evidence of efficacy, will be summarized in Section 7.2.2.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1   Controlled Studies

7.2.1.1   Study 208

Investigators/Locations

Principal investigators and study sites are identified in
Appendix 7.2.1.1.

As discussed in section 5.4, efficacy data from site #13 was
considered of questionable reliability. Thus, the sponsor was
requested to reanalyze the efficacy results of this study, to
exclude site 20813. The review of efficacy results is based on
this reanalysis.

Objectives

The primary objective of this study was to compare the
antidepressant efficacy and safety of venlafaxine ER with
placebo.

Population

A total of 301 outpatients with DSM-III-R major depression were
enrolled. Other inclusion criteria were:

* minimum age of 18 years.
* symptoms of depression for at least one month.
* minimum prestudy 21-item HAM-D total score of 20, with no
greater than a 20% decrease between screening and study day -1.

Relevant exclusion criteria included the following:

* previous venlafaxine treatment.
* history or presence of any psychotic disorder not related to depression, bipolar disorder, or organic mental disorder.
* use of any investigational drug, antipsychotic drug, or ECT within 30 days; fluoxetine within 21 days; MAOI, paroxetine, or sertraline within 14 days; or any other antidepressant, anxiolytic, sedative-hypnotic, or other psychotropic agent within 7 days (except chloral hydrate).
* use of any non-psychopharmacologic drug with psychotropic effects within 7 days of the study unless a stable dose had been maintained for the past month.
* drug or alcohol dependence within 1 year.

Also, the initiation or change in intensity of formal psychotherapy was prohibited during the study.

Design

This was a randomized, double-blind, placebo-controlled, parallel group study conducted at 12 U.S. sites (including site 20813). Depressed patients with a HAM-D total score ≥20 underwent a single-blind placebo run-in for 7±3 days, during which they were evaluated for study eligibility. On study day -1, baseline safety and efficacy assessments were completed and patients who continued to meet selection criteria were randomized to begin either venlafaxine ER, venlafaxine IR, or placebo on day 1.

Treatment was continued for 12 weeks, followed by a tapering of medication for up to 2 weeks. Study visits were scheduled for days 7, 14, 21, 28, 42, 56, and 84; a post-study visit occurred 4-10 days after study medication had been discontinued. The HAM-D, MADRS, and CGI were performed at all visits through day 84 (week 12). An Investigator's and Patient's Subjective Rating as well as a Quality of Life Questionnaire were performed on day 84 (week 12).

A flexible dosing schedule was employed; total daily doses are depicted below for various time intervals during the study.

Period	Venlafaxine ER	Venlafaxine IR
Days 1-14	75mg	75mg
Days 15-84	75 or 150mg	75 or 150mg
Taper Wk 1	0 or 75mg	0 or 75mg
Taper Wk 2	0	0

Venlafaxine ER was administered as a single dose in the morning whereas venlafaxine IR was given BID. Doses could be increased to improve therapeutic response or reduced to improve tolerance within the ranges shown above. Patients unable to tolerate the minimum dose were to be discontinued from the study.

Analysis

The efficacy intent-to-treat (ITT) population included all enrolled patients who had at least a baseline measure on at least one primary efficacy parameter, took at least one dose of study medication, and had at least one evaluation on at least one primary efficacy measure either during treatment or within 3 days after the last dose. A total of XXX patients comprised the efficacy ITT.

This review focused on one-way analysis of variance (ANOVA), with therapy as the factor, for the pairwise comparisons of raw mean change from baseline at each visit in four key efficacy variables: HAM-D and MADRS total scores, HAM-D depressed mood item, and CGI-severity score. Analysis was performed on both observed cases (OC) and last-observation-carried-forward (LOCF) datasets. Statistical significance was defined at the $\alpha = 0.05$ level and all hypothesis testing was 2-sided.

Additionally, the sponsor discovered that the assumption of normality was not met for two variables: HAM-D depressed mood item and CGI-severity. Thus, non-parametric ANCOVA was applied to all key variables at each visit for the LOCF and OC datasets and the results of pairwise comparisons between venlafaxine ER and placebo based on ranks was provided.

Baseline Demographics

Baseline demographic data is displayed in Appendix 7.2.1.1. There were no remarkable differences between groups at baseline with respect to mean age, age range, gender composition, or the proportion of Caucasian patients.

Baseline Severity of Illness

There was no statistically significant difference among groups with respect to mean baseline HAM-D total scores, HAM-D depressed mood item scores, MADRS total scores, or CGI-severity scores.

Patient Disposition

Of the 270 patients randomized, 257 comprised the efficacy ITT, of which 85 were randomized to venlafaxine ER, 91 to placebo, and 81 to venlafaxine IR. The number of completers (i.e. patients with observed data for at least one of the four key efficacy variables), also expressed as a percentage of the efficacy ITT, at each visit is displayed in Appendix 7.2.1.1.

Of the ITT, 58% (49/85) of the venlafaxine ER, 47% (43/91) of the placebo, and 48% (39/81) of the venlafaxine IR patients completed 12 weeks of double-blind treatment; as expected, the most frequent reason for dropout among venlafaxine ER patients was an

adverse event (11% of the patients in the safety ITT), failure to
return for follow-up among placebo patients (16%), and failure to
return for follow-up among venlafaxine IR patients (15%).

Six patients dropped out due to a protocol violation:

* venlafaxine ER patient 20813-018 - took methamphetamine.
* venlafaxine ER patient 20819-004- elevated SGOT at screening;
inadvertantly randomized.
* venlafaxine IR patient 20813-027 - scheduled too early for last
visit.
* venlafaxine IR patient 20816-006 - noncompliant with study
medication.
* placebo patient 20821-025 - failure to keep appointments and
maintain consistent dosage.
* placebo patient 20821-031 - stopped study drug on own.

The visit at which at least 70% of the patients in both groups
were still in-study and had observed efficacy data was week 4,
with 86% of the venlafaxine ER, 77% of the placebo, and 83% of
the venlafaxine IR patients remaining at that timepoint.

Dosing Information

The mean daily dose for all venlafaxine ER and venlafaxine IR
patients at each visit is displayed in Appendix 7.2.1.1. Mean
doses reached a plateau by week 4, with the mean venlafaxine ER
dose slightly higher than the mean venlafaxine IR dose (135 vs.
123 mg/day).

Concomitant Medications

Of all study participants, most patients in each treatment group
received a concomitant medication: venlafaxine ER 89%, placebo
86%, and venlafaxine IR 85%. The two most commonly used classes
of concomitant agents were "anti-inflammatory/non-steroidal
antirheumatics" and "other analgesics/antipyretics."

Four patients (1 venlafaxine ER and 3 placebo) received
antidepressant medication with the study drug:

* placebo patient 20821-031 took Effexor 37.5mg bid beginning on
day 8 and dropped out 4 days later.

* placebo patient 20822-030 took venlafaxine IR on days 2-4, then
dropped out on day 6.

* placebo patient 20820-036 completed 12 weeks of treatment and
started Effexor during the taper phase.

• venlafaxine ER patient 20822-003 took trazodone on day 5, then dropped out 2 days later due to insomnia.

Sedative-hypnotic agents were used by 4% of venlafaxine ER, 10% of placebo, and 10% of venlafaxine IR patients. Chloral hydrate up to 1000 mg at bedtime was permitted for sleep.

The only other psychotropic drug use was one venlafaxine ER patient, who used a psychostimulant, and one placebo patient, who used an anxiolytic drug. The details of this use were not located in the submission but this was not felt to play a significant role in the efficacy findings, particularly in light of the robustness of the results.

Overall, the above described concurrent use of psychotropic medication is not felt to have appreciably influenced the efficacy results of this study.

Efficacy Results

As noted previously, the following review is based on the efficacy reanalysis which excluded site 20813.

This review focused on the raw change from baseline for the four key efficacy variables: the HAM-D total score, HAM-D depressed mood item (item #1), MADRS total score, and the CGI-severity score. Efficacy analysis results are displayed for the LOCF and the OC datasets in Appendix 7.2.1.1.

Venlafaxine ER displayed consistent and highly significant superiority over placebo from week 4 onward for all four key variables in the LOCF analyses.

Similar results were observed from the OC analysis.

The results of non-parametric ANCOVA (including site 20813) likewise provide strong support of efficacy. (Data are displayed in vol. 1.66, pages 33-53).

The sponsor assessed for a treatment-by-center interaction across all study centers at each visit for all four key variables (both OC and LOCF datasets): there was no evidence of a consistent treatment-by-center interaction.

The sponsor also conducted a responder analysis, response being defined as a decrease of ≥50% from baseline in HAM-D total or MADRS total score or a CGI-improvement score of 1 (very much improved) or 2 (much improved). The proportions of efficacy ITT patients meeting response criteria were determined at each visit for both the LOCF and OC datasets. Statistical testing was done using the Fisher's exact test. Data from study week 6 onward are summarized below. This analysis corroborates the above findings.

	Ven ER	Placebo	p-value
HAM-D total (LOCF)			
Week 6	62%	35%	<0.001
Week 8	65%	36%	<0.001
Week 12	70%	32%	<0.001
HAM-D total (OC)			
Week 6	69%	38%	<0.001
Week 8	74%	39%	<0.001
Week 12	77%	48%	0.005
MADRS total (LOCF)			
Week 6	60%	31%	<0.001
Week 8	60%	31%	<0.001
Week 12	65%	27%	<0.001
MADRS total (OC)			
Week 6	67%	33%	<0.001
Week 8	68%	35%	<0.001
Week 12	75%	39%	<0.001
CGI-improvement (LOCF)			
Week 6	73%	42%	<0.001
Week 8	73%	38%	<0.001
Week 12	78%	37%	<0.001
CGI-improvement (OC)			
Week 6	82%	46%	<0.001
Week 8	84%	40%	<0.001
Week 12	88%	55%	<0.001

Conclusions

This study provides solid evidence of antidepressant efficacy.

APPENDIX 7.2.1.1

STUDY 208: PRINCIPAL INVESTIGATORS	
Investigator (Site #)	Location
Barry Baumel, MD (20811)	Neuromedical Research Associates Miami Beach, FL
Lynn A. Cunningham, MD (20812)	Vine Street Clinical Research Center Springfield, IL
Bruce Diamond, PhD (20813)	Biotech Park Augusta, GA
Arthur M. Freeman, III, MD (20814)	Louisiana State University Medical Center-Shreveport Shreveport, LA
Robert W. Gibson, Jr, MD (20815)	Piedmont Research Associates Winston-Salem, NC
Barbara L. Kennedy, MD, PhD (20816)	University of Louisville Louisville, KY
Arifulla Khan, MD (20817)	University of Washington Seattle, WA
Roger O. Patrick, PhD (20818)	Belleview Family Medicine Englewood, CO
Robert A. Riesenberg, MD (20819)	BioBehavioral Research Center Decatur, GA
Ram K. Shrivastava, MD (20820)	Eastside Comprehensive Medical Services New York, NY
Stephen M. Stahl, MD, PhD (20821)	Clinical Neuroscience Research Center San Diego, CA
Kenneth J. Weiss, MD (20822)	Delaware Valley Research Associates, Inc. King of Prussia, PA

APPENDIX 7.2.1.1

STUDY 208: BASELINE DEMOGRAPHIC CHARACTERISTICS (excl. 20813)							
Treatment Groups	N	Age (years)		Sex [N(%)]		Race [N(%)]	
		Mean	Range	Male	Female	White	Non-White
VEN ER	85	40	18-70	29(34)	56(66)	76(89)	9(11)
PLAC	91	40	20-65	39(43)	52(57)	85(93)	6(7)
VEN IR	81	43	19-72	28(35)	53(65)	73(90)	8(10)

STUDY 208: COMPLETERS OVER TIME (excl. 20813)								
Treatment Groups	Randomized	ITT	Completers [N(%)]					
			Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12
VEN ER	90	85	85(100)	80(94)	73(86)	57(67)	58(68)	49(58)
PLAC	92	91	91(100)	83(91)	70(77)	59(65)	54(59)	43(47)
VEN IR	88	81	80(99)	74(91)	67(83)	55(68)	51(63)	39(48)

STUDY 208: MEAN DOSE (mg) OVER TIME (excl. 20813)						
	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12
VEN ER	74.2	76.1	134.9	135.8	138.6	138.0
VEN IR	72.5	75.8	122.7	122.1	123.4	116.5

APPENDIX 7.2.1.1

Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8		Week 12	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
STUDY 208: MEAN CHANGE FROM BASELINE IN HAM-D TOTAL SCORE (excl. 20813)														
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	85	24.40	85	-4.34	85	-6.81	85	-11.44	85	-12.91	85	-13.39	85	-14.93
PLAC	91	24.56	91	-3.97	91	-5.18	91	-8.52	91	-12.91	91	-9.01	91	-8.67
VEN IR	81	23.98	81	-4.28	81	-7.28	81	-10.48	81	-11.70	81	-11.65	81	-12.46
2-sided p-values for pairwise comparisons														
ER vs. P	0.381		0.61		0.08		0.009		<0.001		<0.001		<0.001	
IR vs. P	0.220		0.67		0.03		0.08		0.01		0.02		0.002	
ER vs. IR	0.733		0.94		0.62		0.40		0.29		0.13		0.04	
OBSERVED CASES ANALYSIS														
VEN ER	85	24.40	85	-4.34	80	-6.85	73	-12.21	57	-14.21	58	-14.93	49	-16.90
PLAC	91	24.56	91	-3.97	83	-5.65	70	-9.44	59	-9.61	54	-9.91	43	-11.35
VEN IR	81	23.93	80	-4.34	74	-7.69	67	-11.69	55	-13.40	51	-13.39	39	-14.90
2-sided p-values for pairwise comparisons														
R vs. P	0.381		0.61		0.22		0.02		<0.001		<0.001		<0.001	
IR vs. P	0.220		0.62		0.04		0.07		0.003		0.009		0.03	
ER vs. IR	0.733		0.99		0.40		0.67		0.53		0.24		0.20	

APPENDIX 7.2.1.1

STUDY 208: MEAN CHANGE FROM BASELINE IN HAM-D DEPRESSED MOOD ITEM (excl. 20813)														
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8		Week 12	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	85	2.75	85	-0.65	85	-0.88	85	-1.54	85	-1.71	85	-1.65	85	-1.91
PLAC	91	2.71	91	-0.42	91	-0.58	91	-0.90	91	-0.99	91	-1.01	91	-0.92
VEN IR	81	2.77	81	-0.60	81	-0.95	81	-1.37	81	-1.62	81	-1.52	81	-1.69
2-sided p-values for pairwise comparisons														
ER vs. P	0.887		0.06		0.04		<0.001		<0.001		<0.001		<0.001	
IR vs. P	0.554		0.13		0.01		0.005		<0.001		0.003		<0.001	
ER vs. IR	0.650		0.74		0.64		0.32		0.61		0.45		0.21	
OBSERVED CASES ANALYSIS														
VEN ER	85	2.75	85	-0.65	80	-0.88	73	-1.64	57	-1.96	58	-1.83	49	-2.18
PLAC	91	2.71	91	-0.42	83	-0.63	70	-1.00	59	-1.03	54	-1.07	43	-1.33
VEN IR	81	2.76	80	-0.61	74	-1.01	67	-1.48	55	-1.85	51	-1.73	39	-2.00
2-sided p-values for pairwise comparisons														
ER vs. P	0.887		0.06		0.10		<0.001		<0.001		<0.001		<0.001	
IR vs. P	0.554		0.12		0.01		0.01		<0.001		0.002		0.004	
ER vs. IR	0.650		0.79		0.37		0.37		0.58		0.61		0.42	

APPENDIX 7.2.1.1

STUDY 208: MEAN CHANGE FROM BASELINE IN MADRS TOTAL SCORE (excl. 20813)														
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8		Week 12	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	85	26.41	85	-3.72	85	-5.96	85	-12.12	85	-13.96	85	-14.35	85	-15.86
PLAC	91	26.22	91	-3.84	91	-5.01	91	-8.02	91	-8.77	91	-8.79	91	-8.32
VEN IR	81	26.36	81	-4.79	81	-7.16	81	-11.10	81	-13.12	81	-13.21	81	-13.94
2-sided p-values for pairwise comparisons														
ER vs. P	0.951		0.89		0.40		0.004		<0.001		<0.001		<0.001	
IR vs. P	0.872		0.28		0.06		0.03		0.002		0.002		<0.001	
ER vs. IR	0.820		0.24		0.30		0.48		0.56		0.43		0.20	
OBSERVED CASES ANALYSIS														
VEN ER	85	26.41	85	-3.72	80	-5.99	73	-13.10	57	-15.28	58	-16.16	49	-17.27
PLAC	91	26.22	91	-3.84	83	-5.41	70	-8.84	59	-9.75	54	-9.61	43	-11.88
VEN IR	81	26.33	80	-4.85	74	-7.58	67	-12.21	55	-15.04	51	-15.39	39	-16.72
2-sided p-values for pairwise comparisons														
ER vs. P	0.951		0.89		0.63		0.007		<0.001		<0.001		0.01	
IR vs. P	0.872		0.26		0.08		0.04		0.002		0.001		0.03	
ER vs. IR	0.820		0.21		0.20		0.58		0.88		0.66		0.80	

APPENDIX 7.2.1.1

Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8		Week 12	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
STUDY 208: MEAN CHANGE FROM BASELINE IN CGI-SEVERITY SCORE (excl. 20813)														
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	85	4.18	85	-.32	85	-.66	85	-1.40	85	-1.56	85	-1.79	85	-2.07
PLAC	91	4.21	91	-.31	91	-.49	91	-.92	91	-1.04	91	-1.08	91	-1.00
VEN IR	81	4.09	81	-.28	81	-.64	81	-1.12	81	-1.41	81	-1.46	81	-1.51
2-sided p-values for pairwise comparisons														
ER vs. P	0.270		0.91		0.18		0.005		0.003		<0.001		<0.001	
IR vs. P	0.128		0.78		0.24		0.24		0.04		0.04		0.006	
ER vs. IR	0.683		0.70		0.89		0.11		0.38		0.07		0.003	
OBSERVED CASES ANALYSIS														
VEN ER	85	4.18	85	-0.32	80	-.66	73	-1.52	57	-1.75	58	-1.98	49	-2.20
PLAC	91	4.21	91	-.31	83	-.55	70	-1.01	59	-1.17	54	-1.19	43	-1.35
VEN IR	81	4.09	80	-.29	74	-.68	67	-1.28	55	-1.67	51	-1.75	39	-1.82
2-sided p-values for pairwise comparisons														
ER vs. P	0.270		0.91		0.41		0.008		0.005		<0.001		<0.001	
IR vs. P	0.128		0.81		0.36		0.17		0.02		0.01		0.07	
ER vs. IR	0.683		0.73		0.92		0.22		0.69		0.27		0.13	

provided similar evidence in favor of the efficacy of venlafaxine XR.

