		Paroxetine IR		Placebo		Paroxetine CR vs Placebo		Paroxetine IR vs Placebo	
	Median (Min,Max)	N	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value	Median (95% C.I.)	p-value
Baseline	4	96	4	100	4	99				
Week 2 LOCF	0	93	0	100	0	97	0 (0.0, 0.0)	0.570	0 (0.0, 0.0)	0.979
Week 4 LOCF	-1	93	-1	100	-1	97	0 (0.0, 0.0)	0.448	0 (0.0, 0.0)	0.900
Week 6 LOCF	-1	93	-1	100	-1	97	0 (-1.0, 0.0)	0.046	0 (0.0, 0.0)	0.307
Week 8 LOCF	-1.5	94	-1	100	-1	97	0 (-1.0, 0.0)	0.035	0 (-1.0, 0.0)	0.371
Week 12 LOCF	-2	96	-1	100	-1	99	-1 (-1.0, 0.0)	0.008	0 (-1.0, 0.0)	0.279

Table 7.2.1.9 Study 448: CGI-severity (OC)

Baseline and Change from Baseline in CGI Severity of Illness Score
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons			
	Paroxetine CR		Paroxetine IR		Placebo		Paroxetine CR vs Placebo		Paroxetine IR vs Placebo	
	Median (Min,Max)	N	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value	Median (95% C.I.)	p-value
Baseline	4	96	4	100	4	99				
Week 1	0	91	0	99	0	96	0 (0.0, 0.0)	0.791	0 (0.0, 0.0)	0.940
Week 2	0	80	0	81	0	92	0 (0.0, 0.0)	0.314	0 (0.0, 0.0)	0.723
Week 3	-1	78	-1	85	-1	87	0 (0.0, 0.0)	0.279	0 (0.0, 0.0)	0.400
Week 4	-1	77	-1	81	-1	89	0 (-1.0, 0.0)	0.148	0 (0.0, 0.0)	0.573
Week 6	-1	71	-1	77	-1	84	-1 (-1.0, 0.0)	0.006	0 (-1.0, 0.0)	0.042
Week 8	-2	73	-2	70	-1	75	-1 (-1.0, 0.0)	0.008	0 (-1.0, 0.0)	0.037
Week 12	-2	64	-2	57	-1	65	-1 (-1.0, 0.0)	0.002	0 (-1.0, 0.0)	0.081

Table 7.2.1.10 Study 448: HAM-D Total Score (LOCF) (Excl. Center 2/4)

Baseline and Change from Baseline in HAMD Total Score
Excluding Centre Group 002/004
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	22.9	(0.26)	94	23.3	(0.28)	96	23.2	(0.29)	93						
Week 2 LOCF	-6.6	(0.51)	94	-6.0	(0.52)	96	-6.3	(0.51)	93	-0.3	(-1.66, 1.12)	0.700	0.3	(-1.09, 1.70)	0.667
Week 4 LOCF	-9.8	(0.69)	94	-8.1	(0.70)	96	-9.4	(0.70)	93	-0.4	(-2.31, 1.47)	0.660	1.3	(-0.58, 3.21)	0.173
Week 6 LOCF	-10.6	(0.71)	94	-9.4	(0.72)	96	-9.0	(0.71)	93	-1.6	(-3.53, 0.32)	0.103	-0.4	(-2.36, 1.51)	0.665
Week 8 LOCF	-11.7	(0.75)	94	-10.0	(0.76)	96	-10.3	(0.76)	93	-1.4	(-3.50, 0.62)	0.170	0.3	(-1.82, 2.32)	0.810
Week 12 LOCF	-12.0	(0.81)	94	-10.7	(0.82)	96	-10.7	(0.81)	93	-1.3	(-3.50, 0.93)	0.254	0.1	(-2.14, 2.30)	0.941

Table 7.2.1.11 Study 448: HAM-D Total Score (OC) (Excl. Center 2/4)

Baseline and Change from Baseline in HAMD Total Score
Excluding Centre Group 002/004
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Statistical Analysis Presented at all Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	22.9	(0.26)	94	23.3	(0.28)	96	23.2	(0.29)	93						
Week 1	-3.9	(0.41)	92	-3.6	(0.42)	95	-3.2	(0.41)	92	-0.6	(-1.77, 0.48)	0.258	-0.4	(-1.51, 0.73)	0.496
Week 2	-7.3	(0.55)	80	-6.5	(0.56)	77	-6.3	(0.52)	89	-1.0	(-2.43, 0.47)	0.184	-0.1	(-1.62, 1.35)	0.855
Week 3	-9.6	(0.65)	79	-7.4	(0.66)	79	-7.9	(0.63)	84	-1.7	(-3.45, 0.03)	0.055	0.5	(-1.31, 2.22)	0.613
Week 4	-11.0	(0.73)	78	-9.3	(0.76)	75	-9.8	(0.69)	86	-1.2	(-3.20, 0.70)	0.208	0.5	(-1.51, 2.48)	0.635
Week 6	-12.0	(0.73)	71	-11.6	(0.76)	70	-9.6	(0.70)	79	-2.4	(-4.41, -0.47)	0.015	-2.0	(-4.01, -0.04)	0.045
Week 8	-13.8	(0.71)	72	-13.7	(0.78)	62	-11.6	(0.70)	74	-2.2	(-4.13, -0.26)	0.026	-2.1	(-4.14, -0.06)	0.044
Week 12	-14.4	(0.86)	58	-14.2	(0.96)	50	-12.4	(0.84)	61	-1.9	(-4.27, 0.45)	0.111	-1.8	(-4.23, 0.73)	0.164

Table 7.2.1.12 Study 448: HAM-D Depressed Mood Item (LOCF) (Excl. Center 2/4)

Baseline and Change from Baseline in HAMD Mood Item Score
Excluding Centre Group 002/004
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Mood Item Score and Duration of Current Episode of Depression
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.8	(0.06)	94	2.9	(0.07)	96	2.9	(0.06)	93						
Week 2 LOCF	-0.7	(0.14)	94	-0.6	(0.14)	96	-0.6	(0.14)	93	-0.2	(-0.40, 0.09)	0.213	-0.0	(-0.29, 0.20)	0.697
Week 4 LOCF	-1.3	(0.17)	94	-1.0	(0.16)	96	-1.0	(0.16)	93	-0.3	(-0.58, -0.01)	0.046	-0.0	(-0.31, 0.27)	0.899
Week 6 LOCF	-1.5	(0.17)	94	-1.3	(0.17)	96	-1.0	(0.17)	93	-0.5	(-0.84, -0.25)	<0.001	-0.4	(-0.67, -0.07)	0.015
Week 8 LOCF	-1.6	(0.19)	94	-1.4	(0.19)	96	-1.2	(0.18)	93	-0.4	(-0.77, -0.12)	0.008	-0.2	(-0.53, 0.13)	0.240
Week 12 LOCF	-1.7	(0.20)	94	-1.4	(0.19)	96	-1.2	(0.19)	93	-0.4	(-0.77, -0.09)	0.013	-0.2	(-0.52, 0.16)	0.296

Table 7.2.1.13 Study 448: HAM-D Depressed Mood Item (OC) (Excl. Center 2/4)

Baseline and Change from Baseline in HAMD Depressed Mood Item Score
Excluding Centre Group 002/004
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Depressed Mood Item and Duration of Current Episode of Depression
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.8	(0.06)	94	2.9	(0.07)	96	2.9	(0.06)	93						
Week 1	-0.1	(0.11)	92	-0.1	(0.11)	95	-0.0	(0.11)	92	-0.1	(-0.27, 0.10)	0.382	-0.1	(-0.27, 0.11)	0.408
Week 2	-0.8	(0.15)	80	-0.6	(0.15)	77	-0.6	(0.14)	89	-0.2	(-0.49, 0.04)	0.090	-0.0	(-0.28, 0.26)	0.943
Week 3	-1.2	(0.16)	79	-0.9	(0.16)	79	-0.8	(0.15)	84	-0.4	(-0.69, -0.12)	0.005	-0.1	(-0.42, 0.16)	0.369
Week 4	-1.5	(0.17)	78	-1.2	(0.17)	75	-1.1	(0.16)	86	-0.4	(-0.67, -0.08)	0.014	-0.1	(-0.39, 0.22)	0.596
Week 6	-1.8	(0.17)	71	-1.6	(0.17)	70	-1.1	(0.17)	79	-0.7	(-0.98, -0.36)	<0.001	-0.5	(-0.84, -0.21)	0.001
Week 8	-1.8	(0.18)	72	-1.8	(0.18)	62	-1.3	(0.17)	74	-0.5	(-0.86, -0.19)	0.002	-0.4	(-0.79, -0.10)	0.012
Week 12	-1.9	(0.20)	58	-1.8	(0.19)	50	-1.4	(0.19)	61	-0.5	(-0.83, -0.10)	0.012	-0.4	(-0.79, -0.01)	0.043