This reviewer consulted Dr. Dubitsky (HFD-120) regarding the most important efficacy variables. They are "Change from Baseline in HAM-D Total", "Change from Baseline in HAM-D Depressed Mood Item", "Change from Baseline in CGI Severity of Illness", and "Change from Baseline in MADRS Total."

1. Study 600B-208-US

The Table of some Design and Enrolled Patients Aspects and Names of Investigators are in the attached Table 0.1.1.

Essential features of the study, including details of the Design and study conduct, (Patient) Population, Results, and Conclusions may be seen in the synopsis provided by the sponsor in the pages iii to vi of the statistical vol. 1.113. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

1A. Objective

The primary objective of this study was to compare the antidepressant efficacy and safety of venlafaxine XR with placebo. A secondary objective was to compare the overall profile of venlafaxine XR with that of venlafaxine IR.

1B. Disposition of Patients

Patient Disposition is presented as the attached Tables 1.1.1 to 1.1.3. Figure 1.1.4 of Percentage of Patients Continuing Over Time involves only those patients for whom efficacy measures were accepted for analysis in those weeks.

Fifteen of the 293 patients who received randomly assigned study medication had no primary evaluations on therapy or within 3 days of study drug discontinuation. The remaining 278 patients were included in the intent-to-treat efficacy analysis.

The percentage of patients completing the study was 59%, 71%, and 60% respectively for the placebo, Effexor XR, and Effexor IR groups.

The placebo group differed statistically significantly from the other groups with respect to (wrt) Adverse Reaction (less) and Unsatisfactory Response/Efficacy (more).

Adverse Event occurred more during Week 1, and "Failed to Return" and "Unsatisfactory Response/Efficacy" occurred more during Weeks 6-12.

1C. Baseline Comparability of Treatment Groups

The sponsor stated, "There were no statistically significant differences between the treatment groups for the demographic and baseline characteristics. None of the patients had any known illnesses at baseline that might have interfered with the activity of the study medication or the interpretation of the results."

In the Intent-to-Treat patients set,

the percentage of females varied as: 59% (placebo), 63% (Effexor XR), and 67% (Effexor IR), and

the percentage of patients with baseline severity score of 4(mild) varied as: 69% (placebo), 58% (Effexor XR), and 83% (Effexor IR).

1D. Efficacy Results (Sponsor's Analyses)

Following are the (Raw) Mean Changes From Baseline for all three treatment groups, and the venlafaxine XR vs placebo mean differences and p-values. The Tables and Graphs for adjusted Mean Changes From Baseline are attached as Tables 1.3.1 and 1.3.2 (HAM-D Total), 1.4.1 and 1.4.2 (HAM-D Depressed Mood Item), 1.5.1 and 1.5.2 (CGI Severity of Illness), and 1.6.1 and 1.6.2 (MADRS), and as Figures 1.3.3 and 1.3.4 (HAMD-Total), 1.4.3 and 1.4.4 (HAM-D Depressed Mood Item), 1.5.3 and 1.5.4 (CGI Severity of Illness), and 1.6.3 and 1.6.4 (MADRS).

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HAMILTON DEPRESSION SCALE - 21-ITEM TOTAL

LOCF

MEAN CHANGE FROM BASELINE

WEEK	Effexor XR		Effexor IR		PLACEBO		Effexor XR Vs Placebo	
	N	MEAN	N	MEAN	N	MEAN	Difference	P-value
1	92	-4.82	87	-4.32	99	-4.37	-0.45	0.32
2	92	-7.34	87	-7.53	99	-5.61	-1.73	0.02 *
3	92	-9.26	87	-8.87	99	-7.72	-1.54	0.05 *
4	92	-11.75	87	-10.63	99	-8.89	-2.86	<0.001 *
6	92	-13.10	87	-11.72	99	-9.17	-3.93	<0.001 *
8	92	-13.59	87	-11.62	99	-9.30	-4.29	<0.001 *
12	92	-15.00	87	-12.25	99	-9.02	-5.98	<0.001 *

* Indicates statistical significance at the 0.05 level for ANOVA.

OBSERVED

MEAN CHANGE FROM BASELINE

WEEK	Effexor XR		Effexor IR		PLACEBO		Effexor XR Vs Placebo	
	N	MEAN	N	MEAN	N	MEAN	Difference	P-value
1	92	-4.82	86	-4.37	99	-4.37	-0.45	0.32
2	86	-7.37	80	-7.93	89	-5.99	-1.38	0.08
3	81	-9.68	76	-9.79	86	-8.42	-1.26	0.11
4	78	-12.46	71	-11.89	75	-9.67	-2.79	0.001 *
6	61	-14.25	58	-13.69	63	-9.89	-4.36	<0.001 *
8	62	-14.98	53	-13.53	57	-10.18	-4.80	<0.001 *
12	52	-16.85	42	-14.64	44	-11.41	-5.44	<0.001 *

* Indicates statistical significance at the 0.05 level for ANOVA.

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HAMILTON DEPRESSION SCALE - Depressed Mood Item

LOCF

MEAN CHANGE FROM BASELINE

| | Effexor XR | | Effexor IR | | PLACEBO | | Effexor XR Vs Placebo | |
WEEK	N	MEAN	N	MEAN	N	MEAN	Difference	P-value
1	92	-0.72	87	-0.61	99	-0.41	-0.31	0.02 *
2	92	-0.97	87	-0.99	99	-0.58	-0.39	0.01 *
3	92	-1.35	87	-1.24	99	-0.90	-0.45	0.005 *
4	92	-1.61	87	-1.41	99	-0.92	-0.69	<0.001 *
6	92	-1.77	87	-1.61	99	-0.96	-0.81	<0.001 *
8	92	-1.70	87	-1.52	99	-0.99	-0.71	<0.001 *
12	92	-1.95	87	-1.66	99	-0.91	-1.04	<0.001 *

* Indicates statistical significance at the 0.05 level for ANOVA.

OBSERVED

MEAN CHANGE FROM BASELINE

| | Effexor XR | | Effexor IR | | PLACEBO | | Effexor XR Vs Placebo | |
WEEK	N	MEAN	N	MEAN	N	MEAN	Difference	P-value
1	92	-0.72	86	-0.62	99	-0.41	-0.31	0.02 *
2	86	-0.95	80	-1.05	89	-0.62	-0.33	0.06
3	81	-1.42	76	-1.32	86	-0.98	-0.44	0.03 *
4	78	-1.69	71	-1.52	75	-1.03	-0.66	<0.001 *
6	61	-2.00	58	-1.88	63	-1.00	-1.00	<0.001 *
8	62	-1.84	53	-1.75	57	-1.05	-0.79	<0.001 *
12	52	-2.21	42	-1.98	44	-1.30	-0.91	<0.001 *

* Indicates statistical significance at the 0.05 level for ANOVA.

CLINICAL GLOBAL IMPRESSIONS SCALE - SEVERITY OF ILLNESS

LOCF

MEAN CHANGE FROM BASELINE

WEEK	Effexor XR		Effexor IR		PLACEBO		Effexor XR Vs Placebo	
	N	MEAN	N	MEAN	N	MEAN	Difference	P-value
1	92	-0.39	87	-0.29	99	-0.36	-0.03	0.72
2	92	-0.74	87	-0.67	99	-0.54	-0.20	0.07
3	92	-1.09	87	-0.89	99	-0.77	-0.32	0.03 *
4	92	-1.47	87	-1.16	99	-0.99	-0.48	0.001 *
6	92	-1.63	87	-1.43	99	-1.09	-0.54	<0.001 *
8	92	-1.84	87	-1.45	99	-1.11	-0.73	<0.001 *
12	92	-2.12	87	-1.49	99	-1.04	-1.08	<0.001 *

* Indicates statistical significance at the 0.05 level for ANOVA.

OBSERVED

MEAN CHANGE FROM BASELINE

WEEK	Effexor XR		Effexor IR		PLACEBO		Effexor XR Vs Placebo	
	N	MEAN	N	MEAN	N	MEAN	Difference	P-value
1	92	-0.39	86	-0.29	99	-0.36	-0.03	0.72
2	86	-0.74	80	-0.70	89	-0.57	-0.17	0.07
3	81	-1.15	76	-0.97	86	-0.81	-0.34	0.03 *
4	78	-1.58	71	-1.31	75	-1.05	-0.53	0.001 *
6	61	-1.80	58	-1.72	63	-1.21	-0.59	<0.001 *
8	62	-2.02	53	-1.75	57	-1.21	-0.81	<0.001 *
12	52	-2.27	42	-1.81	44	-1.34	-0.93	<0.001 *

* Indicates statistical significance at the 0.05 level for ANOVA.

MONTGOMERY/ASBERG SCALE - TOTAL SCORE

LOCF

MEAN CHANGE FROM BASELINE

	Effexor XR		Effexor IR		PLACEBO		Effexor XR Vs Placebo	
WEEK	N	MEAN	N	MEAN	N	MEAN	Difference	P-value
1	92	-4.29	87	-4.82	99	-3.92	-0.37	0.59
2	92	-6.50	87	-7.26	99	-5.17	-1.33	0.17
3	92	-9.34	87	-9.66	99	-6.97	-2.37	0.02 *
4	92	-12.42	87	-11.21	99	-8.12	-4.30	<0.001 *
6	92	-14.15	87	-13.10	99	-8.89	-5.26	<0.001 *
8	92	-14.49	87	-12.98	99	-8.85	-5.64	<0.001 *
12	92	-15.92	87	-13.48	99	-8.44	-7.48	<0.001 *

* Indicates statistical significance at the 0.05 level for ANOVA.

OBSERVED

MEAN CHANGE FROM BASELINE

	Effexor XR		Effexor IR		PLACEBO		Effexor XR Vs Placebo	
WEEK	N	MEAN	N	MEAN	N	MEAN	Difference	P-value
1	92	-4.29	86	-4.87	99	-3.92	-0.37	0.59
2	86	-6.53	80	-7.66	89	-5.40	-1.13	0.32
3	81	-9.80	76	-10.61	86	-7.48	-2.32	0.03 *
4	78	-13.35	71	-12.28	75	-8.77	-4.58	<0.001 *
6	61	-15.38	58	-15.28	63	-9.76	-5.62	<0.001 *
8	62	-16.16	53	-15.32	57	-9.61	-6.55	<0.001 *
12	52	-17.42	42	-16.17	44	-11.86	-5.56	<0.001 *

* Indicates statistical significance at the 0.05 level for ANOVA.

We see, from the above sponsor's results, that Study 208-US provides strong statistical evidence in favor of venlafaxine XR. The analyses (not presented in this review) provided by the sponsor in the Sept. 18, 1996 submission, excluding data from Dr. Diamond's site (under investigation for alleged research misconduct), provided similarly strong results.

1E. Reviewer's Comments and Conclusions on Study 208-US

Based on the sponsor's submitted results, Study 208-US provided strong statistical evidence in favor of the efficacy of venlafaxine XR. This reviewer's analyses by 2-sample Wilcoxon test and the sponsor's supplemental analyses based on ANCOVA on ranks provided similar evidence.

The sponsor stated in the protocol, "A two-way analysis of covariance with treatment and investigator as factors will be used, provided that the assumptions of the analyses appear to be satisfied (otherwise a suitable transformation or a nonparametric test will be sought.)" As an introduction to the above supplemental analyses, the sponsor stated in the report, "Due to the breakdown of the normality assumption on the CGI severity and the Depressed Mood item (...); non-parametric ANCOVA was applied to all the key efficacy parameters ..."

The Mean Daily Dose for the Effexor XR group was almost always (at each week) greater than that in the Effexor IR group; the highest for the Effexor XR group was 139.6 mg (Week 9) and that for the Effexor IR group was 125.1 mg (Week 5). Average number of capsules in the placebo group was not provided. [p.45 of Stat. Vol. 1.113]

Mean HAM-D Total scores for subgroups of patients dropping out at different times are in Figures 1.3.5 to 1.3.7. Among the patients dropping out just after Week 8, venlafaxine (XR and IR) patients had better HAM-D Total scores compared to the placebo patients (less true with respect to HAM-D Item 1 or CGI Sev.). This fact is likely to favor the placebo group in the OC analyses after Week 8. Except for this subgroup (for placebo, those dropping after Week 6), the subgroup of patients who completed the study had the best scores.

Those who dropped just after Week 4 and just after Week 6 showed trends somewhat opposite to those mentioned above. Consequently, the OC results may be slightly inflated in favor of venlafaxine XR for week 6 and, especially, Week 8. However, combined with the effect in the previous paragraph, the OC results after Week 8 should not be inflated in favor of venlafaxine.

Those patients who dropped out just after Week 2, generally, had worse scores (compared with those of patients dropping out at other times or of completers), irrespective of the treatment group (except placebo patients wrt CGI sev.).

To address the missing data problem, the sponsor applied ETRANK and longitudinal data analyses to the HAM-D total score, to compare the

FIGURE. 0.2.4

Cumulative Percent Vs HAM–D Total Scores
Study 208

Legend:
- Final Venlafaxine ER
- Final Venlafaxine IR
- Final Placebo
- Baseline Venlafaxine ER
- Baseline Venlafaxine IR
- Baseline Placebo

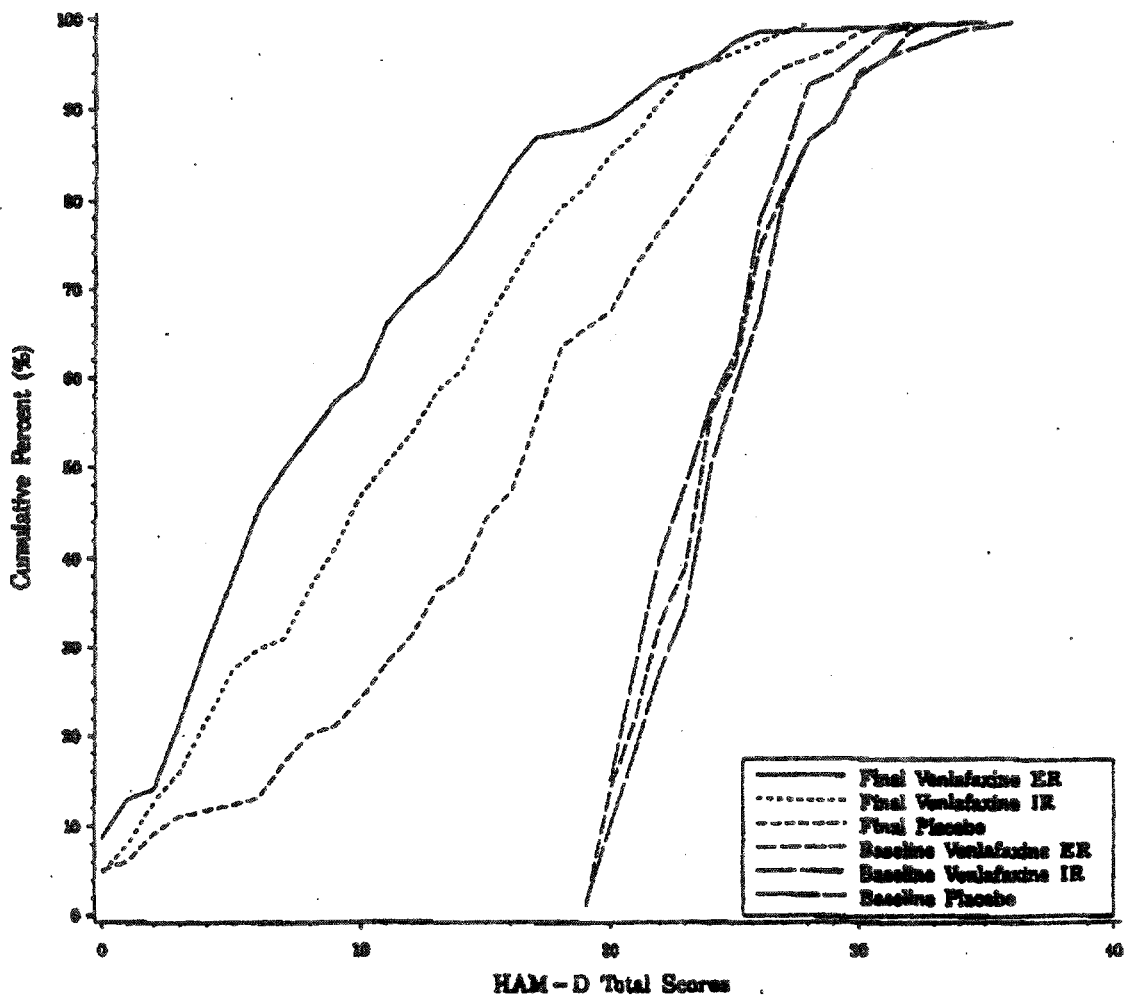Y-axis: Cumulative Percent (%)
X-axis: HAM–D Total Scores

7

FIGURE 0.2.7

Mean Difference Between Venl ER and Placebo with 95% Confidence Intervals
Using HAM–D Total Change from Baseline Scores from
Final On–Therapy Values for Protocol 208
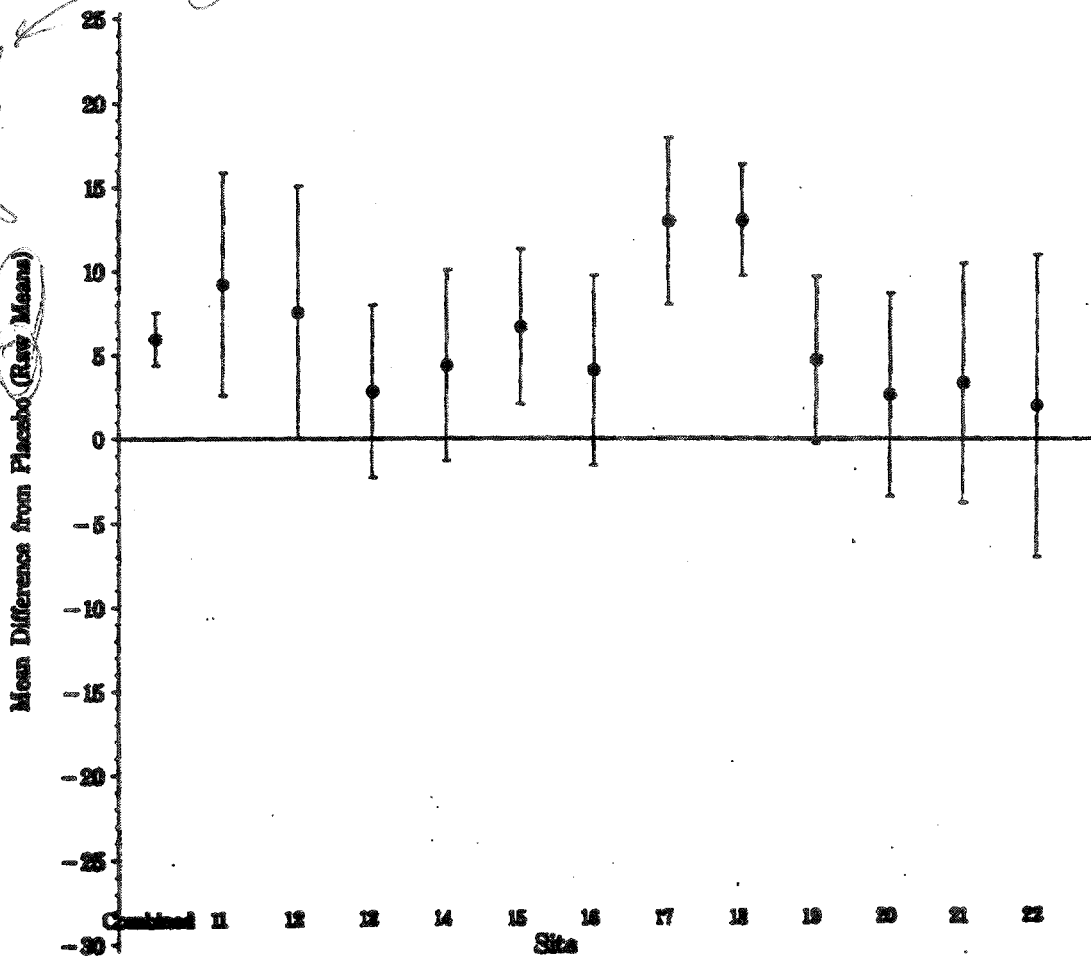
TABLE 1.1.2   208-US

NUMBER (%) OF PATIENTS WHO WITHDREW
BY PRIMARY REASON

Reason	Placebo (n = 100)	Venlafaxine ER (n = 97)	Venlafaxine IR (n = 96)	p-value[a]
Any Reason	41 (41)	28 (29)	38 (40)	
Adverse Reaction	2 (2)	11 (11)	12 (13)	0.015
Failed to return	16 (16)	9 (9)	14 (15)	
Patient/Subject Request	3 (3)	1 (1)	3 (3)	
Unsatisfactory Response/Efficacy	12 (12)	2 (2)	4 (4)	0.01
Protocol Violation	2 (2)	2 (2)	2 (2)	
Other Medical Event	2 (2)	1 (1)	2 (2)	
Other non-medical event	4 (4)	2 (2)	1 (1)	

a: Fisher's Exact Test was used in the comparison between treatment groups.

FIGURE 1-1.4

PERCENTAGE OF PATIENTS OVER TIME
STUDY 208

16
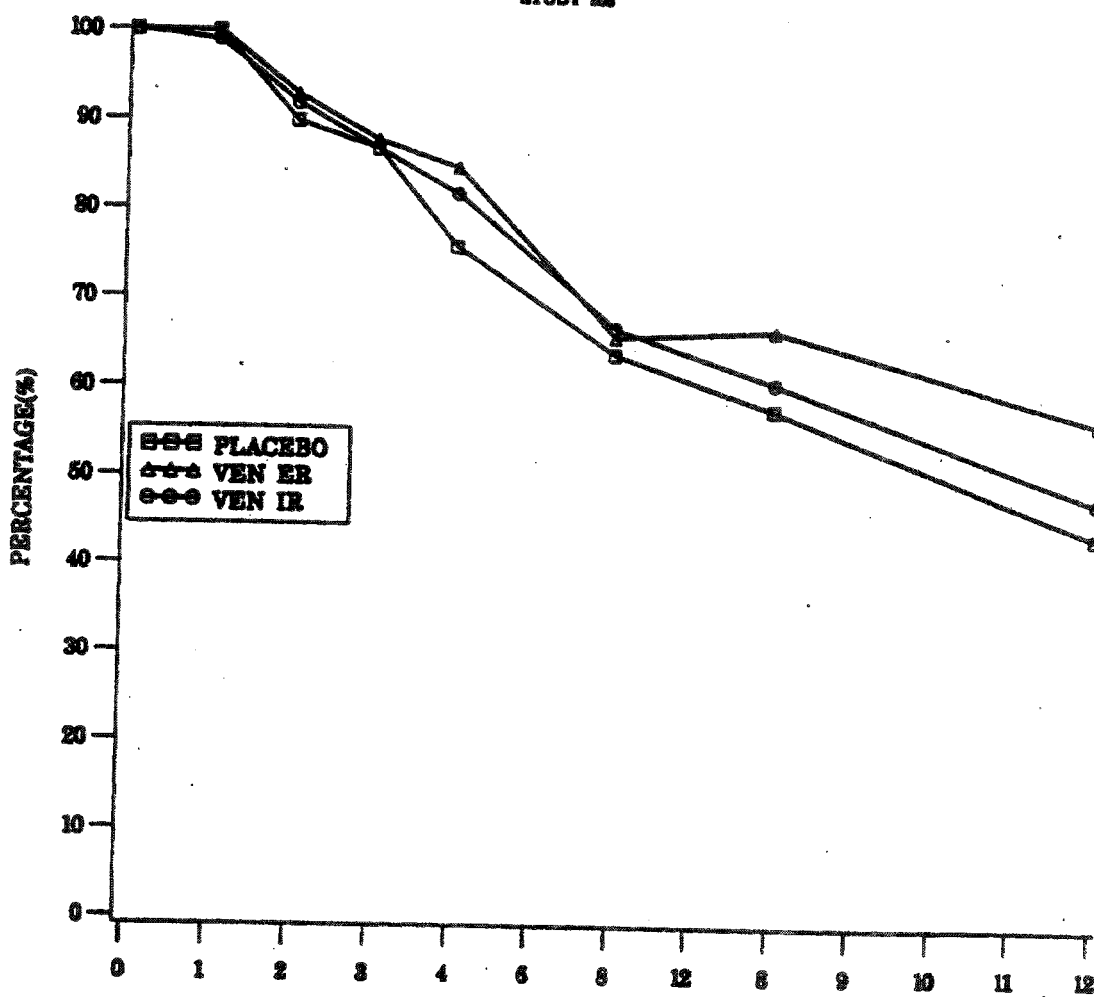
FIGURE 1.3.3

HAM-D TOTAL VS TIME ON THERAPY
LOCF ANALYSIS
STUDY 208
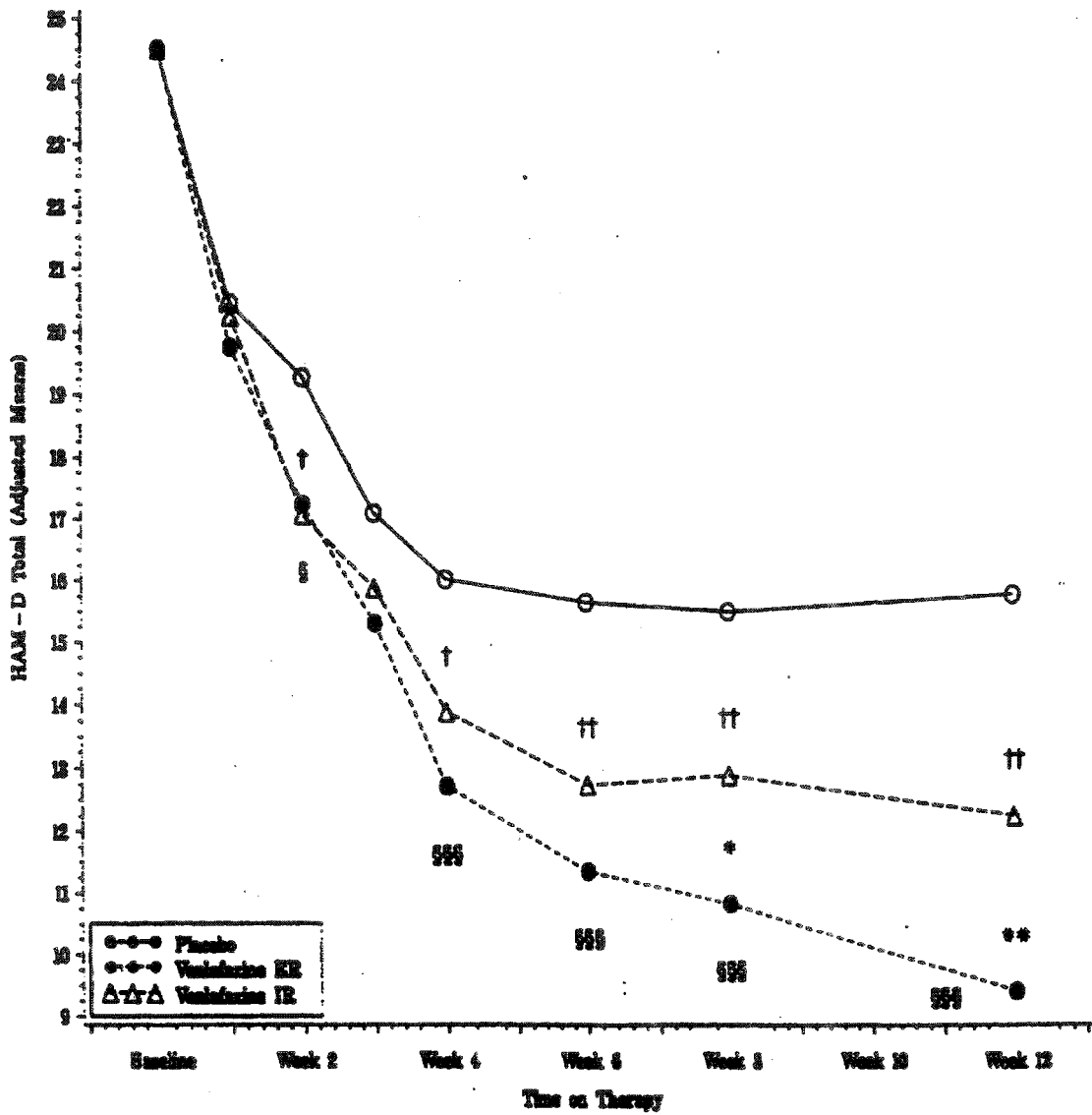
HAM-D Total (Adjusted Means)

25
24
23
22
21
20
19
18
17
16
15
14
13
12
11
10
9

Baseline　Week 2　Week 4　Week 6　Week 8　Week 10　Week 12

Time on Therapy

Legend:
- ●—●—● Placebo
- ●—●—● Venlafaxine ER
- △—△—△ Venlafaxine IR

Placebo vs Ven ER Significance:	§ = p≤.05	§§ = p≤.01	§§§ = p≤.001
Placebo vs Ven IR Significance:	† = p≤.05	†† = p≤.01	††† = p≤.001
Ven ER vs Ven IR Significance:	* = p≤.05	** = p≤.01	*** = p≤.001

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FIGURE 1.3.4

HAM-D TOTAL VS TIME ON THERAPY
OBSERVED CASES ANALYSIS
STUDY 208

Placebo vs Ven ER Significance: § = p ≤ .05   §§ = p ≤ .01   §§§ = p ≤ .001
Placebo vs Ven IR Significance: † = p ≤ .05   †† = p ≤ .01   ††† = p ≤ .001
Ven ER vs Ven IR Significance: * = p ≤ .05   ** = p ≤ .01   *** = p ≤ .001

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FIGURE 1.3.5

Mean HAM-D Total Score
Protocol 208
Therapy: Placebo
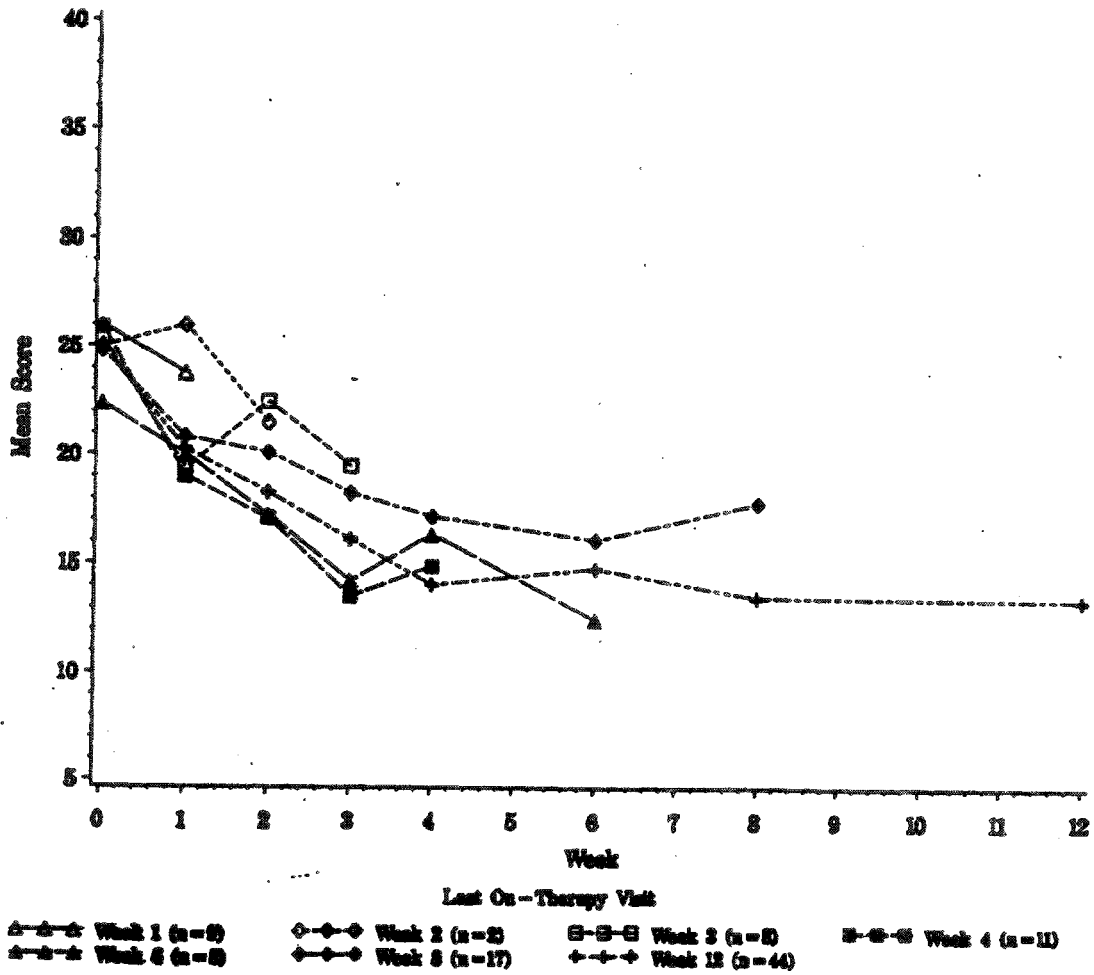
FIGURE 1.3.6