Table 7.2.1.14 Study 448: CGI-severity (LOCF) (Excl. Center 2/4)

Baseline and Change from Baseline in CGI Severity of Illness Score
Excluding Centre Group 002/004
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons			
	Paroxetine CR		Paroxetine IR		Placebo		Paroxetine CR vs Placebo		Paroxetine IR vs Placebo	
	Median (Min,Max)	N	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value	Median (95% C.I.)	p-value
Baseline	4	88	4	92	4	91				
Week 2 LOCF	0	85	0	92	0	89	0 (0.0, 0.0)	0.980	0 (0.0, 0.0)	0.586
Week 4 LOCF	-1	85	-1	92	-1	89	0 (0.0, 0.0)	0.792	0 (0.0, 0.0)	0.618
Week 6 LOCF	-1	85	-1	92	-1	89	0 (-1.0, 0.0)	0.163	0 (0.0, 0.0)	0.522
Week 8 LOCF	-1	86	-1	92	-1	89	0 (-1.0, 0.0)	0.120	0 (0.0, 0.0)	0.764
Week 12 LOCF	-2	88	-1	92	-1	91	0 (-1.0, 0.0)	0.085	0 (0.0, 0.0)	0.785

Table 7.2.1.15 Study 448: CGI-severity (OC) (Excl. Center 2/4)

Baseline and Change from Baseline in CGI Severity of Illness Score
Excluding Centre Group 002/004
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons			
	Paroxetine CR		Paroxetine IR		Placebo		Paroxetine CR vs Placebo		Paroxetine IR vs Placebo	
	Median (Min,Max)	N	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value	Median (95% C.I.)	p-value
Baseline	4	88	4	94	4	91				
Week 1	0	83	0	91	0	88	0 (0.0, 0.0)	0.782	0 (0.0, 0.0)	0.947
Week 2	0	72	0	74	0	85	0 (0.0, 0.0)	0.638	0 (0.0, 0.0)	0.870
Week 3	-1	70	-1	77	-1	80	0 (0.0, 0.0)	0.726	0 (0.0, 0.0)	0.995
Week 4	-1	69	-1	73	-1	82	0 (-1.0, 0.0)	0.320	0 (0.0, 0.0)	0.816
Week 6	-1	64	-1	69	-1	76	0 (-1.0, 0.0)	0.033	0 (-1.0, 0.0)	0.111
Week 8	-2	65	-1.5	62	-1	70	0 (-1.0, 0.0)	0.033	0 (-1.0, 0.0)	0.143
Week 12	-2	56	-2	50	-2	59	0 (-1.0, 0.0)	0.045	0 (-1.0, 0.0)	0.357

APPENDIX 7.2.2

EFFICACY DATA: STUDY 449

Table 7.2.2.1
Study 449: Investigators/Sites

Investigators and Their Hospital of University Affiliation		
Investigator	**Affiliated Institution**	**Location**
Bijan Bastani, MD	Comprehensive Psychiatric Services	Akron, OH
Barry Baumel, MD	Neuromedical Research Associates	Miami Beach, FL
Robert J. Bielski, MD	Institute for Health Studies	Okemos, MI
William J. Burke, MD	University of Nebraska Medical Center	Omaha, NE
Cal Cohn, MD	Hauser Clinic	Houston, TX
Howard Conter, MD	MSHJ Research Associates, Inc.	Halifax, NS
Robert DuPont, MD	The Inst. for Behavioral and Health, Inc.	Rockville, MD
Dwight I. Evans, MD	University of Florida College of Medicine	Gainesville, FL
Maurizio Fava, MD	Massachuseus General Hospital	Boston, MA
Al Feiger, MD	Feiger Health Research Center	Wheat Ridge, CO
Robert Fiddes, MD	Southern California Research Institute	Whittier, CA
Jon Heiser, MD	Pharmacology Research Institute	Newport Beach, CA
Michael Liebowitz, MD	New York State Psychiatric Institute	New York, NY
Peter Londborg, MD	Seattle Clinical Research Center	Seattle, WA
Nilesh J. Patel, MD	R/D Clinical Research, Inc.	Lake Jackson, TX
Robin Reessal, MD	Western Canadian Behaviour Res. Centre	Alberta, CG
Robert Riesenberg, MD	Behavioral Atlanta	Decatur, GA
Ward T. Smith, MD	Pacific Northwest Clinical Research	Portland, OR
Theresa G. Walsh, MD Nicholas W. Telew, MD	Oregon Center for Clin. Investigations, Inc.	Eugene, OR
Kenneth Weiss, MD	Delaware Valley Research Associates, Inc.	King of Prussia, PA
Source: Appendix A, Curriculum Vitae		

APPEARS THIS WAY
ON ORIGINAL

Table 7.2.2.2
Study 449: Baseline Characteristics

Demographic Characteristics of Patients Included in the Intention To Treat Population

	Paroxetine CR N=108		Paroxetine IR N=112		Placebo N=110	
	n	%	n	%	n	%
Age (years)						
18 - 24	4	3.70	10	8.93	7	6.36
25 - 34	27	25.00	30	26.79	35	31.82
35 - 44	27	25.00	31	27.68	23	20.91
45 - 54	34	31.48	20	17.86	26	23.64
55 - 65	16	14.81	20	17.86	19	17.27
>65	0	0.00	1	0.89	0	0.00
Mean Age (SD) (years)	42.38 ± 10.8		40.55 ± 12.14		40.71 ± 11.58	
Minimum Age						
Maximum Age						
Mean Weight (SD) (Lb)	177.58 ± 46.19		174.74 ± 35.78		173.42 ± 41.08	
Minimum Weight						
Maximum Weight						
	CR	**N=108**	**IR**	**N=112**	**Placebo**	**N=110**
	n	%	n	%	n	%
Gender						
Female	72	66.67	83	74.11	66	60.00
Male	36	33.33	29	25.89	44	40.00
Race						
Black	6	5.56	8	7.14	2	1.82
Oriental	2	1.85	0	0.00	0	0.00
Other	8	7.41	10	8.93	14	12.73
White	92	85.19	94	83.93	94	85.45

Source: Data Source Table 13.4b, Section 13, Appendix B Listing 13.4

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ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table 7.2.2.3
Study 449: Patients In-Study by Visit

Number (%) of Patients in the ITT Population Remaining at Each Visit

	Paroxetine CR		Paroxetine IR		Placebo		Total	
	N	%	N	%	N	%	N	%
Baseline	108	100.0	112	100.0	110	100.0	330	100
Week 1	104	96.3	102	91.1	104	94.5	310	93.9
Week 2	103	95.4	99	88.4	102	92.7	304	92.1
Week 3	97	89.8	96	85.7	97	88.2	290	87.9
Week 4	94	87.0	90	80.4	94	85.5	278	84.2
Week 6	89	82.4	84	75.0	89	80.9	262	79.4
Week 8	85	78.7	79	70.5	81	73.6	245	74.2
Week 12*	81	75.0	75	67.0	77	70.0	233	70.6

Data Source: Data source Table 13.3.2b, Appendix B, Listing 13.3b
* (see Section 11.1, and Data Source Table 13.13)

APPEARS THIS WAY
ON ORIGINAL

Table 7.2.2.4 Study 449: HAM-D Total Score

Baseline and Change from Baseline in HAMD Total Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Intention to Treat Population