Mean HAM−D Total Score
Protocol 208
Therapy: Venlafaxine ER
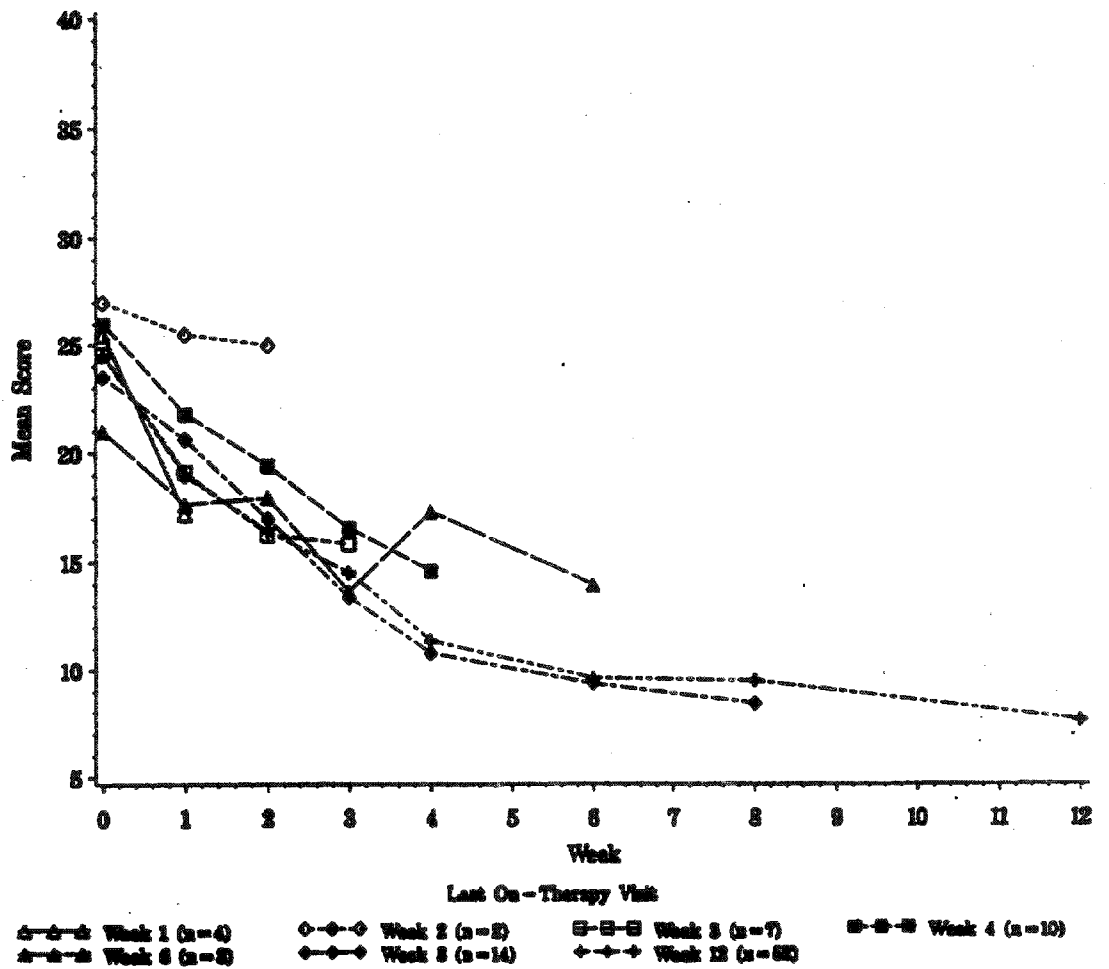
FIGURE 1.3.7

Mean HAM – D Total Score
Protocol 208
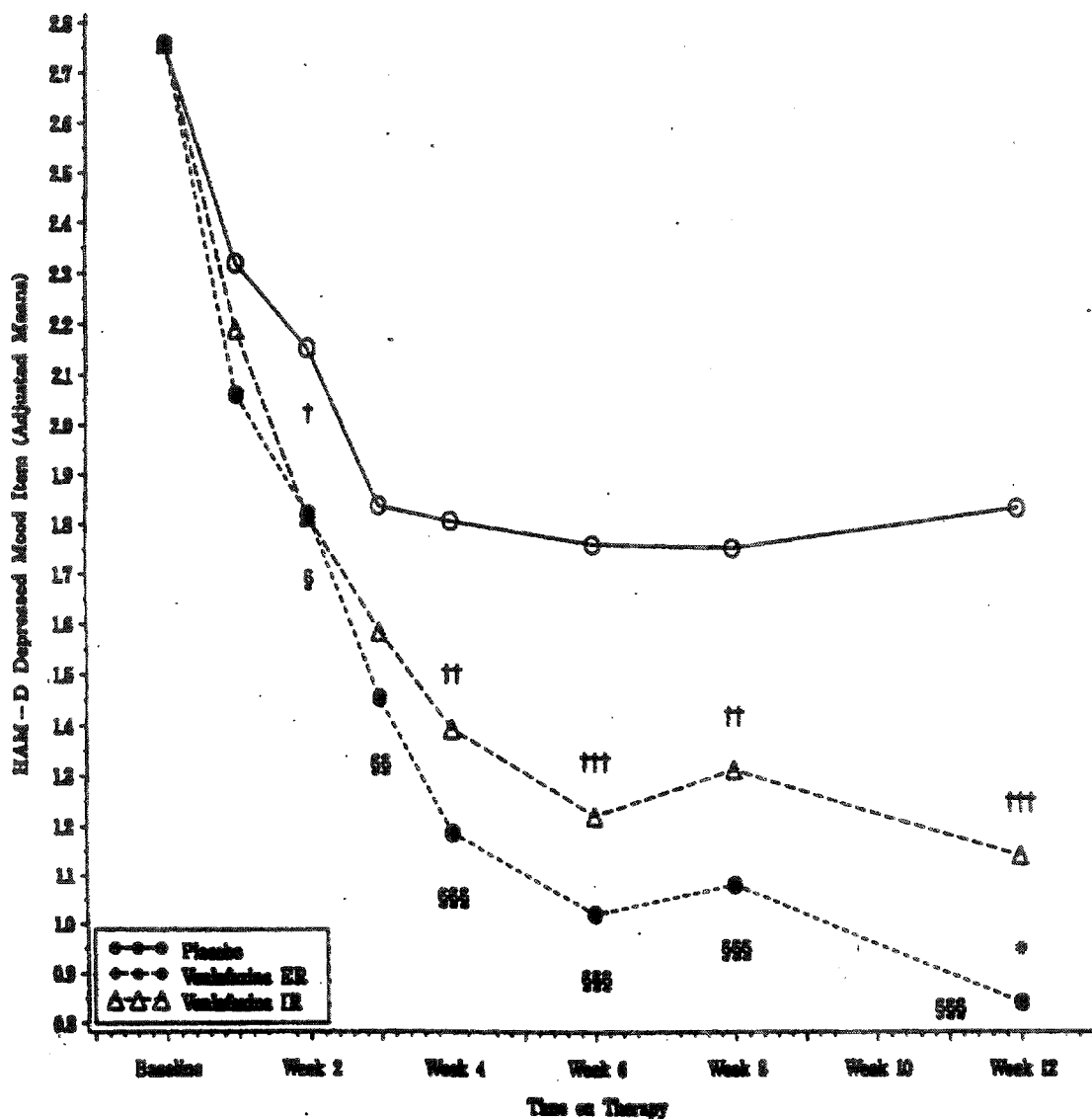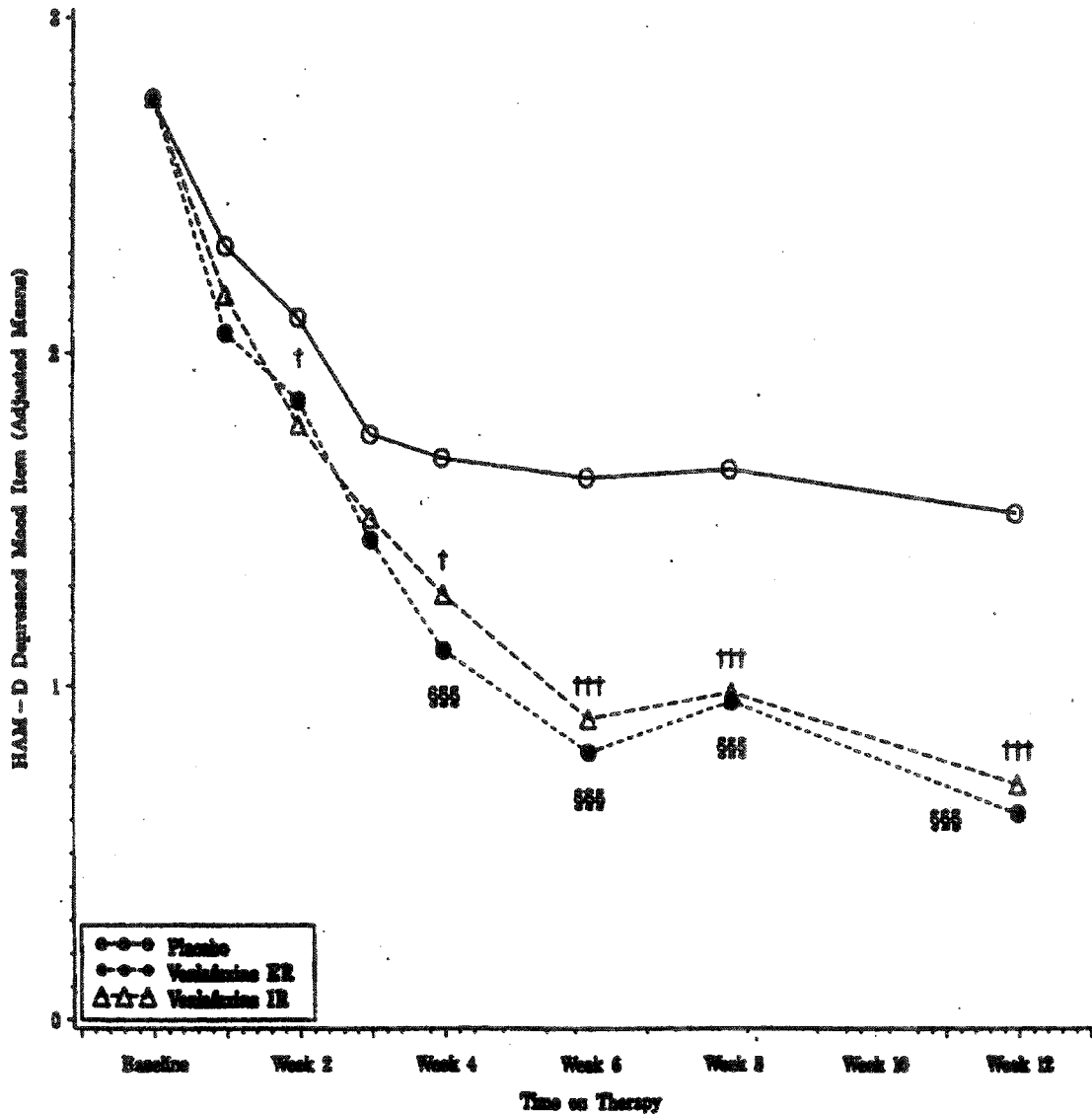### Therapy: Venlafaxine IR
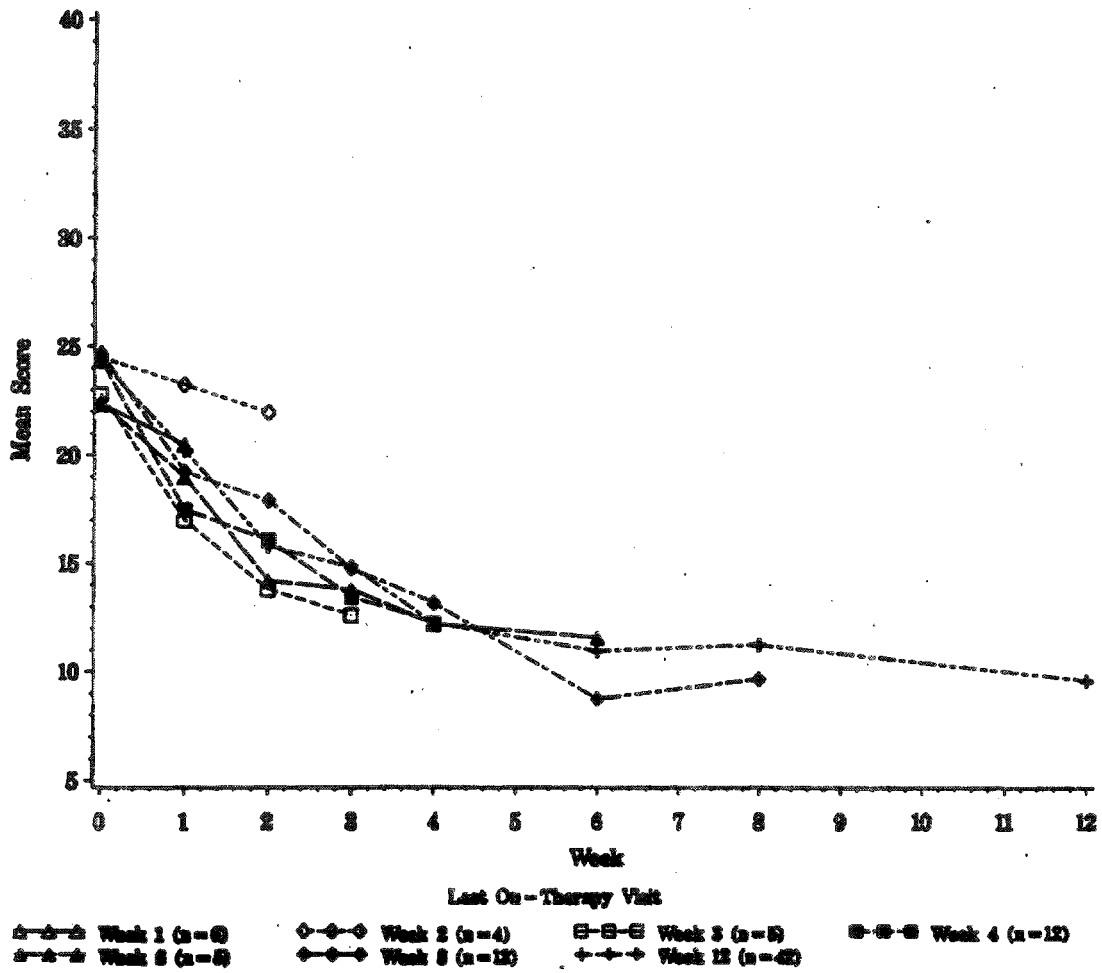
FIGURE 1.4.3

HAM-D DEPRESSED MOOD ITEM VS TIME ON THERAPY
LOCF ANALYSIS
STUDY 208

Placebo vs Ven ER Significance:	§ = p≤ .05	§§ = p≤ .01	§§§ = p≤ .001
Placebo vs Ven IR Significance:	† = p≤ .05	†† = p≤ .01	††† = p≤ .001
Ven ER vs Ven IR Significance:	* = p≤ .05	** = p≤ .01	*** = p≤ .001

FIGURE 1.4.4

HAM-D DEPRESSED MOOD ITEM VS TIME ON THERAPY
OBSERVED CASES ANALYSIS
STUDY 208

Placebo vs Ven ER Significance: § = p ≤ .05   §§ = p ≤ .01   §§§ = p ≤ .001
Placebo vs Ven IR Significance: † = p ≤ .05   †† = p ≤ .01   ††† = p ≤ .001
Ven ER vs Ven IR Significance: * = p ≤ .05   ** = p ≤ .01   *** = p ≤ .001
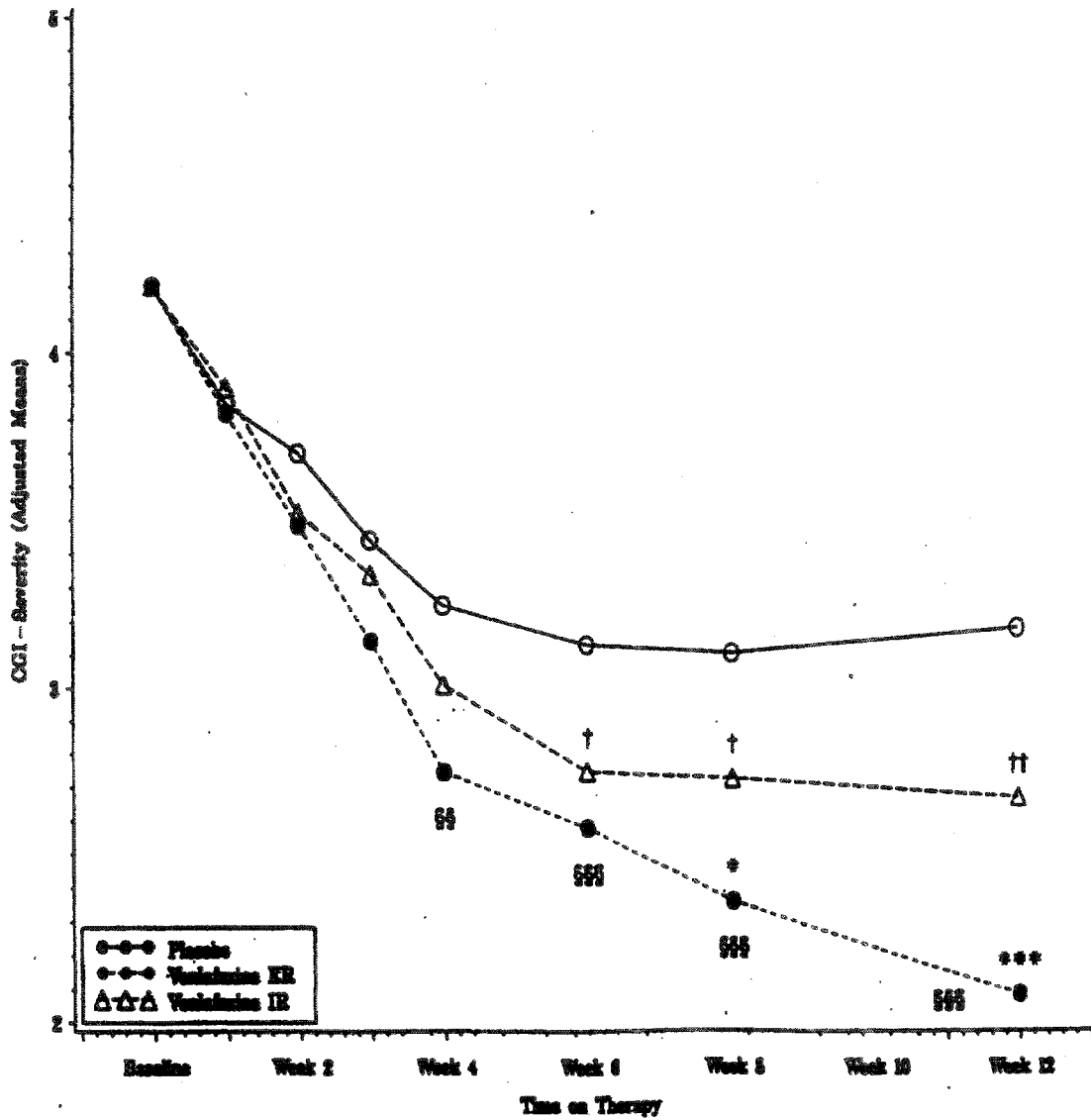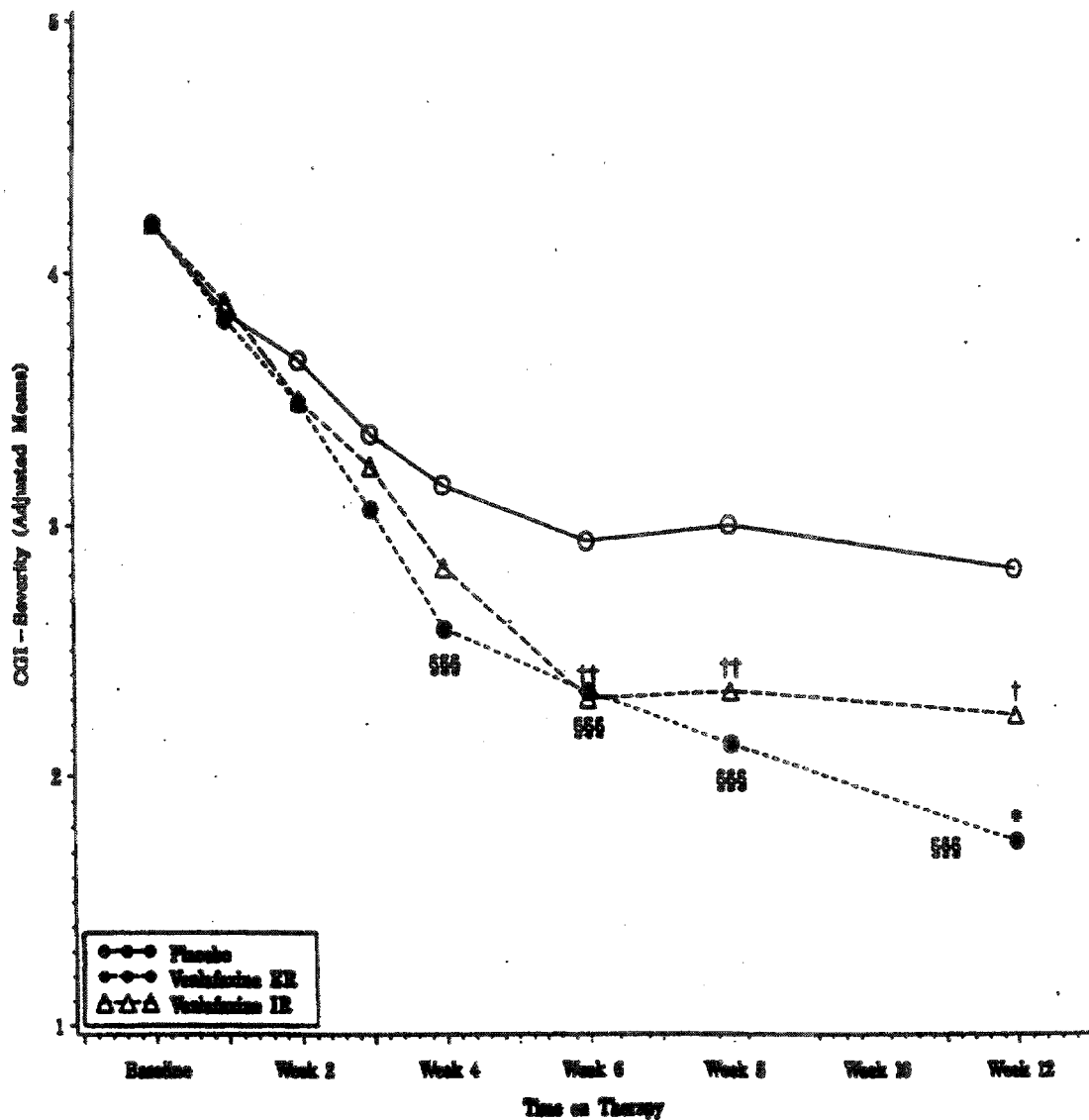
FIGURE 1.5.3

CGI-SEVERITY SCORES VS TIME ON THERAPY
LOCF ANALYSIS
STUDY 208

Placebo vs Ven ER Significance: § = p≤ .05   §§ = p≤ .01   §§§ = p≤ .001
Placebo vs Ven IR Significance: † = p≤ .05   †† = p≤ .01   ††† = p≤ .001
Ven ER vs Ven IR Significance: * = p≤ .05   ** = p≤ .01   *** = p≤ .001

FIGURE 1.5.4.

CGI-SEVERITY SCORES VS TIME ON THERAPY
OBSERVED CASES ANALYSIS
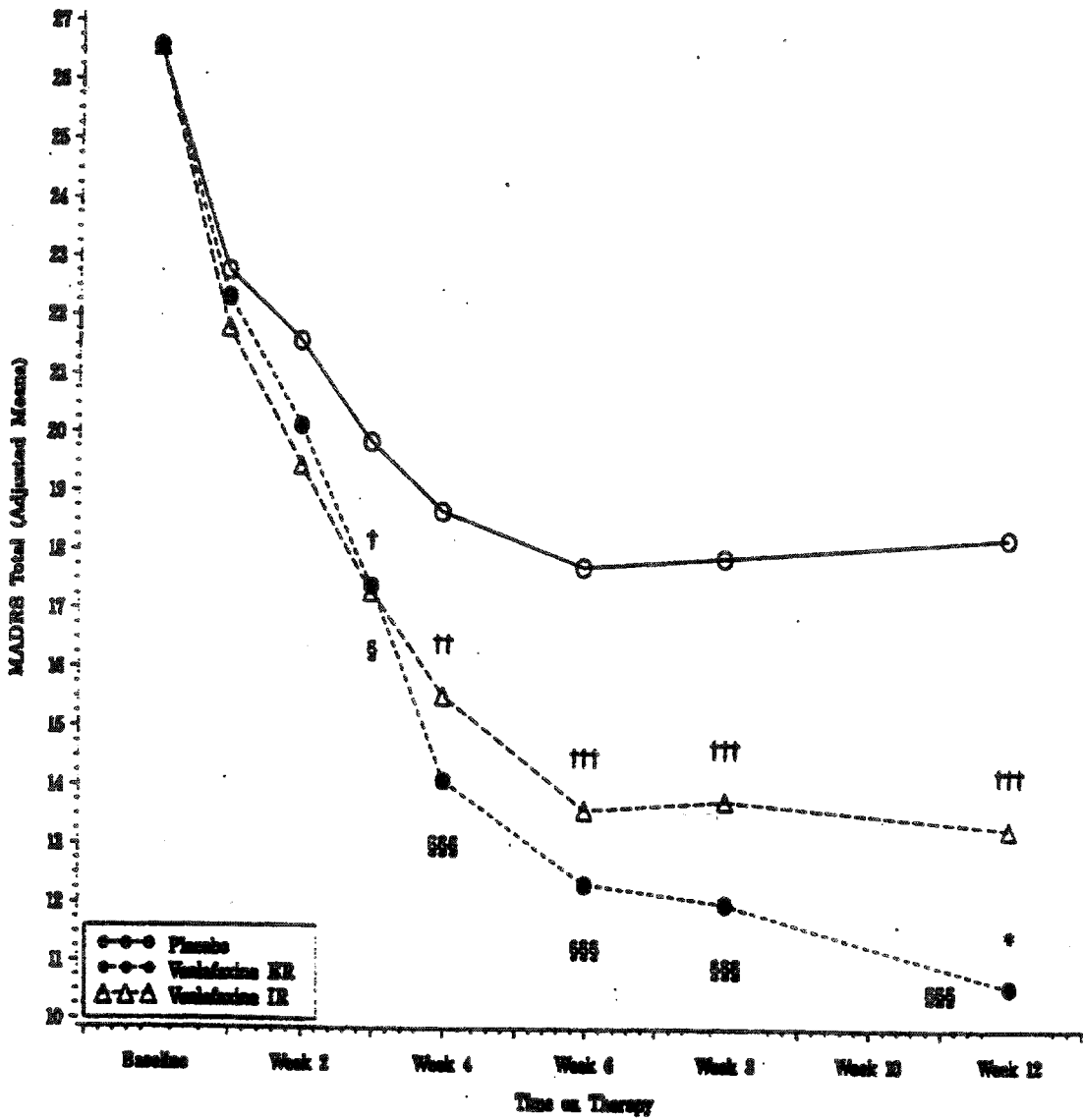## STUDY 208

Placebo vs Ven ER Significance: § = p≤ .05   §§ = p≤ .01   §§§ = p≤ .001
Placebo vs Ven IR Significance: † = p≤ .05   †† = p≤ .01   ††† = p≤ .001
Ven ER vs Ven IR Significance: * = p≤ .05   ** = p≤ .01   *** = p≤ .001

FIGURE 1.6.3

MADRS TOTAL VS TIME ON THERAPY
LOCF ANALYSIS
STUDY 208

FIGURE 1.6.4

MADRS TOTAL VS TIME ON THERAPY
OBSERVED CASES ANALYSIS
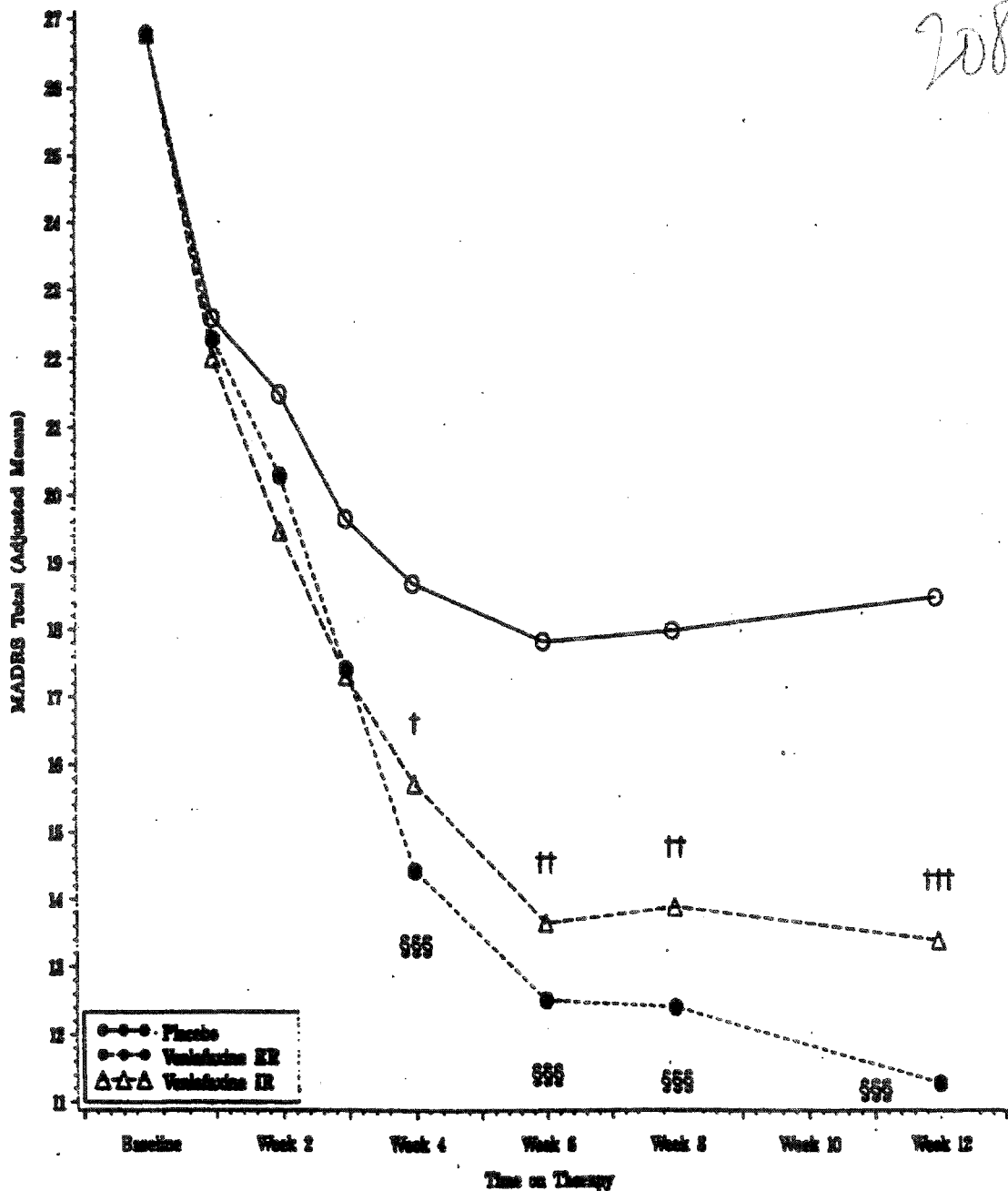
Placebo vs Ven ER Significance:	§ = p≤ .05	§§ = p≤ .01	§§§ = p≤ .001
Placebo vs Ven IR Significance:	† = p≤ .05	†† = p≤ .01	††† = p≤ .001
Ven ER vs Ven IR Significance:	* = p≤ .05	** = p≤ .01	*** = p≤ .001

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7.2.1.2   Study 209

Investigators/Locations

Principal investigators and study sites are listed in Appendix 7.2.1.2.