	Treatment Groups									Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	23.8	(0.33)	108	23.7	(0.29)	110	23.5	(0.30)	110						
Week 1	-4.0	(0.47)	106	-3.5	(0.46)	108	-4.1	(0.45)	109						
Week 2	-7.0	(0.57)	101	-6.5	(0.57)	99	-5.9	(0.57)	102						
Week 3	-9.0	(0.63)	98	-8.6	(0.64)	93	-8.3	(0.63)	98						
Week 4	-10.8	(0.67)	95	-10.8	(0.68)	89	-9.9	(0.67)	93	-1.0	(-2.76, 0.81)	0.282	-0.9	(-2.76, 0.92)	0.326
Week 6	-12.9	(0.72)	93	-11.6	(0.73)	87	-10.0	(0.72)	91						
Week 8	-14.7	(0.74)	83	-13.6	(0.74)	83	-11.0	(0.73)	87	-3.7	(-5.64, -1.73)	<0.001	-2.6	(-4.63, -0.64)	0.010
Week 12	-15.7	(0.86)	77	-13.9	(0.93)	66	-12.4	(0.89)	72	-3.3	(-5.59, -1.01)	0.005	-1.5	(-3.91, 0.99)	0.241
70% End Point	-12.7	(0.74)	108	-11.5	(0.72)	110	-9.6	(0.72)	110	-3.1	(-5.04, -1.15)	0.002	-1.9	(-3.87, 0.04)	0.055
Wk 12 End Point	-13.3	(0.79)	108	-12.1	(0.78)	110	-10.2	(0.78)	110	-3.1	(-5.18, -0.99)	0.004	-1.9	(-3.96, 0.24)	0.083

Table 7.2.2.5 Study 449: HAM-D Depressed Mood Item

Baseline and Change from Baseline in HAMD Depressed Mood Item Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Depressed Mood Item and Duration of Current Episode of Depression
Intention to Treat Population

	Treatment Groups									Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.9	(0.06)	108	2.9	(0.06)	110	2.8	(0.06)	110						
Week 1	-0.3	(0.12)	106	-0.2	(0.12)	108	-0.1	(0.12)	109						
Week 2	-0.4	(0.16)	101	-0.4	(0.17)	99	-0.1	(0.16)	102						
Week 3	-0.8	(0.17)	98	-0.9	(0.17)	93	-0.7	(0.17)	98						
Week 4	-1.1	(0.18)	95	-1.1	(0.18)	89	-0.8	(0.19)	93	-0.3	(-0.54, 0.03)	0.082	-0.3	(-0.56, 0.02)	0.069
Week 6	-1.3	(0.21)	93	-1.3	(0.21)	87	-0.7	(0.21)	91						
Week 8	-1.7	(0.26)	83	-1.6	(0.27)	83	-1.1	(0.27)	87	-0.6	(-0.92, -0.34)	<0.001	-0.5	(-0.80, -0.20)	<0.001
Week 12	-1.4	(0.29)	77	-1.3	(0.31)	66	-1.0	(0.31)	72	-0.4	(-0.77, -0.08)	0.016	-0.3	(-0.62, 0.11)	0.169
70% End Point	-1.4	(0.16)	108	-1.2	(0.17)	110	-0.8	(0.16)	110	-0.6	(-0.88, -0.29)	<0.001	-0.4	(-0.70, -0.11)	0.008
Wk 12 End Point	-1.3	(0.17)	108	-1.2	(0.18)	110	-0.8	(0.17)	110	-0.5	(-0.81, -0.18)	0.002	-0.4	(-0.70, -0.07)	0.017

Table 7.2.2.6 Study 449: CGI-severity

Baseline and Change from Baseline in CGI Severity of Illness Score
Intention to Treat Population

	Treatment Groups: Paroxetine CR			Paroxetine IR			Placebo			Pairwise Comparisons: Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Median	(Min,Max)	N	Median	(Min,Max)	N	Median	(Min,Max)	N	Median	(95% C.I.)	p-value	Median	(95% C.I.)	p-value
Baseline	4		99	4		102	4		99						
Week 1	0		97	0		99	0		96						
Week 2	0		92	0		90	0		93						
Week 3	-0.5		90	-1		85	-1		90						
Week 4	-1		87	-1		83	-1		83	0	(-1.0, 0.0)	0.227	0	(-1.0, 0.0)	0.102
Week 6	-1		84	-1		79	-1		83	-1	(-1.0, 0.0)	0.007	0	(-1.0, 0.0)	0.066
Week 8	-2		76	-2		76	-1		79	0	(-1.0, 0.0)	0.147	0	(-1.0, 0.0)	0.638
Week 12	-2		70	-2		60	-2		64						
70% End Point	-1		99	-1		102	-1		98	0	(-1.0, 0.0)	0.013	0	(-1.0, 0.0)	0.135
Wk 12 End Point	-2		99	-2		102	-1		98	0	(-1.0, 0.0)	0.042	0	(-1.0, 0.0)	0.335

Table 7.2.2.7 Study 449: HAM-D Total Score (Excl. Center 17)

Baseline and Change from Baseline in HAMD Total Score
Excluding Centre 017
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Intention to Treat Population

	Treatment Groups: Paroxetine CR			Paroxetine IR			Placebo			Pairwise Comparisons: Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	23.9	(0.33)	103	23.9	(0.30)	104	23.7	(0.31)	104						
Week 1	-4.0	(0.49)	101	-3.6	(0.48)	102	-4.3	(0.48)	104						
Week 2	-6.9	(0.59)	97	-6.7	(0.60)	93	-6.0	(0.59)	97						
Week 3	-9.0	(0.65)	94	-8.9	(0.67)	87	-8.4	(0.64)	95						
Week 4	-11.0	(0.69)	90	-11.1	(0.71)	83	-10.1	(0.69)	89	-0.9	(-2.76, 0.90)	0.317	-1.0	(-2.88, 0.93)	0.314
Week 6	-13.1	(0.74)	88	-12.0	(0.76)	82	-10.2	(0.74)	87						
Week 8	-14.8	(0.77)	78	-14.1	(0.78)	78	-11.1	(0.74)	84	-3.7	(-5.74, -1.73)	<0.001	-3.0	(-5.05, -0.92)	0.005
Week 12	-15.8	(0.87)	74	-14.3	(0.96)	63	-12.4	(0.90)	71	-3.3	(-5.65, -1.02)	0.005	-1.9	(-4.35, 0.62)	0.140
70% End Point	-12.8	(0.76)	103	-11.8	(0.76)	104	-9.8	(0.75)	104	-3.0	(-5.05, -1.00)	0.004	-2.0	(-4.05, 0.03)	0.054
Wk 12 End Point	-13.3	(0.82)	103	-12.3	(0.81)	104	-10.4	(0.81)	104	-3.0	(-5.13, -0.79)	0.008	-2.0	(-4.15, 0.23)	0.080

Table 7.2.2.8 Study 449: HAM-D Depressed Mood Item (Excl. Center 17)

Baseline and Change from Baseline in HAMD Depressed Mood Item Score
Excluding Centre 017
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Depressed Mood Item and Duration of Current Episode of Depression
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.9	(0.06)	103	2.9	(0.06)	104	2.8	(0.06)	104						
Week 1	-0.3	(0.13)	101	-0.3	(0.13)	102	-0.2	(0.13)	104						
Week 2	-0.4	(0.16)	97	-0.4	(0.17)	93	-0.1	(0.16)	97						
Week 3	-0.9	(0.17)	94	-1.0	(0.17)	87	-0.7	(0.17)	95						
Week 4	-1.2	(0.18)	90	-1.2	(0.18)	83	-0.9	(0.19)	89	-0.2	(-0.52, 0.05)	0.110	-0.3	(-0.59, 0.00)	0.051
Week 6	-1.3	(0.21)	88	-1.4	(0.21)	82	-0.8	(0.21)	87						
Week 8	-1.7	(0.26)	78	-1.7	(0.26)	78	-1.1	(0.26)	84	-0.6	(-0.92, -0.34)	<0.001	-0.6	(-0.88, -0.28)	<0.001
Week 12	-1.5	(0.29)	74	-1.4	(0.31)	63	-1.0	(0.30)	71	-0.4	(-0.77, -0.08)	0.017	-0.4	(-0.72, 0.02)	0.061
70% End Point	-1.4	(0.16)	103	-1.3	(0.17)	104	-0.8	(0.16)	104	-0.5	(-0.85, -0.24)	<0.001	-0.4	(-0.75, -0.14)	0.004
Wk 12 End Point	-1.2	(0.17)	103	-1.2	(0.18)	104	-0.8	(0.17)	104	-0.5	(-0.77, -0.13)	0.006	-0.4	(-0.76, -0.11)	0.009