Objectives

The study objective was to compare the antidepressant efficacy and safety of venlafaxine ER with placebo.

Population

A total of 204 outpatients with DSM-IV major depression were enrolled.   Other inclusion criteria were:

* minimum age of 18 years.
* symptoms of depression for at least one month.
* minimum prestudy 21-item HAM-D total score of 20, with no greater than a 20% decrease between screening and study day -1.

Relevant exclusion criteria included the following:

* previous venlafaxine treatment.
* history or presence of any psychotic disorder not related to depression, bipolar disorder, or mental disorder due to a medical condition.
* use of any investigational drug, antipsychotic drug, or ECT within 30 days; fluoxetine within 21 days; MAOI within 14 days; or any antidepressant, anxiolytic, sedative-hypnotic, or other psychotropic agent within 7 days (except chloral hydrate).
* use of any non-psychopharmacologic drug with psychotropic effects within 7 days of the study unless a stable dose had been maintained for the past month.
* drug or alcohol dependence within 1 year.

Also, the initiation or change in intensity of formal psychotherapy was prohibited during the study.

Design

This was a randomized, double-blind, placebo-controlled, parallel group study conducted at 12 U.S. sites. Depressed patients with a HAM-D total score ≥20 underwent a single-blind placebo run-in for 7±3 days, during which they were evaluated for study eligibility. On study day -1, baseline safety and efficacy assessments were completed and patients who continued to meet selection criteria were randomized to begin either venlafaxine ER or placebo on day 1.

Double-blind treatment was continued for 8 weeks, followed by

medication tapering for up to 2 weeks. Study visits occurred on days 7, 14, 21, 28, 42, and 56; the HAM-D, MADRS, and CGI were administered at each visit. Also, an Investigator's and Patient's Subjective Rating was done on days 14, 21, and 56, and a Quality of Life Questionnaire was done on day 56.

A flexible dosing regimen was employed as shown below.

Period	Venlafaxine ER Dose
Days 1-14	75mg
Days 15-28	75 or 150mg
Days 29-56	75 or 150 or 225mg
Taper Wk 1	0 or 75 or 150mg
Taper Wk 2	0 or 75mg

Patients were instructed to take the study medication once daily in the morning. Doses were increased if clinically indicated to improve response. The dose could be reduced at any time to improve tolerance, with a minimum dose of 75mg after day 7.

Analysis

The efficacy intent-to-treat (ITT) population included all enrolled patients who had at least a baseline measure on at least one efficacy parameter, took at least one dose of study medication, and had at least one evaluation on at least one efficacy measure either during treatment or within 3 days after the last dose. A total of 191 patients comprised the efficacy ITT.

The efficacy analysis discussed below is based on an overall F-test, comparing the venlafaxine ER group with the placebo group, with respect to the raw mean change from baseline at each visit for four key efficacy variables: HAM-D and MADRS total scores, HAM-D depressed mood item, and CGI-severity score. Analysis was performed on both observed cases (OC) and last-observation-carried-forward (LOCF) datasets. Statistical significance was defined at the $\alpha = 0.05$ level and all hypothesis testing was 2-sided.

Additionally, since the assumption of normality for the HAM-D depressed mood item and CGI-severity was not met, the sponsor provided the results of a non-parametric ANCOVA for all key variables at each visit for both the LOCF and OC datasets.

Baseline Demographics

Baseline demographic data is displayed in Appendix 7.2.1.2. There were no statistically significant differences between groups at baseline with respect to age, sex, or race ($p = 0.26$, 0.50, and 0.68, respectively).

Baseline Severity of Illness

The difference in baseline HAM-D scores between groups approached statistical significance: mean score for venlafaxine ER= 24.53 and for placebo= 23.63, p= 0.07. However, the difference in baseline MADRS scores was not significant: venlafaxine ER mean= 27.99 and placebo mean= 27.75, p= 0.75.

Mean CGI-severity scores at baseline were roughly comparable; most patients in each group were rated as "mild" (64% of venlafaxine ER vs. 74% of placebo patients).

The relationship between baseline scores and outcome will be explored by the statistical reviewer.

Patient Disposition

Of the 204 patients enrolled, 197 were randomized and 191 comprised the efficacy ITT, of which 91 were randomized to venlafaxine ER and 100 to placebo. The number of completers (i.e. patients with observed data for at least one of the four key efficacy variables), also expressed as a percentage of the efficacy ITT, at each visit is displayed in Appendix 7.2.1.2.

Of the ITT, 66% (60/91) of the venlafaxine ER and 51% (51/100) of the placebo patients completed 8 weeks of double-blind treatment; as expected, the most frequent reason for dropout among venlafaxine ER patients was an adverse event (11% of the patients in the safety ITT) and the most frequent reason in the placebo group was lack of adequate response (22% of the safety ITT).

Three patients (2 venlafaxine ER and 1 placebo) dropped out for protocol violations:

• venlafaxine ER patient 20905-031 - discontinued study medication.
• venlafaxine ER patient 20910-007 - drug screen positive for drugs of exclusion.
• placebo patient 20906-014 - noncompliant with daily use of study medication.

The visit at which at least 70% of the patients in both groups were still in-study and had observed efficacy data was week 4, with 86% of the venlafaxine ER and 80% of the placebo patients remaining at that timepoint.

Dosing Information

The mean daily dose for all venlafaxine ER patients at each visit is displayed in Appendix 7.2.1.2. The mean dose appears to have reached a plateau at slightly over 170 mg/day during the last half of the study.

Concomitant Medications

Concomitant medication use was very common but generally similar between groups with respect to the proportion of patients taking given classes of agents. The most commonly used medications were analgesics/antipyretics (56% of both groups) and anti-inflammatory/non-steroidal antirheumatic agents (33% of venlafaxine ER and 43% of placebo patients).

It is notable that 3 venlafaxine ER and 3 placebo patients received an antidepressant drug during the study. Of the 3 venlafaxine ER patients, 2 (20901-027 and 20902-002) dropped out on days 35 and 28, respectively, due to inadequate therapeutic response; they were prescribed the antidepressants (venlafaxine IR and sertraline, respectively) during the taper periods. The third patient (20901-020) completed the study but was started on venlafaxine IR during the taper period. Similarly, the 3 placebo patients dropped out due to lack of efficacy and took antidepressant medication during the taper period. Given that none of these 3 patients took an antidepressant during the critical 8 week period for evaluating efficacy, this use should not affect the efficacy results of the study.

Efficacy Results

This review focused on the raw change from baseline for the four key efficacy variables: the HAM-D total score, HAM-D depressed mood item (item #1), MADRS total score, and CGI-severity score. Efficacy analysis results are displayed for the OC and LOCF datasets in Appendix 7.2.1.2.

The LOCF analyses demonstrate consistent and statistically significant superiority of venlafaxine ER over placebo for all 4 variables at the end of weeks 4, 6, and 8; this difference was highly significant at the end of week 8 ($p < 0.001$).

For the OC analyses, findings were not consistent over these visits. Differences were significant at the end of week 4, except for the MADRS total score which was in the trend range ($p=0.08$). This was followed, at the end of week 6, by a sizable decrease in both sample sizes, continued overall improvement in both groups, and loss of statistical significance despite numerical superiority of drug over placebo. Then at the end of week 8, there was further attrition in both groups but more so in the placebo group; venlafaxine ER patients showed further overall improvement while the placebo patients did not improve, restoring statistical superiority to the drug.

The results of the non-parametric, rank-based comparisons of venlafaxine ER and placebo similarly support the efficacy of venlafaxine ER; as with the parametric analyses, the OC results were not as consistent over time as the LOCF results. These data

are displayed in vol. 1.75, pages 25-46.

The sponsor assessed for a treatment-by-center interaction across all study centers at each visit for all four key variables (both OC and LOCF datasets): there was no evidence of a consistent treatment-by-center interaction.

The sponsor also conducted a responder analysis, response being defined as a decrease of $\geq 50\%$ from baseline in HAM-D total or MADRS total score or a CGI-improvement score of 1 (very much improved) or 2 (much improved). The proportions of efficacy ITT patients meeting response criteria were determined at each visit for both the LOCF and OC datasets. Statistical testing was done using the Fisher's exact test. Statistically significant differences are summarized below.

	Ven ER	Placebo	p-value
HAM-D total (LOCF)			
Week 6	49%	34%	0.04
Week 8	58%	29%	<0.001
HAM-D total (OC)			
Week 8	73%	45%	0.003
MADRS total (LOCF)			
Week 8	48%	28%	0.005
MADRS total (OC)			
Week 8	63%	43%	0.04
CGI-improvement (LOCF)			
Week 6	58%	42%	0.03
Week 8	60%	37%	0.001
CGI-improvement (OC)			
Week 8	73%	55%	0.05

Conclusions

The LOCF analysis provides strong evidence of antidepressant efficacy from Week 4 onward. The OC analysis, while not as strong probably as a result of both attrition and placebo response, also is considered to support the LOCF results. Finally, the responder analysis shows clear differences between drug and placebo at the end of weeks 6 and 8. Overall, this study provides solid evidence of antidepressant efficacy for venlafaxine ER.

APPENDIX 7.2.1.2

| STUDY 209: PRINCIPAL INVESTIGATORS ||
Investigator (Site #)	Location
John Carman, MD (20901)	Carman Research Atlanta, GA
Lorna Charles, MD (20902)	Southern New Jersey Medical Institute Stratford, NJ
Cal Cohn, MD (20903)	The Cohn Research Center Houston, TX
James Farrell, DO (20904)	Midwest Pharmaceutical Research, Inc. St. Peters, MO
Maurizio Fava, MD (20905)	Massachusetts General Hospital Boston, MA
John Feighner, MD (20906)	Feighner Research Institute Poway, CA
Alan Feiger, MD (20907)	Feiger PsychMed Center Wheat Ridge, CO
James Ferguson, MD (20908)	Pharmacology Research Corporation Salt Lake City, UT
Kimberly Yonkers, MD (20909)	The University of Texas Southwestern Medical Center Dallas, TX
Susanna Goldstein, MD (20910)	Center for Psychobiology New York, NY
Michael Thase, MD (20911)	University of Pittsburgh Pittsburgh, PA
Richard Weisler, MD (20912)	Holly Hill Hospital Raleigh, NC

APPENDIX 7.2.1.2

STUDY 209: BASELINE DEMOGRAPHIC CHARACTERISTICS							
Treatment Groups	N	Age (years)		Sex [N(%)]		Race [N(%)]	
		Mean	Range	Male	Female	White	Non-White
VEN ER	91	40	18-66	33(36%)	58(64%)	86(95%)	5(5%)
PLAC	100	42	21-77	41(41%)	59(59%)	97(97%)	3(3%)

STUDY 209: COMPLETERS OVER TIME								
Treatment Groups	Randomized	ITT	Completers [N(%)]					
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8
VEN ER	95	91	89(98)	82(90)	82(90)	78(86)	65(71)	60(66)
PLAC	102	100	99(99)	93(93)	88(88)	80(80)	63(63)	51(51)

STUDY 209: MEAN DOSE (mg) OVER TIME						
Treatment Group	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8
VEN ER	73.6	76.0	124.5	135.8	176.4	176.6

APPENDIX 7.2.1.2

STUDY 209: MEAN CHANGE FROM BASELINE IN HAM-D TOTAL SCORE														
Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	91	24.53	91	-3.87	91	-6.51	91	-7.86	91	-9.22	91	-10.52	91	-11.66
PLAC	100	23.63	100	-3.34	100	-4.81	100	-6.34	100	-6.45	100	-7.71	100	-6.78
2-sided p-values for pairwise comparisons														
V vs. P	0.07		0.76		0.07		0.16		0.008		0.02		<0.001	
OBSERVED CASES ANALYSIS														
VEN ER	91	24.53	89	-3.96	82	-6.82	82	-8.11	78	-9.62	65	-11.78	60	-14.38
PLAC	100	23.63	99	-3.37	93	-4.98	88	-6.68	80	-7.23	62	-9.94	51	-9.25
2-sided p-values for pairwise comparisons														
V vs. P	0.07		0.72		0.04		0.30		0.03		0.19		<0.001	

APPENDIX 7.2.1.2

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 6		Week 8	
STUDY 209: MEAN CHANGE FROM BASELINE IN HAM-D DEPRESSED MOOD ITEM														
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	91	2.79	91	-0.60	91	-0.80	91	-1.01	91	-1.15	91	-1.31	91	-1.47
PLAC	100	2.79	100	-0.40	100	-0.56	100	-0.70	100	-0.74	100	-0.82	100	-0.71
2-sided p-values for pairwise comparisons														
V vs. P	N/R		0.09		0.08		0.02		0.005		0.002		<0.001	
OBSERVED CASES ANALYSIS														
VEN ER	91	2.79	89	-0.62	82	-0.79	82	-1.05	78	-1.19	65	-1.38	60	-1.82
PLAC	100	2.79	99	-0.40	93	-0.55	88	-0.77	80	-0.86	62	-1.05	51	-1.12
2-sided p-values for pairwise comparisons														
V vs. P	N/R		0.08		0.11		0.09		0.05		0.10		0.005	

APPENDIX 7.2.1.2

Treatment Group	STUDY 209: MEAN CHANGE FROM BASELINE IN MADRS TOTAL SCORE														
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	91	27.99	91	-4.10	91	-6.92	91	-8.22	91	-9.69	91	-11.75	91	-12.38
PLAC	100	27.75	100	-4.38	100	-5.22	100	-6.28	100	-6.79	100	-8.54	100	-7.01
2-sided p-values for pairwise comparisons														
V vs. P	0.75		0.64		0.14		0.10		0.02		0.02		<0.001	
OBSERVED CASES ANALYSIS														
VEN ER	91	27.99	89	-4.19	82	-7.09	82	-8.52	78	-10.35	65	-13.42	60	-16.02
PLAC	100	27.75	98	-4.47	93	-5.39	86	-6.53	79	-7.71	63	-11.32	51	-10.14
2-sided p-values for pairwise comparisons														
V vs. P	0.75		0.62		0.18		0.21		0.08		0.21		0.005	

APPENDIX 7.2.1.2

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
STUDY 209: MEAN CHANGE FROM BASELINE IN CGI-SEVERITY SCORE														
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	91	4.43	91	-0.29	91	-0.74	91	-0.96	91	-1.16	91	-1.42	91	-1.53
PLAC	100	4.30	100	-0.31	100	-0.44	100	-0.64	100	-0.75	100	-0.93	100	-0.82
2-sided p-values for pairwise comparisons														
V vs. P	N/R		0.56		0.03		0.03		0.004		0.004		<0.001	
OBSERVED CASES ANALYSIS														
VEN ER	91	4.43	89	-0.29	82	-0.76	81	-1.00	77	-1.25	65	-1.58	60	-1.92
PLAC	100	4.30	99	-0.31	93	-0.46	88	-0.69	80	-0.88	62	-1.23	51	-1.24
2-sided p-values for pairwise comparisons														
V vs. P	N/R		0.58		0.03		0.10		0.02		0.17		0.01	

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treatment differences between the two groups over time (pages 25 to 32 of Vol.1.116). The sponsor concluded, "... confirm significant advantages of both Venlafaxine-XR and Venlafaxine-IR over the placebo treated patients as shown in Table 6."

The sponsor stated (p 202, vol. 1.1), "... the results of a study that directly compared venlafaxine XR and venlafaxine IR (study 600B-208-US) in which venlafaxine XR was significantly more effective than venlafaxine IR for all primary efficacy parameters at week 12."

2. Study 600B-209-US

The Table of some Design and Enrolled Patients Aspects and Names of Investigators are in the attached Table 0.1.2.

Essential features of the study, including investigators, details of the Design and study conduct, (Patient) Population, Results, and Conclusions may be seen in the synopsis provided by the sponsor on the pages iii to v of the statistical vol. 1.123. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

2A. Objective

This study was conducted to compare the antidepressant efficacy and safety of venlafaxine ER with those of placebo.

2B. Disposition of Patients

Various types of information related with Patient Disposition are presented as the attached Tables 2.1.1 to 2.1.3. Figure 2.1.4 of Percentage of Patients Continuing Over Time involves only those patients for whom efficacy measures were accepted for analysis in those weeks.

Six of the 197 patients who received randomly assigned study medication had no primary evaluations on therapy. The remaining 191 patients were included in the intent-to-treat (same as the "all patient" in this study) efficacy analysis.

The percentages of patients completing the study were 60% and 73%

respectively for the placebo and Effexor XR groups. However, the corresponding percentages of patients in the OC analyses at Week 8 were only 50% and 63%.

The placebo group differed statistically significantly from the Effexor ER group with respect to (wrt) Unsatisfactory Response/Efficacy (especially, during Weeks 8-10: 6 for placebo and 1 for Effexor XR).

"Adverse Event" occurred more (1 from placebo and 5 from Effexor XR) during Week 1 compared with any other week (maximum of 3).

2C.Baseline Comparability of Treatment Groups

The sponsor stated, "There were no statistically significant differences between the treatment groups for the demographic and baseline characteristics. None of the patients had any known illnesses at baseline that might have interfered with the activity of the study medication or the interpretation of the results."

In the Intent-to-Treat patients set,

the percentage of females varied as: 59% (placebo)and 64% (Effexor XR), and

the percentage of patients with baseline severity score of 4(mild) varied as: 74% (placebo) and 64% (Effexor XR).

2D. Efficacy Results (Sponsor's Analyses)

Following are the (Raw) Mean Changes From Baseline for the treatment groups, and the (venlafaxine ER or XR vs placebo) mean differences and p-values. The Tables and Graphs for adjusted Mean Changes From Baseline are attached as Tables 2.3.1 and 2.3.2 (HAM-D Total), 2.4.1 and 2.4.2 (HAM-D Depressed Mood Item), 2.5.1 and 2.5.2 (CGI Severity of Illness), and 2.6.1 and 2.6.2 (MADRS), and as Figures 2.3.3 and 2.3.4 (HAMD-Total), 2.4.3 and 2.4.4 (HAM-D Depressed Mood Item), 2.5.3 and 2.5.4 (CGI Severity of Illness), and 2.6.3 and 2.6.4 (MADRS).

BEST POSSIBLE COPY

STUDY 209-US

HAMILTON DEPRESSION SCALE - 21-ITEM TOTAL

LOCF

MEAN CHANGE FROM BASELINE

WEEK	Effexor XR		PLACEBO		Effexor XR Vs Placebo	
	N	MEAN	N	MEAN	Difference	P-value
1	91	-3.87	100	-3.34	-0.53	0.76
2	91	-6.51	100	-4.81	-1.70	0.07
3	91	-7.86	100	-6.34	-1.52	0.16
4	91	-9.22	100	-6.45	-2.77	0.008 *
6	91	-10.52	100	-7.71	-2.81	0.02 *
8	91	-11.66	100	-6.78	-4.88	<0.001 *

* Indicates statistical significance at the 0.05 level for ANOVA.

OBSERVED

MEAN CHANGE FROM BASELINE

WEEK	Effexor XR		PLACEBO		Effexor XR Vs Placebo	
	N	MEAN	N	MEAN	Difference	P-value
1	89	-3.96	99	-3.37	-0.59	0.72
2	82	-6.82	93	-4.98	-1.84	0.04 *
3	82	-8.11	88	-6.68	-1.43	0.30
4	78	-9.62	80	-7.23	-2.39	0.03 *
6	65	-11.78	62	-9.94	-1.84	0.19
8	60	-14.38	51	-9.25	-5.13	< 0.001 *

* Indicates statistical significance at the 0.05 level for ANOVA.

HAMILTON DEPRESSION SCALE - Depressed Mood Item

LOCF

MEAN CHANGE FROM BASELINE

	Effexor XR			PLACEBO		Effexor XR Vs Placebo	
WEEK	N	MEAN		N	MEAN	Difference	P-value
1	91	-0.60		100	-0.40	-0.20	0.09
2	91	-0.80		100	-0.56	-0.24	0.08
3	91	-1.01		100	-0.70	-0.31	0.02 *
4	91	-1.15		100	-0.74	-0.41	0.005 *
6	91	-1.31		100	-0.82	-0.49	0.002 *
8	91	-1.47		100	-0.71	-0.76	<0.001 *

* Indicates statistical significance at the 0.05 level for ANOVA.

OBSERVED

MEAN CHANGE FROM BASELINE

	Effexor XR			PLACEBO		Effexor XR Vs Placebo	
WEEK	N	MEAN		N	MEAN	Difference	P-value
1	89	-0.62		99	-0.40	-0.22	0.08
2	82	-0.79		93	-0.55	-0.24	0.11
3	82	-1.05		88	-0.77	-0.28	0.09
4	78	-1.19		80	-0.86	-0.33	0.05 *
6	65	-1.38		62	-1.05	-0.33	0.10
8	60	-1.82		51	-1.12	-0.70	0.005 *

* Indicates statistical significance at the 0.05 level for ANOVA.

CLINICAL GLOBAL IMPRESSIONS SCALE - SEVERITY OF ILLNESS

LOCF

MEAN CHANGE FROM BASELINE

WEEK	Effexor XR		PLACEBO		Effexor XR Vs Placebo	
	N	MEAN	N	MEAN	Difference	P-value
1	91	-0.29	100	-0.31	0.02	0.56
2	91	-0.74	100	-0.44	-0.30	0.03 *
3	91	-0.96	100	-0.64	-0.32	0.03 *
4	91	-1.16	100	-0.75	-0.41	0.004 *
6	91	-1.42	100	-0.93	-0.49	0.004 *
8	91	-1.53	100	-0.82	-0.71	<0.001 *

* Indicates statistical significance at the 0.05 level for ANOVA.

OBSERVED

MEAN CHANGE FROM BASELINE

WEEK	Effexor XR		PLACEBO		Effexor XR Vs Placebo	
	N	MEAN	N	MEAN	Difference	P-value
1	89	-0.29	99	-0.31	0.02	0.58
2	92	-0.76	93	-0.46	-0.30	0.03 *
3	82	-1.00	88	-0.69	-0.31	0.10
4	78	-1.25	80	-0.88	-0.37	0.02 *
6	65	-1.58	62	-1.23	-0.35	0.17
8	60	-1.92	51	-1.24	-0.68	0.01 *

* Indicates statistical significance at the 0.05 level for ANOVA.

MONTGOMERY/ASBERG SCALE - TOTAL SCORE

LOCF

MEAN CHANGE FROM BASELINE

WEEK	Effexor XR		PLACEBO		Effexor XR Vs Placebo	
	N	MEAN	N	MEAN	Difference	P-value
1	91	-4.10	100	-4.38	0.28	0.64
2	91	-6.92	100	-5.22	-1.70	0.14
3	91	-8.22	100	-6.28	-1.94	0.10
4	91	-9.69	100	-6.79	-2.90	0.02 *
6	91	-11.75	100	-8.54	-3.21	0.02 *
8	91	-12.38	100	-7.01	-5.37	<0.001 *

* Indicates statistical significance at the 0.05 level for ANOVA.

OBSERVED

MEAN CHANGE FROM BASELINE

WEEK	Effexor XR		PLACEBO		Effexor XR Vs Placebo	
	N	MEAN	N	MEAN	Difference	P-value
1	89	-4.19	99	-4.47	0.28	0.62
2	82	-7.09	93	-5.39	-1.70	0.18
3	82	-8.52	88	-6.53	-1.99	0.21
4	78	-10.35	80	-7.71	-2.64	0.08
6	65	-13.42	62	-11.32	-2.10	0.21
8	60	-16.02	51	-10.14	-5.88	0.005 *

* Indicates statistical significance at the 0.05 level for ANOVA.

We see, from the above sponsor's results, that Study 209-US provides overall reasonable statistical evidence in favor of venlafaxine XR or ER, although the observed (OC) results are weaker.

2E. Reviewer's Comments and Conclusions on Study 209-US

Although the OC results were weaker, based on the sponsor's submitted results, Study 209-US provided reasonable (at least towards the later weeks) statistical evidence in favor of the efficacy of venlafaxine XR. This reviewer's analyses applying 2-sample Wilcoxon test provided similar evidence. Out of the many supplemental analyses provided by the sponsor (Vol. 125), there was hardly any where at least the Week 8 result was not significant.

The sponsor stated in the protocol, "A two-way analysis of covariance with treatment and investigator as factors will be used, provided that the assumptions of the analyses appear to be satisfied (otherwise a suitable transformation or a nonparametric test will be sought.)" As an introduction to the above supplemental analyses, the sponsor stated in the report, "Due to the breakdown of the normality assumption on the CGI severity and the Depressed Mood item (...); non-parametric ANCOVA was applied to all the key efficacy parameters ..."

The mean daily dose for the Effexor XR group was the highest at Week 7 and was 179.7 mg (p.39 of vol. 1.123). Average number of capsules in the placebo group was not provided.

Mean HAM-D Total score for subgroups of patients dropping out at different times are in Figures 2.3.5 to 2.3.6. In the venlafaxine group, 7 patients, who dropped after Week 2 and after Week 3, had better responses than the completers. A similar statement cannot be made for the placebo group. This fact is likely to favor the placebo group in the OC analyses after Week 3.

To address the missing data problem, the sponsor applied ETRANK and longitudinal data analyses to the HAM-D total score, to compare the treatment differences between the two groups over time (pages 16 to 24 of Vol.1.125). The sponsor concluded, "The two longitudinal parametric approaches, confirm significant advantages of both Venlafaxine-XR over the placebo treated patients as shown in Table 5." This statement is correct for GEE longitudinal analysis but not quite correct for "Proc Mixed" (p-value = .117). However, the totality of all ETRANK and longitudinal results are no worse than other results discussed before.

3. Study 600B-367-EU

The Table of some Design and Enrolled Patients Aspects and Names of Investigators are in the attached Table 0.1.3.

FIGURE 0.2.5

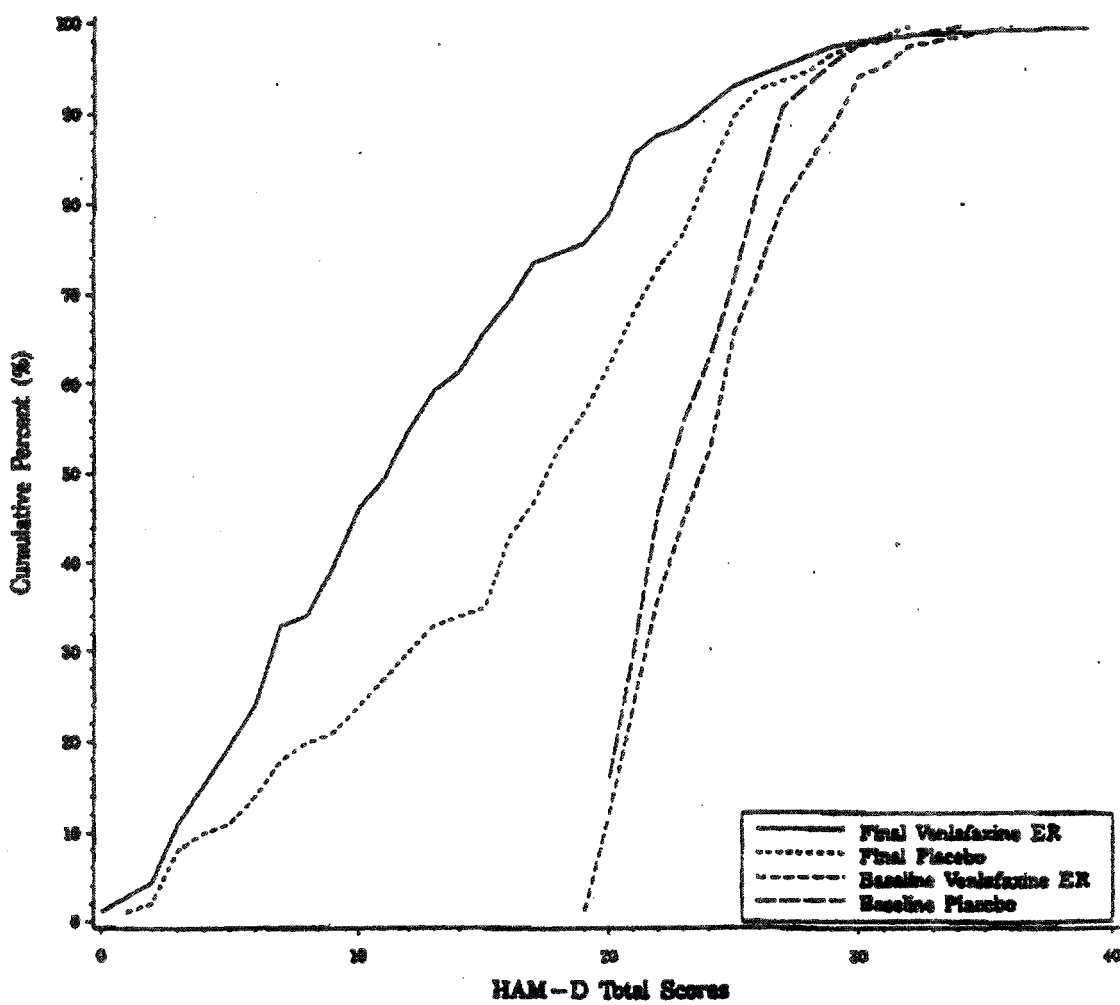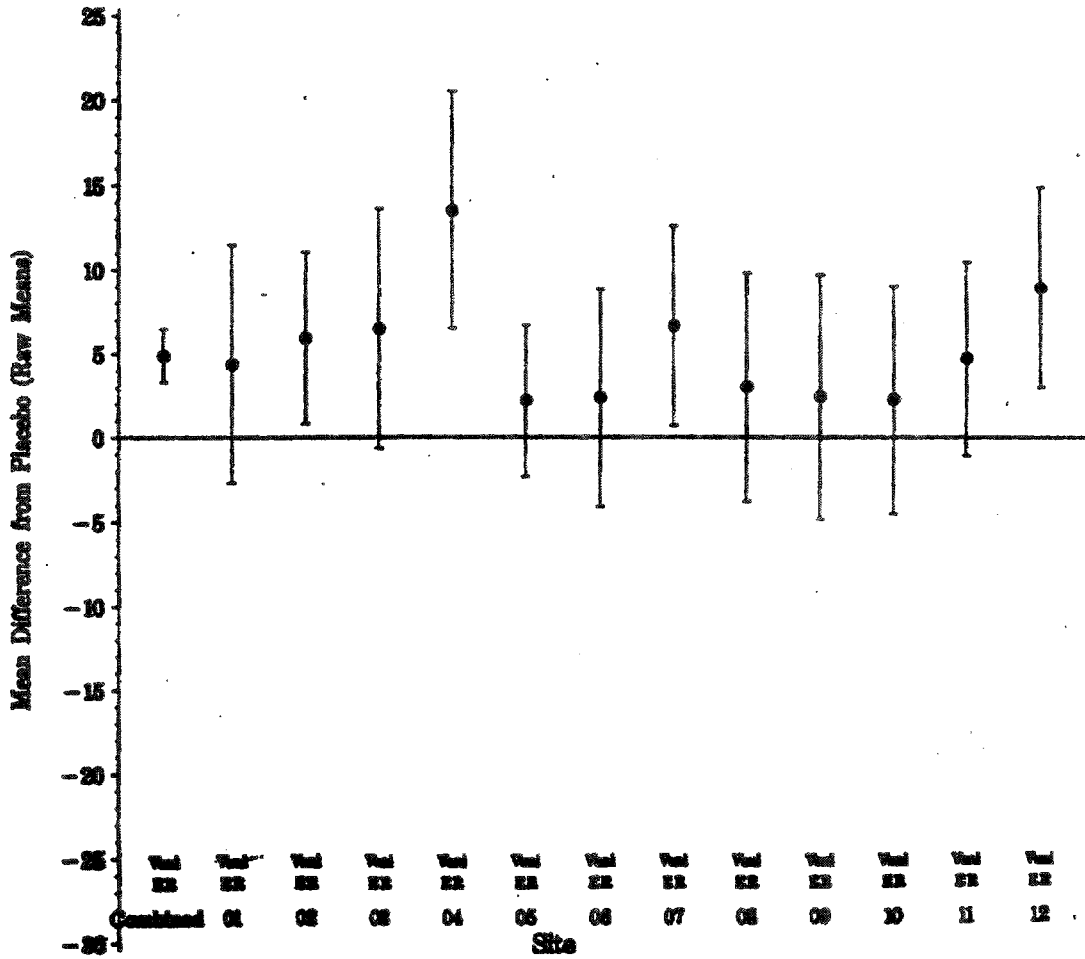## Cumulative Percent Vs HAM-D Total Scores
Study 209

FIGURE 10.2.8

Mean Difference Between Therapy and Placebo with 95% Confidence Intervals
Using HAM-D Total Change from Baseline Scores from
Final On-Therapy Values for Protocol 209