Table 7.2.2.9 Study 449: CGI-severity (Excl. Center 17)

Baseline and Change from Baseline in CGI Severity of Illness Score
Excluding Centre 017
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Median	(Min,Max)	N	Median	(Min,Max)	N	Median	(Min,Max)	N	Median	(95% C.I.)	p-value	Median	(95% C.I.)	p-value
Baseline	4		94	4		96	4		93						
Week 1	0		92	0		93	0		92						
Week 2	0		88	0		84	0		88						
Week 3	-1		86	-1		79	-1		87						
Week 4	-1		82	-1		77	-1		79	0	(-1.0, 0.0)	0.285	0	(-1.0, 0.0)	0.139
Week 6	-1		79	-1		74	-1		79						
Week 8	-2		71	-2		71	-1		76	-1	(-1.0, 0.0)	0.009	0	(-1.0, 0.0)	0.063
Week 12	-2		67	-2		57	-2		63	0	(-1.0, 0.0)	0.148	0	(-1.0, 0.0)	0.515
70% End Point	-1.5		94	-1		96	-1		93	0	(-1.0, 0.0)	0.022	0	(-1.0, 0.0)	0.189
Wk 12 End Point	-2		94	-2		96	-1		93	0	(-1.0, 0.0)	0.074	0	(-1.0, 0.0)	0.395

APPENDIX 7.2.3

EFFICACY DATA: STUDY 487

Table 7.2.3.1
Study 487: Investigators/Sites

Investigators and Their Hospital of University Affiliation			
Investigator	**Center No.**	**Affiliated Institution**	**Location**
Lawrence W. Adler, M.D.	001	Clinical Insights, Inc.	Glen Burnie, MD
Joseph Baugher Bryer, M.D.	002	Clary Research Associates	New Castle, DE
Louise M. Dabiri, M.D.	003	IPS Research Co.	Oklahoma City, OK
Alan Gelenberg, M.D	004	University of Arizona	Tucson, AZ
Michael W. DePriest, M.D.	005	Pharmacology Research Corp.	Las Vegas, NV
Bradley C. Diner, M.D.	006	Clinical Investigation Specialists, Inc.	Little Rock, AR
David Louis Dunner, M.D.	007	University of Washington	Seattle, WA
James Mecham Ferguson, M.D.	008	Pharmacology Research Corp.	Salt Lake City, UT
Leslie van Hosten Taylor, M.D.	009	Dean Foundation for Health, Research, and Education, Inc	Madison, WI
John Sutherland Kennedy, M.D.*	010	Vanderbilt University Medical Center	Nashville, TN
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
Michael R. Liebowitz, M.D.	013	New York State Psychiatric Institute	New York, NY
Charles H. Meredith, M.D.	014	Affiliated Research Institute	San Diego, CA
Raj Nakra, M.D.	015	Washington University School of Medicine	Chesterfield, MO
Charles B. Nemeroff, M.D., Ph.D.*	016	Emory University Department of Psychiatry	Atlanta, GA
Mark H. Rapaport, M.D.	017	University of California at San Diego	La Jolla, CA
Carl Salzman, M.D.	018	Massachusetts Mental Health Center	Boston, MA
Andrew Satlin, M.D.	019	McLean Hospital	Belmont, MA
Lon S. Schneider, M.D.	020	University of Southern California School of Medicine	Los Angeles, CA
Ram Kumar Shrivastava, M.D.	021	Private Practice	New York, NY
Ward Tolbert Smith, M.D.	022	Pacific Northwest Clinical Research Center	Portland, OR
Steven D. Targum, M.D.	023	Delaware Valley Clinical Studies Center	Philadelphia, PA
Nicholas William Telew, M.D.	024	Oregon Center for Clinical Invest.	Eugene, OR
Dan L. Zimbroff, M.D.	025	Behavioral Medicine Center	Upland, CA
Dr. Howard S. Coster, M.D.	026	MSHJ Research Associates, Inc	Halifax, NS, CA
Dr. M. S. Renuka Prasad	027	Royal University Hospital	Saskatoon, SK, Canada
Lynn A. Cunningham, M.D.	028	Vine Street Clinical Research Center	Springfield, IL
Jeffrey T. Apter, M.D.	029	Princeton Biomedical Research	Princeton, NJ
Mark Edwin Kmak, M.D.	031	Houston VA Medical Center	Houston, TX
David Ira Margolin, M.D.	032	Private Practice	Fresno, CA
Source: Appendix A, Curriculum Vitae / * Screened patients only, no patients randomized			

Table 7.2.3.2
Study 487: Baseline Characteristics
Demographic Characteristics of Patients Included in the Intention To Treat Population

	Paroxetine CR N=104		Paroxetine IR N=106		Placebo N=109	
Age (years)	n	%	n	%	n	%
60-65	21	20.19	27	25.47	27	24.77
66-74	57	54.81	54	50.94	63	57.80
75-84	25	24.04	23	21.70	19	17.43
≥ 85	1	0.96	2	1.89	0	0.00
Mean Age (SD) in years	70.39 (5.93)		70.05 (6.59)		69.39 (5.40)	
Minimum Age						
Maximum Age						
Mean Weight (SD) in lbs.	175.43 (34.20)		173.03 (42.12)		170.01 (33.86)	
Minimum Weight						
Maximum Weight						
Gender	n	%	n	%	n	%
Female	50	48.08	60	56.60	69	63.30
Male	54	51.92	46	43.40	40	36.70
Race	n	%	n	%	n	%
Black	2	1.92	1	0.94	2	1.83
Other	2	1.92	2	1.89	4	3.67
White	100	96.15	101	95.28	103	94.50
Oriental	0	0.0	2	1.89	0	0.0

Source: Data Source Table 13.4b, Appendix B Listing 13.4

Table 7.2.3.3
Study 487: Patients In-Study by Visit
Number (%) of Patients in the ITT Population Entering Each Visit Window

	Paroxetine CR		Paroxetine IR		Placebo		Total	
	N	%	N	%	N	%	N	%
Baseline	104	100.0	106	100.0	109	100.0	319	100.0
Week 1	102	98.1	99	93.4	102	93.6	303	95.0
Week 2	97	93.3	97	91.5	99	90.8	293	91.8
Week 3	94	90.4	94	88.7	98	89.9	286	89.7
Week 4	90	86.5	90	84.9	97	89.0	277	86.8
Week 6	89	85.6	84	79.2	91	83.5	264	82.8
Week 8	84	80.8	79	74.5	90	82.6	253	79.3
Week 10	83	79.8	78	73.6	85	78.0	246	77.1
Week 12	81	77.9	77	72.6	84	77.1	242	75.9
Completed	81	77.9	76	71.7	84	77.1	241	75.5

Data Source: Data source Table 13.3.2b, 13.1.1, Appendix B, Listing 13.3b

Table 7.2.3.4 Study 487: HAM-D Total Score (LOCF)

Baseline and Change from Baseline in HAMD Total Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean (95% C.I.)		p-value	Mean (95% C.I.)		p-value
Baseline	22.1	(0.34)	103	22.3	(0.31)	103	22.1	(0.29)	107						
Week 2 LOCF	-5.8	(0.52)	103	-5.6	(0.50)	103	-5.3	(0.51)	107	-0.4 (-1.77,	0.91)	0.530	-0.3 (-1.61,	1.01)	0.655
Week 4 LOCF	-9.2	(0.64)	103	-8.5	(0.61)	103	-8.2	(0.62)	107	-1.0 (-2.63,	0.65)	0.236	-0.2 (-1.85,	1.36)	0.763
Week 6 LOCF	-10.2	(0.66)	103	-10.1	(0.64)	103	-8.6	(0.64)	107	-1.7 (-3.35,	0.05)	0.057	-1.5 (-3.20,	0.13)	0.071
Week 8 LOCF	-11.2	(0.68)	103	-10.9	(0.66)	103	-9.5	(0.66)	107	-1.7 (-3.45,	0.05)	0.057	-1.4 (-3.07,	0.37)	0.122
Week 10 LOCF	-11.8	(0.71)	103	-11.9	(0.69)	103	-9.5	(0.70)	107	-2.3 (-4.14,	-0.46)	0.015	-2.4 (-4.22,	-0.61)	0.009
Week 12 LOCF	-12.1	(0.73)	103	-12.3	(0.70)	103	-9.5	(0.71)	107	-2.6 (-4.47,	-0.73)	0.007	-2.8 (-4.65,	-0.99)	0.003

Table 7.2.3.5 Study 487: HAM-D Total Score (OC)

Baseline and Change from Baseline in HAMD Total Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Statistical Analysis Presented at all Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean (95% C.I.)		p-value	Mean (95% C.I.)		p-value
Baseline	22.1	(0.34)	103	22.3	(0.31)	103	22.1	(0.29)	107						
Week 1	-3.0	(0.44)	102	-3.7	(0.42)	102	-3.7	(0.43)	106	0.6 (-0.50,	1.76)	0.273	-0.0 (-1.15,	1.06)	0.936
Week 2	-5.8	(0.53)	98	-5.7	(0.53)	94	-5.5	(0.52)	98	-0.3 (-1.72,	1.05)	0.635	-0.2 (-1.62,	1.13)	0.730
Week 3	-9.4	(0.60)	98	-7.9	(0.58)	95	-7.4	(0.59)	91	-2.0 (-3.52,	-0.41)	0.014	-0.1 (-1.51,	1.43)	0.930
Week 4	-9.9	(0.63)	93	-8.8	(0.62)	92	-8.7	(0.61)	97	-1.2 (-2.87,	0.40)	0.138	-0.2 (-1.75,	1.45)	0.851
Week 6	-11.5	(0.66)	86	-10.9	(0.64)	89	-9.1	(0.63)	94	-2.4 (-4.14,	-0.71)	0.006	-1.8 (-3.45,	-0.16)	0.031
Week 8	-12.9	(0.62)	85	-12.1	(0.62)	82	-10.7	(0.60)	89	-2.2 (-3.82,	-0.59)	0.008	-1.5 (-3.06,	0.13)	0.072
Week 10	-13.8	(0.69)	83	-13.5	(0.68)	77	-10.6	(0.65)	90	-3.2 (-4.96,	-1.41)	<0.001	-2.9 (-4.67,	-1.16)	0.001
Week 12	-14.4	(0.70)	88	-13.9	(0.70)	73	-10.5	(0.68)	80	-3.8 (-5.65,	-1.97)	<0.001	-3.4 (-5.18,	-1.56)	<0.001

Table 7.2.3.6 Study 487: HAM-D Depressed Mood Item (LOCF)

Baseline and Change from Baseline in HAMD Mood Item Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Mood Item Score and Duration of Current Episode of Depression
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.7	(0.06)	103	2.8	(0.06)	103	2.7	(0.06)	107						
Week 2 LOCF	-0.8	(0.12)	103	-0.5	(0.12)	103	-0.4	(0.12)	107	-0.2	(-0.40, 0.08)	0.180	-0.1	(-0.30, 0.17)	0.576
Week 4 LOCF	-1.1	(0.14)	103	-1.0	(0.14)	103	-0.8	(0.14)	107	-0.3	(-0.56, -0.00)	0.048	-0.2	(-0.45, 0.10)	0.210
Week 6 LOCF	-1.2	(0.14)	103	-1.1	(0.14)	103	-0.8	(0.14)	107	-0.3	(-0.60, -0.07)	0.014	-0.3	(-0.54, -0.01)	0.039
Week 8 LOCF	-1.3	(0.14)	103	-1.2	(0.14)	103	-0.9	(0.14)	107	-0.4	(-0.63, -0.08)	0.013	-0.3	(-0.57, -0.02)	0.035
Week 10 LOCF	-1.4	(0.15)	103	-1.5	(0.15)	103	-0.9	(0.15)	107	-0.5	(-0.75, -0.18)	0.001	-0.6	(-0.85, -0.29)	<0.001
Week 12 LOCF	-1.4	(0.15)	103	-1.4	(0.15)	103	-0.9	(0.15)	107	-0.5	(-0.81, -0.22)	<0.001	-0.5	(-0.83, -0.26)	<0.001

Table 7.2.3.7 Study 487: HAM-D Depressed Mood Item (OC)

Baseline and Change from Baseline in HAMD Depressed Mood Item Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Depressed Mood Item and Duration of Current Episode of Depression
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.7	(0.06)	103	2.8	(0.06)	103	2.7	(0.06)	107						
Week 1	-0.2	(0.10)	102	-0.3	(0.10)	102	-0.1	(0.10)	106	-0.0	(-0.21, 0.19)	0.928	-0.1	(-0.32, 0.07)	0.202
Week 2	-0.6	(0.12)	98	-0.5	(0.13)	94	-0.5	(0.13)	98	-0.1	(-0.40, 0.10)	0.235	-0.0	(-0.29, 0.21)	0.742
Week 3	-0.9	(0.13)	90	-0.6	(0.13)	95	-0.7	(0.14)	91	-0.2	(-0.45, 0.10)	0.208	0.1	(-0.15, 0.38)	0.392
Week 4	-1.1	(0.14)	93	-1.0	(0.15)	92	-0.8	(0.14)	97	-0.4	(-0.65, -0.07)	0.014	-0.2	(-0.48, 0.11)	0.222
Week 6	-1.3	(0.13)	86	-1.1	(0.13)	89	-0.7	(0.13)	94	-0.5	(-0.81, -0.26)	<0.001	-0.4	(-0.68, -0.11)	0.009
Week 8	-1.4	(0.14)	85	-1.2	(0.14)	82	-0.9	(0.14)	89	-0.5	(-0.80, -0.24)	<0.001	-0.3	(-0.60, -0.04)	0.025
Week 10	-1.6	(0.14)	83	-1.7	(0.15)	77	-1.0	(0.14)	90	-0.6	(-0.93, -0.34)	<0.001	-0.7	(-0.96, -0.37)	<0.001
Week 12	-1.7	(0.15)	80	-1.6	(0.15)	73	-0.9	(0.15)	80	-0.7	(-1.06, -0.43)	<0.001	-0.6	(-0.93, -0.30)	<0.001

Table 7.2.3.8 Study 487: CGI-severity (LOCF)

Baseline and Change from Baseline in CGI Severity of Illness Score
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR		Paroxetine IR		Placebo		Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Median (Min,Max)	N	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value		Median (95% C.I.)	p-value	
Baseline	4	103	4	103	4	106						
Week 2 LOCF	-1	103	0	103	0	106	0 (0.0,	0.0)	0.371	0 (0.0,	0.0)	0.911
Week 4 LOCF	-1	103	-1	103	-1	106	0 (0.0,	0.0)	0.441	0 (0.0,	0.0)	0.582
Week 6 LOCF	-1	103	-1	103	-1	106	0 (-1.0,	0.0)	0.075	0 (0.0,	0.0)	0.404
Week 8 LOCF	-1	103	-1	103	-1	106	0 (-1.0,	0.0)	0.165	0 (0.0,	0.0)	0.650
Week 10 LOCF	-2	103	-2	103	-1	106	0 (-1.0,	0.0)	0.086	0 (-1.0,	0.0)	0.046
Week 12 LOCF	-2	103	-2	103	-1	106	0 (-1.0,	0.0)	0.022	0 (-1.0,	0.0)	0.019

Table 7.2.3.9 Study 487: CGI-severity (OC)

Baseline and Change from Baseline in CGI Severity of Illness Score
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR		Paroxetine IR		Placebo		Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Median (Min,Max)	N	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value		Median (95% C.I.)	p-value	
Baseline	4	103	4	103	4	106						
Week 1	0	102	0	102	0	105	0 (0.0,	0.0)	0.337	0 (0.0,	0.0)	0.801
Week 2	-1	99	0	94	0	97	0 (0.0,	0.0)	0.493	0 (0.0,	0.0)	0.975
Week 3	-1	90	-1	95	-1	90	0 (0.0,	0.0)	0.263	0 (0.0,	0.0)	0.504
Week 4	-1	93	-1	92	-1	96	0 (0.0,	0.0)	0.291	0 (0.0,	0.0)	0.603
Week 6	-1	86	-1	88	-1	93	0 (-1.0,	0.0)	0.012	0 (0.0,	0.0)	0.278
Week 8	-2	85	-1	82	-1	88	0 (-1.0,	0.0)	0.042	0 (0.0,	0.0)	0.441
Week 10	-2	83	-2	76	-1	88						
Week 12	-2	80	-2	73	-1	79	-1 (-1.0,	0.0)	<0.001	-1 (-1.0,	0.0)	0.004

APPENDIX 8.1

SAFETY FINDINGS

TABLE 8.1.2.2: Line Listing of Non-Fatal Serious Adverse Events					
Patient ID	**Age (yrs)**	**Sex**	**Dose at Onset (mg/day)**	**Exposure before Onset (days)[1]**	**Serious Event(s)**
PHASE 1 STUDIES					
Paroxetine CR					
480.001.00033	34	F	75	2	Accidental overdose.
485.003.00308	21	M	30	6	Car accident → hospitalization.
452.006.00508	28	F	30	2	Nausea, vomiting, headache.
Placebo					
452.003.00259	22	F	-	3	Unintended pregnancy.
Prototype Formulations					
452.006.00499	36	F	60	2	Accidental overdose.
PHASE 3 STUDIES					
Paroxetine CR					
448.012.00014	50	F	0	1 (+14)	Convulsion (post-tx).
448.012.00097	55	M	0	106 (+21)	Myocardial infarction (post-tx).
449.020.00735	26	F	62.5	59	Unintended pregnancy.
449.021.00658	46	M	37.5	48	Pancreatitis.
449.008.00904	54	M	0	96 (+7)	Depression (post-tx).
487.001.01461	78	F	37.5	17	Depression.
487.007.01562	73	M	37.5	45	Intestinal obstruction.
487.008.01637	69	M	37.5 0	80 104 (+23)	Angina pectoris. GI hemorrhage, colitis (post-tx).
487.025.01240	68	M	50	53	Prostate disorder (BPH).
487.029.01552	76	M	12.5	23	Chronic lymphocytic leukemia.

[1] For events occurring post-treatment, + = number of days after treatment discontinuation at event onset.

487.031.01503	82	M	0 12.5	28 (+16) 11	Anxiety (post-tx). Depression, emotional lability.
Placebo					
448.010.00181	45	F	-	82	Enlarged uterine fibroids.
448.016.00465	40	M	-	36	Gall bladder disorder.
448.019.00390	29	F	-	45	Dehydration.
448.019.00421	31	F	-	62	Accidental overdose.
449.006.00763	58	F	-	38	Hypertension (exacerbation).
487.001.01221	70	F	-	71	Gastroenteritis.
487.001.01522	61	M	-	76	Skin melanoma.
487.003.01258	66	F	- - -	46 91 99 (+2)	SGPT increased. SGOT increased. Nausea (post-tx).
487.005.01590	66	F	-	35	Cystitis.
487.021.01694	60	M	-	19 (+7)	Varicose veins (post-tx).
487.029.01558	77	F	-	4	Chest pain, AV block, hyperventilation.
Paroxetine IR					
448.010.00044	25	F	40	48	Emotional lability.
448.010.00183	18	F	40	17	Depression, emotional lability.
448.010.00211	37	F	0	113[2]	Hepatocellular jaundice.
448.012.00226	24	M	50	68	Manic reaction.
448.019.00391	27	F	40	23	Emotional lability.
449.006.00759	34	F	50	42	Abortion.
449.014.00742	23	F	50	77	Unintended pregnancy.
449.015.00838	21	F	20	42	Unintended pregnancy.
449.021.00788	18	F	20	65	Emotional lability.

[2] Patient continued treatment with paroxetine IR after study completion.

487.005.01303	66	M	0	103 (+8)	Chest pain (post-tx).
487.006.01233	72	F	20	82	Pneumonia.
487.011.01271	65	M	40	46	Trauma, pneumothorax.
487.011.01542	74	M	10	74	Pneumonia, bronchitis.
487.017.01318	68	F	10	15	Trauma.
487.017.01409	70	M	30	57	Hematuria.
487.021.01250	75	M	0	84	Accidental overdose.
487.021.01575	77	F	0	4 (+1)	Gastroenteritis (post-tx).
487.024.01707	75	M	10	4	Hyponatremia.

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ON ORIGINAL

TABLE 8.1.4.2.1: TREATMENT EMERGENT ADVERSE EVENTS OCCURRING IN ≥1% OF PAROXETINE CR PATIENTS IN THE POOL OF STUDIES 448 & 449 [3,4]		
Body System/Adverse Event	**% Reporting Event**	
	Par CR (N=212)	**Placebo (N=211)**
Body as a Whole		
Headache	27%	20%
Asthenia	14%	9%
Infection[5]	8%	5%
Abdominal Pain	7%	4%
Back Pain	5%	3%
Trauma[6]	5%	1%
Pain[7]	3%	1%
Allergic Reaction[8]	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation[9]	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry Mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%
Decreased Appetite	4%	2%
Vomiting	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido Decreased	7%	3%
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%

[3] Adverse events for which the paroxetine CR reporting incidence was less than or equal to the placebo incidence are not included. These events are: abnormal dreams, anxiety, arthralgia, depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia, nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency, and weight gain.
[4] <1% means greater than zero and less than 1%.
[5] Mostly flu.
[6] A wide variety of injuries with no obvious pattern.
[7] Pain in a variety of locations with no obvious pattern.
[8] Most frequently seasonal allergic symptoms.
[9] Usually flushing.

Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough Increased	2%	1%
Bronchitis	1%	0%
Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal Vision[10]	5%	1%
Taste Perversion	2%	0%
Urogenital System		
Abnormal Ejaculation[11,12]	26%	1%
Female Genital Disorder[5,13]	10%	<1%
Impotence[5]	5%	3%
Urinary Tract Infection	3%	1%
Menstrual Disorder[5]	2%	<1%
Vaginitis[5]	2%	0%

[10] Mostly blurred vision.
[11] Based on the number of males or females.
[12] Mostly anorgasmia or delayed ejaculation.
[13] Mostly anorgasmia or delayed orgasm.

TABLE 8.1.4.3: TREATMENT EMERGENT ADVERSE EVENTS OCCURRING IN ≥5% OF PAROXETINE CR PATIENTS IN STUDY 487 [14,15]		
Body System/Adverse Event	**% Reporting Event**	
	Par CR (N=104)	**Placebo (N=109)**
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%
Infection	6%	2%
Digestive System		
Dry Mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%
Dyspepsia	13%	10%
Decreased Appetite	12%	5%
Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%
Insomnia	10%	8%
Dizziness	9%	5%
Libido Decreased	8%	<1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	<1%
Urogenital System		
Abnormal Ejaculation[16,17]	17%	3%
Impotence[16]	9%	3%

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[14] Adverse events for which the paroxetine CR reporting incidence was less than or equal to the placebo incidence are not included. These events are nausea and respiratory disorder.
[15] <1% means greater than zero and less than 1%.
[16] Based on the number of males.
[17] Mostly anorgasmia or delayed ejaculation.

Table 8.1.4.5: Other Events Observed During Premarketing Depression Studies (448, 449, 487) with Paroxetine CR[18,19,20]
Body as a Whole
Cellulitis, chest pain, fever, malaise.
Cardiovascular System
Angina pectoris, arrhythmia, bradycardia, bundle branch block, hypertension*, hypotension*, palpitation, postural hypotension.
Digestive System
Dysphagia, eructation, gastroenteritis, gastrointestinal disorder, gingivitis, glossitis, hepatosplenomegaly, intestinal obstruction, liver function tests abnormal*, melena, peptic ulcer, stomach ulcer, tooth caries, tooth disorder*, ulcerative stomatitis.
Endocrine System
Hyperthyroidism.
Hemic and Lymphatic System
Anemia, chronic lymphocytic leukemia, eosinophilia.
Metabolic and Nutritional Disorders
Generalized edema, hyperglycemia, peripheral edema.
Musculoskeletal System
Bursitis.
Nervous System
Amnesia, concentration impaired, depression*, emotional lability, lack of emotion, myoclonus*, neuropathy, paralysis, thinking abnormal, vertigo.
Respiratory System
Asthma, dyspnea.
Skin and Appendages
Dry skin, herpes simplex, pruritis, seborrhea.
Special Senses
Abnormality of accomodation, conjunctivitis*, eye appendage disorder, otitis media, tinnitus.
Urogenital System
Albuminuria, hematuria, kidney function abnormal, prostate disorder, testes disorder, urine abnormality, urinary incontinence.

[18] Events listed in Table 8.1.4.2.1 or 8.1.4.2.2 are excluded.
[19] All events in this table were reported at a frequency between 1/100 and 1/1,000 within the pool of studies 448, 449, and 487 (N=316), except for those marked with an asterisk (*), indicating a frequency ≥1/100.
[20] Gender-specific event rates have been corrected for the number of males (N=132) or females (N=184), as appropriate.

TABLE 8.1.5.2.1: CRITERIA FOR IDENTIFYING LABORATORY VALUES OF POTENTIAL CLINICAL CONCERN (STUDIES 448 AND 449)

Parameter	Values of Concern	Reference Ranges
Hematology		
Hemoglobin - Male	≤ 115 g/l	138-172 g/l
Hemoglobin - Female	≤ 95 g/l	120-156 g/l
Hematocrit - Male	≤ 37 %	41-50%
Hematocrit - Female	≤ 32 %	35-46 %
WBC	≤ 2.8 or ≥ 16.0 x 10^9/l	3.8-10.8 x 10^9/l
Lymphocytes	≥ 75%	16-46 %
Monocytes	≥ 15%	0-12%
Basophils	≥ 10%	0-2 %
Eosinophils	≥ 10%	0-7%
Segmented Neutrophils	≤ 15%	40-75 %
Platelets	≤ 75 or ≥ 700 x 10^9/l	130-400 x 10^9/l
Clinical Chemistry		
Blood Urea Nitrogen	≥ 30 mg/dl	4-30 mg/dl[a]
Serum creatinine	≥ 2.3 mg/dl	0.7-1.8[a]
Total bilirubin	≥ 2.0 mg/dl	0-1.3 mg/dl[a]
AST (SGOT)	≥ 150 U/l	0-42 U/l
ALT (SGPT)	≥ 165 U/l	0-48 U/l
Alkaline phosphatase	≥ 390 U/l	20-125 U/l
T3 (Total)	≤ 87 ≥ 189 ng/dl	60-181 ng/dl
T4 (Total)	≤ 4.5 ≥ 12.5 mcg/dl nmol/l	4.5-12.5 mcg/dl
Thyroid Stimulating Hormone (TSH)	>10 mIU/l	0.4-5.5 mIU/l
Chloride	≤ 90 >118 mmol/l	95-108 mmol/l
Potassium	≤ 3 ≥ 6 mmol/l	3.5-5.3 mmol/l
Sodium	≤ 126 ≥ 156 mmol/l	135-146 mmol/l

[a]Some ranges are broadened to encompass two or more narrower ranges based on patient gender or age.

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TABLE 8.1.5.2.2: CRITERIA FOR IDENTIFYING LABORATORY VALUES OF POTENTIAL CLINICAL CONCERN (STUDIES 487)

Variable	Flagged values
Hematology	
Hemoglobin - Male	< 115 g/l
Hemoglobin - Female	< 95 g/l
Hematocrit - Male	< 37 %
Hematocrit - Female	< 32 %
WBC	< 2.8 or > 16.0 x109/l
Neutrophils	<15%
Lymphocytes	> 75%
Monocytes	> 15%
Basophils	> 10%
Eosinophils	> 10%
Platelets	< 75 or > 700 x109/l
Bands	> 10%
Segmented Neutrophils	< 15%
RBC - Male	> 8 x1012/l
RBC - Female	> 10 x1012/l
Clinical Chemistry	
BUN	> 10.71 mmol/l
Serum creatinine	> 176.8 mcmol/l
Total bilirubin	> 34.2 mcmol/l
SGOT (AST)	> 150 U/l
SGPT (ALT)	> 165 U/l
Alkaline phosphatase	> 390 U/l
Total protein	< 45 or > 100 g/l
Globulin	< 10 g/l
Albumin	< 25 g/l
T3 (Total)	< 1.3 > 2.84 nmol/l
T4 (Total)	< 57.91 > 160.87 nmol/l
Chloride	< 90 >118 mmol/l
Potassium	< 3 > 6 mmol/l
Sodium	< 126 > 156 mmol/l

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ON ORIGINAL

TABLE 8.1.5.3.1.1: PROPORTIONS OF PATIENTS EXPERIENCING POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN LABORATORY VALUES (STUDIES 448 & 449)

	Paroxetine CR			Placebo		
	N	Abnormal		N	Abnormal	
		#	%		#	%
↓Hematocrit	212	1	<1%	211	1	<1%
↑Potassium	212	1	<1%	210	0	0%
↓Platelets	212	1	<1%	211	1	<1%
↑TSH	212	2	<1%	211	2	<1%
↑WBC	212	1	<1%	211	0	0%
↓WBC	212	3	1%	211	0	0%

TABLE 8.1.5.3.1.2: PROPORTIONS OF PATIENTS EXPERIENCING POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN LABORATORY VALUES (STUDY 487)

	Paroxetine CR			Placebo		
	N	Abnormal		N	Abnormal	
		#	%		#	%
↑ALT	104	2	2%	109	0	0%
↑AST	104	3	3%	109	0	0%
↑BUN	104	2	2%	109	2	2%
↑Eosinophils	104	3	3%	109	1	<1%
↓Hematocrit	104	4	4%	109	2	2%
↓Hemoglobin	104	2	2%	109	0	0%
↑Lymphocytes	104	1	1%	109	0	0%
↑Monocytes	104	2	2%	109	0	0%
↑TSH	104	2	2%	109	0	0%
↑T. Bilirubin	104	1	1%	109	1	<1%
↑WBC	104	1	1%	109	0	0%
↓WBC	104	1	1%	109	0	0%

APPEARS THIS WAY

TABLE SERIES 8.1.5.3.2

VITAL SIGN MEASUREMENTS OF POTENTIAL CLINICAL CONCERN

Table Series 8.1.5.3.2: Proportions of Patients with Potentially Clinically Significant Changes in Vital Sign Measures (Studies 448 and 449)

Sitting Diastolic BP (mmHg)

Treatment Groups	PAROXETINE CR		PAROXETINE IR		PLACEBO	
	N	%	N	%	N	%
High	2	0.9	2	0.9	3	1.4
Low	4	1.9	2	0.9	2	0.9
Significant Increase	4	1.9	3	1.4	2	0.9
Significant Decrease	17	8.1	13	6.1	13	6.2
Number with Assessment	212	100.0	217	100.0	211	100.0
Number with Base and Post-base Assessment	211	99.5	214	98.6	211	100.0

Key
High - greater that 105mmHg
Low - less than 50mmHg
Significant Increase - increase of 30mmHg or more from baseline
Significant Decrease - decrease of 20mmHg or more from baseline
Number with Assessment - number of patients who had a sitting diastolic blood pressure measurement at any time

Table Series 8.1.5.3.2: Proportions of Patients with Potentially Clinically Significant Changes in Vital Sign Measures (Studies 448 and 449)

Sitting Systolic BP (mmHg)

Treatment Groups	PAROXETINE CR		PAROXETINE IR		PLACEBO	
	N	%	N	%	N	%
High	1	0.5	0	0.0	1	0.5
Low	0	0.0	4	1.8	3	1.4
Significant Increase	1	0.5	3	1.4	1	0.5
Significant Decrease	9	4.3	3	1.4	9	4.3
Number with Assessment	212	100.0	217	100.0	211	100.0
Number with Base and Post-base Assessment	211	99.5	214	98.6	211	100.0

Key
High - greater than 180mmHg
Low - less than 90mmHg
Significant Increase - increase of 40mmHg or more from baseline
Significant Decrease - decrease of 30mmHg or more from baseline
Number with Assessment - number of patients who had a sitting systolic blood pressure measurement at any time

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Table Series 8.1.5.3.2: Proportions of Patients with Potentially Clinically Significant Changes in Vital Sign Measures (Studies 448 and 449)

Sitting Pulse (beats per min)

Treatment Groups	PAROXETINE CR		PAROXETINE IR		PLACEBO	
	N	%	N	%	N	%
High	0	0.0	0	0.0	0	0.0
Low	5	2.4	1	0.5	3	1.4
Significant Increase	9	4.3	3	1.4	3	1.4
Significant Decrease	5	2.4	1	0.5	1	0.5
Number with Assessment	212	100.0	217	100.0	211	100.0
Number with Base and Post-base Assessment	211	99.5	214	98.6	211	100.0

Key
High - greater than 120 BPM
Low - less than 50 BPM
Significant Increase - increase of 30 BPM or more from baseline
Significant Decrease - decrease of 30 BPM or more from baseline
Number with Assessment - number of patients who had a sitting pulse rate measurement at any time

Table Series 8.1.5.3.2: Proportions of Patients with Potentially Clinically Significant Changes in Vital Sign Measures (Studies 448 and 449)

Weight (lbs)

Treatment Groups	PAROXETINE CR		PAROXETINE IR		PLACEBO	
	N	%	N	%	N	%
High	0	0.0	0	0.0	0	0.3
Low	0	0.0	0	0.0	0	0.0
Significant Increase	8	3.8	9	4.2	3	1.4
Significant Decrease	9	4.3	5	2.3	3	1.4
Number with Assessment	212	100.0	217	100.0	211	100.0
Number with Base and Post-base Assessment	211	99.5	214	98.6	211	100.0

Key
High - not relevant
Low - not relevant
Significant Increase - increase of 7% or more from baseline
Significant Decrease - decrease of 7% or more from baseline
Number with Assessment - number of patients who had their weight measured at any time

Table Series 8.1.5.3.2: Proportions of Patients with Potentially Clinically Significant Changes in Vital Sign Measures (Study 487)

Sitting Systolic BP (mmHg)

Treatment Groups	PAROXETINE CR		PAROXETINE IR		PLACEBO	
	N	%	N	%	N	%
High	1	1.0	2	1.9	1	0.9
Low	0	0.0	1	0.9	1	0.9
Significant Increase	4	3.8	2	1.9	3	2.8
Significant Decrease	19	18.3	18	17.0	22	20.6
Number with Assessment	104	100.0	106	100.0	109	100.0
Number with Base and Post-base Assessment	104	100.0	106	100.0	107	98.2

Key
High - greater than 180mmHg
Low - less than 90mmHg
Significant Increase - increase of 40mmHg or more from baseline
Significant Decrease - decrease of 30mmHg or more from baseline
Number with Assessment - number of patients who had a sitting systolic blood pressure measurement at any time

Table Series 8.1.5.3.2: Proportions of Patients with Potentially Clinically Significant Changes in Vital Sign Measures (Study 487)

Standing Systolic BP (mmHg)

Treatment Groups	PAROXETINE CR		PAROXETINE IR		PLACEBO	
	N	%	N	%	N	%
High	2	1.9	3	2.8	2	1.8
Low	2	1.9	0	0.0	4	3.7
Significant Increase	2	1.9	2	1.9	2	1.9
Significant Decrease	23	22.1	19	17.9	15	14.0
Number with Assessment	104	100.0	106	100.0	109	100.0
Number with Base and Post-base Assessment	104	100.0	106	100.0	107	98.2

Key
High - greater than 180mmHg
Low - less than 90mmHg
Significant Increase - increase of 40mmHg or more from baseline
Significant Decrease - decrease of 30mmHg or more from baseline
Number with Assessment - number of patients who had a sitting systolic blood pressure measurement at any time

Table Series 8.1.5.3.2: Proportions of Patients with Potentially Clinically Significant Changes in Vital Sign Measures (Study 487)

Sitting Diastolic BP (mmHg)

Treatment Groups	PAROXETINE CR		PAROXETINE IR		PLACEBO	
	N	%	N	%	N	%
High	3	2.9	2	1.9	0	0.0
Low	4	3.8	5	4.7	0	0.0
Significant Increase	0	0.0	1	0.9	0	0.0
Significant Decrease	21	20.2	25	23.6	17	15.9
Number with Assessment	104	100.0	106	100.0	109	100.0
Number with Base and Post-base Assessment	104	100.0	106	100.0	107	98.2

Key
High - greater than 105mmHg
Low - less than 50mmHg
Significant Increase - increase of 30mmHg or more from baseline
Significant Decrease - decrease of 20mmHg or more from baseline
Number with Assessment - number of patients who had a sitting diastolic blood pressure measurement at any time

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Table Series 8.1.5.3.2: Proportions of Patients with Potentially Clinically Significant Changes in Vital Sign Measures (Study 487)

Standing Diastolic BP (mmHg)

Treatment Groups	PAROXETINE CR		PAROXETINE IR		PLACEBO	
	N	%	N	%	N	%
High	4	3.8	2	1.9	1	0.9
Low	2	1.9	4	3.8	0	0.0
Significant Increase	4	3.8	1	0.9	0	0.0
Significant Decrease	16	15.4	21	19.8	12	11.2
Number with Assessment	104	100.0	106	100.0	109	100.0
Number with Base and Post-base Assessment	104	100.0	106	100.0	107	98.2

Key
High - greater than 105mmHg
Low - less than 50mmHg
Significant Increase - increase of 30mmHg or more from baseline
Significant Decrease - decrease of 20mmHg or more from baseline
Number with Assessment - number of patients who had a sitting diastolic blood pressure measurement at any time

Table Series 8.1.5.3.2: Proportions of Patients with Potentially Clinically Significant Changes in Vital Sign Measures (Study 487)

Sitting Pulse (beats per min)

Treatment Groups	PAROXETINE CR		PAROXETINE IR		PLACEBO	
	N	%	N	%	N	%
High	1	1.0	0	0.0	0	0.0
Low	0	0.0	5	4.7	2	1.8
Significant Increase	1	1.0	0	0.0	2	1.9
Significant Decrease	4	3.8	4	3.8	2	1.9
Number with Assessment	104	100.0	106	100.0	109	100.0
Number with Base and Post-base Assessment	104	100.0	106	100.0	107	98.2

Key
High - greater than 120 BPM
Low - less than 50 BPM
Significant Increase - increase of 30 BPM or more from baseline
Significant Decrease - decrease of 30 BPM or more from baseline
Number with Assessment - number of patients who had a sitting pulse rate measurement at any time

Table Series 8.1.5.3.2: Proportions of Patients with Potentially Clinically Significant Changes in Vital Sign Measures (Study 487)

Weight (kg)

Treatment Groups	PAROXETINE CR		PAROXETINE IR		PLACEBO	
	N	%	N	%	N	%
High	0	0.0	0	0.0	0	0.0
Low	0	0.0	0	0.0	0	0.0
Significant Increase	2	1.9	1	0.9	0	0.0
Significant Decrease	3	2.9	6	5.7	3	2.8
Number with Assessment	104	100.0	106	100.0	109	100.0
Number with Base and Post-base Assessment	104	100.0	106	100.0	107	98.2

Key
High - not relevant
Low - not relevant
Significant Increase - increase of 7% or more from baseline
Significant Decrease - decrease of 7% or more from baseline
Number with Assessment - number of patients who had their weight measured at any time