TABLE 2.1.1

PATIENT STATUS OVER TIME FOR ALL RANDOMIZED PATIENTS

WITH DATA: NUMBER OF PATIENTS

Time (week)	No.	C[a]	D[b]	CD[c]	No.	C	D	CD
			--- -Placebo- - -			- - -Venlafaxine ER- - -		
Randomized patients with data	102				95			
Week 1		99	3	3		89	6	6
2		94	5	8		88	1	7
3		89	5	13		83	5	12
4		83	6	19		80	3	15
5		80	3	22		76	4	19
6		74	6	28		74	2	21
7		72	2	30		72	2	23
8		63	9	39		71	1	24
>8		61	2	41		69	2	26
Total			-	41			-	26

a: Number of patients who completed the time period.
b: Number of patients who discontinued within the specified time interval.
c: Cumulative number of patients who discontinued earlier or within the specified time interval.
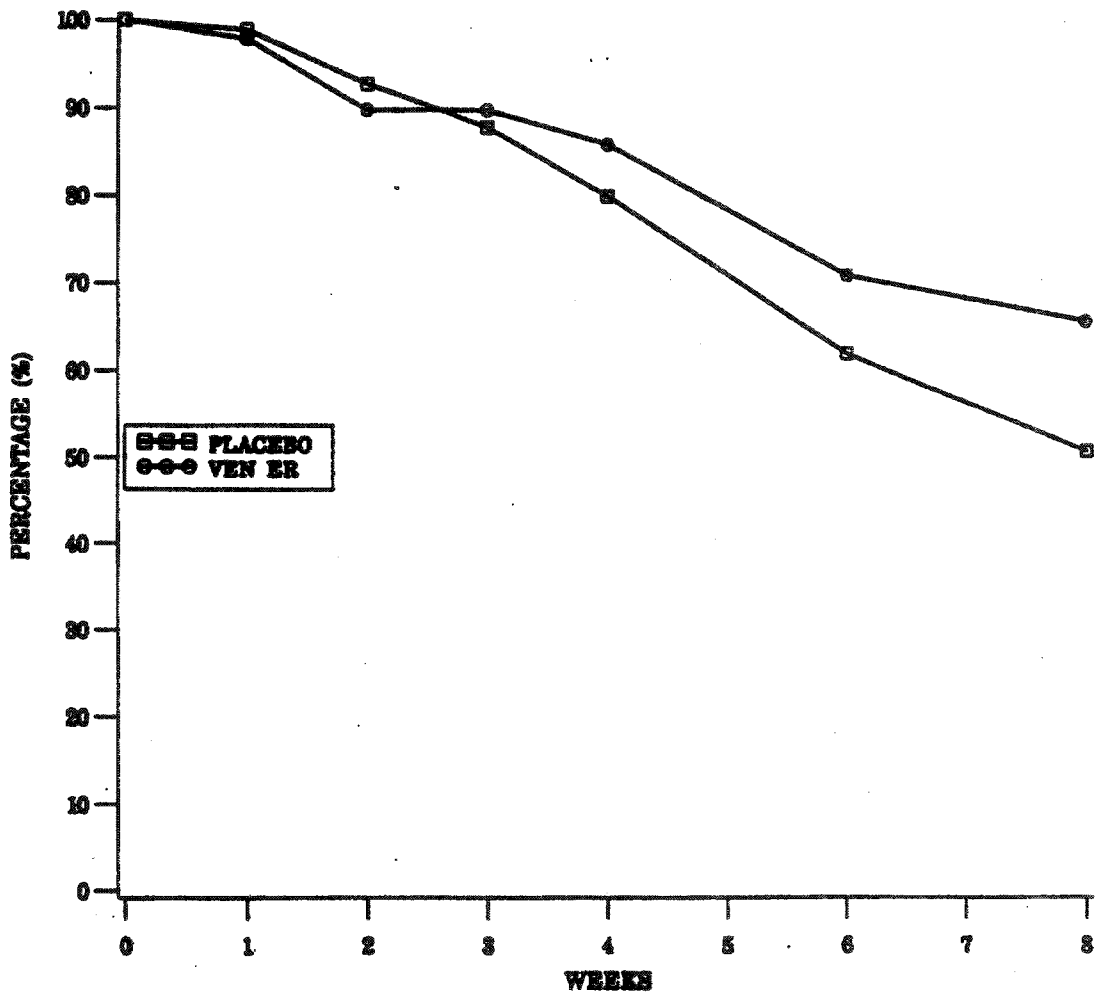
TABLE 2.1.2

NUMBER (%) OF PATIENTS WHO WITHDREW
PREMATURELY BY PRIMARY REASON

Reason	Placebo (n = 102)	Venlafaxine ER (n = 95)
Any reason	41 (40)	26 (27)
Adverse reaction	6 (6)	10 (11)
Failed to return	6 (6)	8 (8)
Patient/subject request	4 (4)	0 (0)
Unsatisfactory response/efficacy	22 (22)	5 (5)*
Protocol violation	1 (1)	2 (2)
Other medical event	1 (1)	0 (0)
Other non-medical event	1 (1)	1 (1)

* Significantly different from placebo: p ≤ 0.001. Fisher's exact test.

FIGURE 2.1.4

PERCENTAGE OF PATIENTS OVER TIME
STUDY 209

TABLE 2.3.1 HAM-D TOTAL
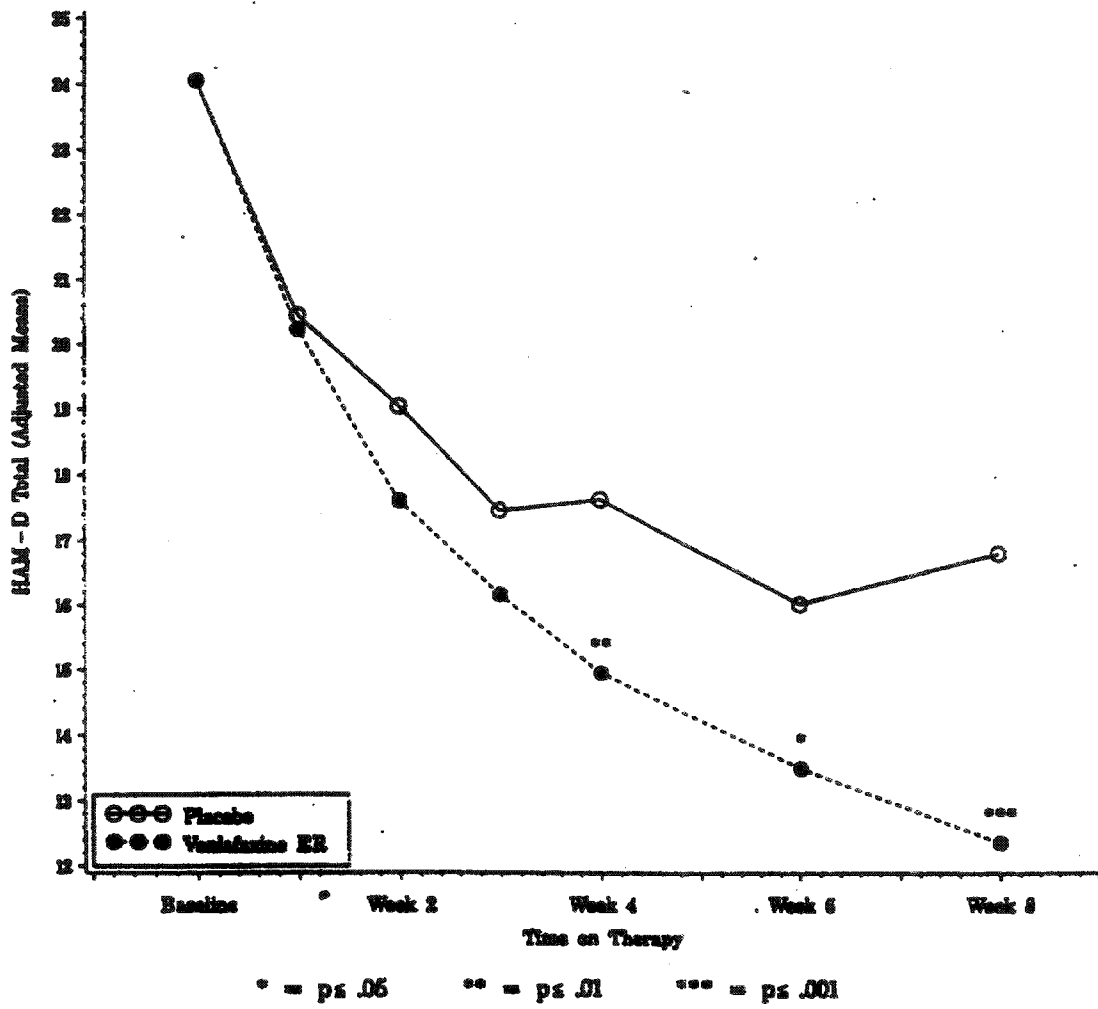### COMPARISON BETWEEN PBO AND VEN ER - LOCF VALUE ANALYSIS

Week on Therapy	Therapy Group	Number of Patients	Adj Change From Baseline	Adj Means (95% CL)	Diff Adj Means (95% CL) Pbo-Ven ER	F-test[a]
1	Pbo	100	-3.61	20.45 (19.48.21.41)		
	Ven ER	91	-3.83	20.23 (19.22.21.25)	0.22 (-1.17,1.60)	.76
2	Pbo	100	-5.01	19.05 (17.97.20.14)		
	Ven ER	91	-6.44	17.61 (16.47.18.76)	1.44 (-0.12.2.99)	.07
3	Pbo	100	-6.59	17.47 (16.20.18.74)		
	Ven ER	91	-7.89	16.17 (14.83.17.51)	1.30 (-0.52.3.13)	.16
4	Pbo	100	-6.42	17.63 (16.28.18.99)		
	Ven ER	91	-9.10	14.96 (13.53.16.39)	2.67 (0.73.4.61)	.008
6	Pbo	100	-8.04	16.02 (14.55.17.50)		
	Ven ER	91	-10.57	13.49 (11.94.15.04)	2.53 (0.42.4.64)	.02
8	Pbo	100	-7.24	16.81 (15.27.18.35)		
	Ven ER	91	-11.70	12.36 (10.74.13.98)	4.45 (2.25.6.66)	<.001

a: p-values for the F-test.

$t = 3.96$
$P = .000108$

FIGURE 2.3.3

HAM–D TOTAL VS TIME ON THERAPY
LOCF ANALYSIS
STUDY 209

* = p≤ .05   ** = p≤ .01   *** = p≤ .001

FIGURE 2.3.4

HAM-D TOTAL VS TIME ON THERAPY
OBSERVED ANALYSIS
STUDY 209

* = p ≤ .05   ** = p ≤ .01   *** = p ≤ .001

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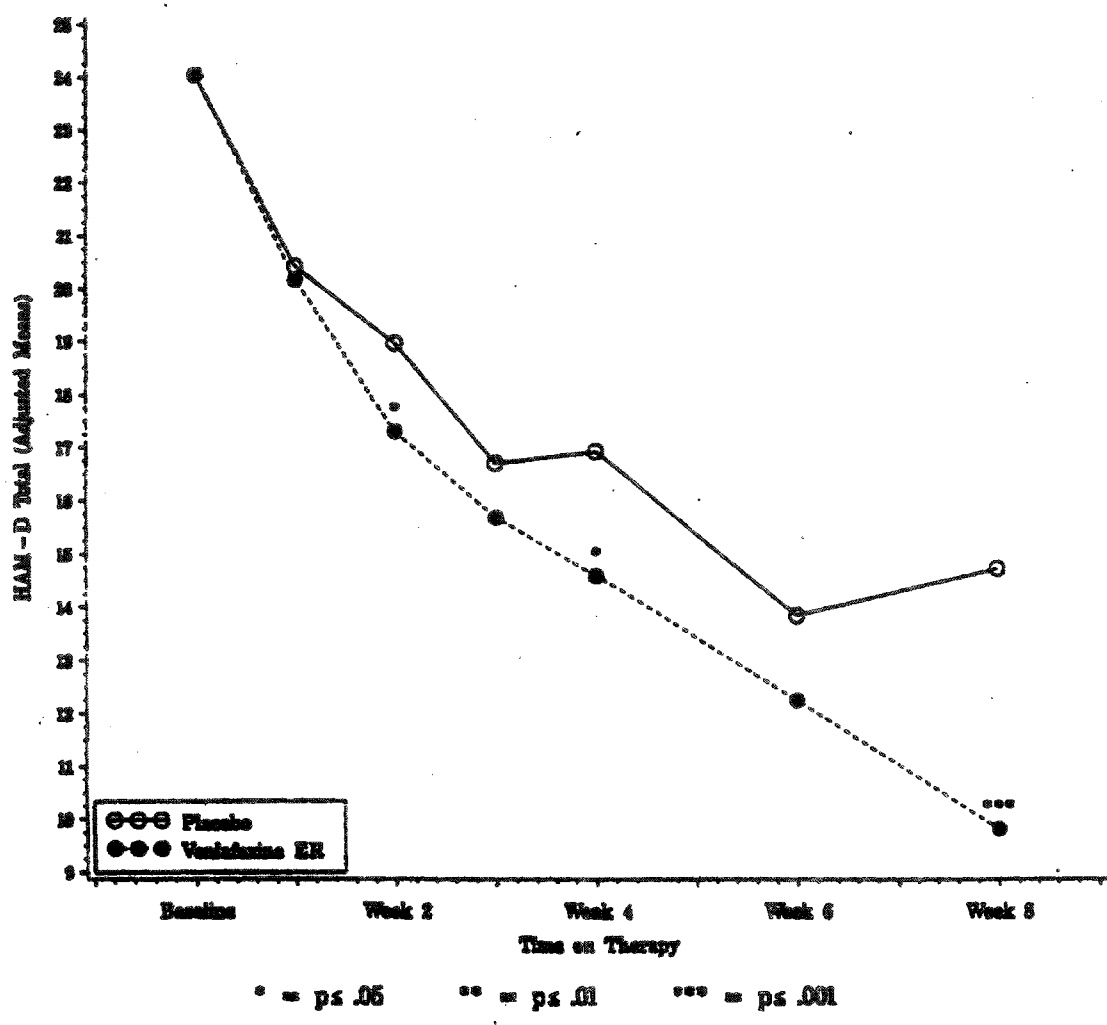
FIGURE 2.3.5.

Mean HAM–D Total Score
Protocol 209
Therapy: Placebo

Last On–Therapy Visit

△–△–△ Week 1 (n=2)   ◇–◇–◇ Week 2 (n=7)   ▱–▱–▱ Week 3 (n=9)
■–■–■ Week 4 (n=17)   ▲–▲–▲ Week 6 (n=14)   ◆–◆–◆ Week 8 (n=51)

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FIGURE 2 3.6

Mean HAM–D Total Score
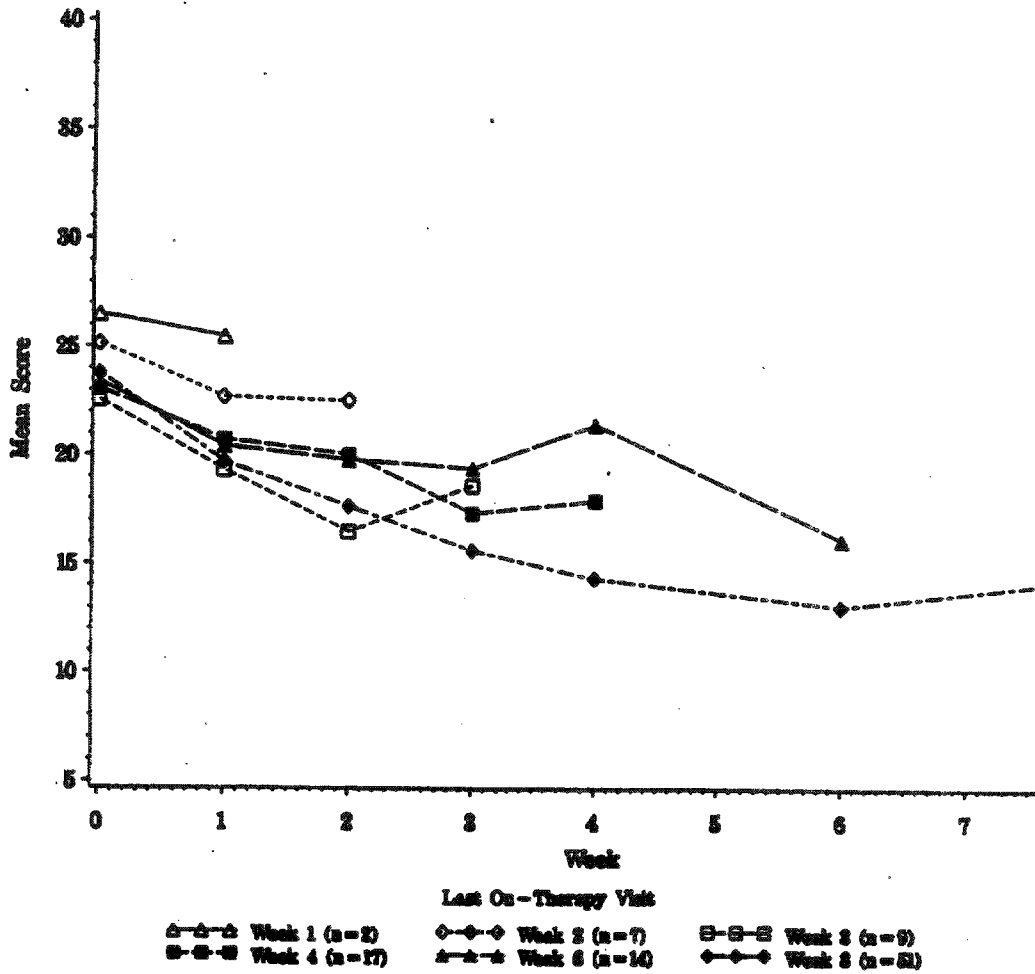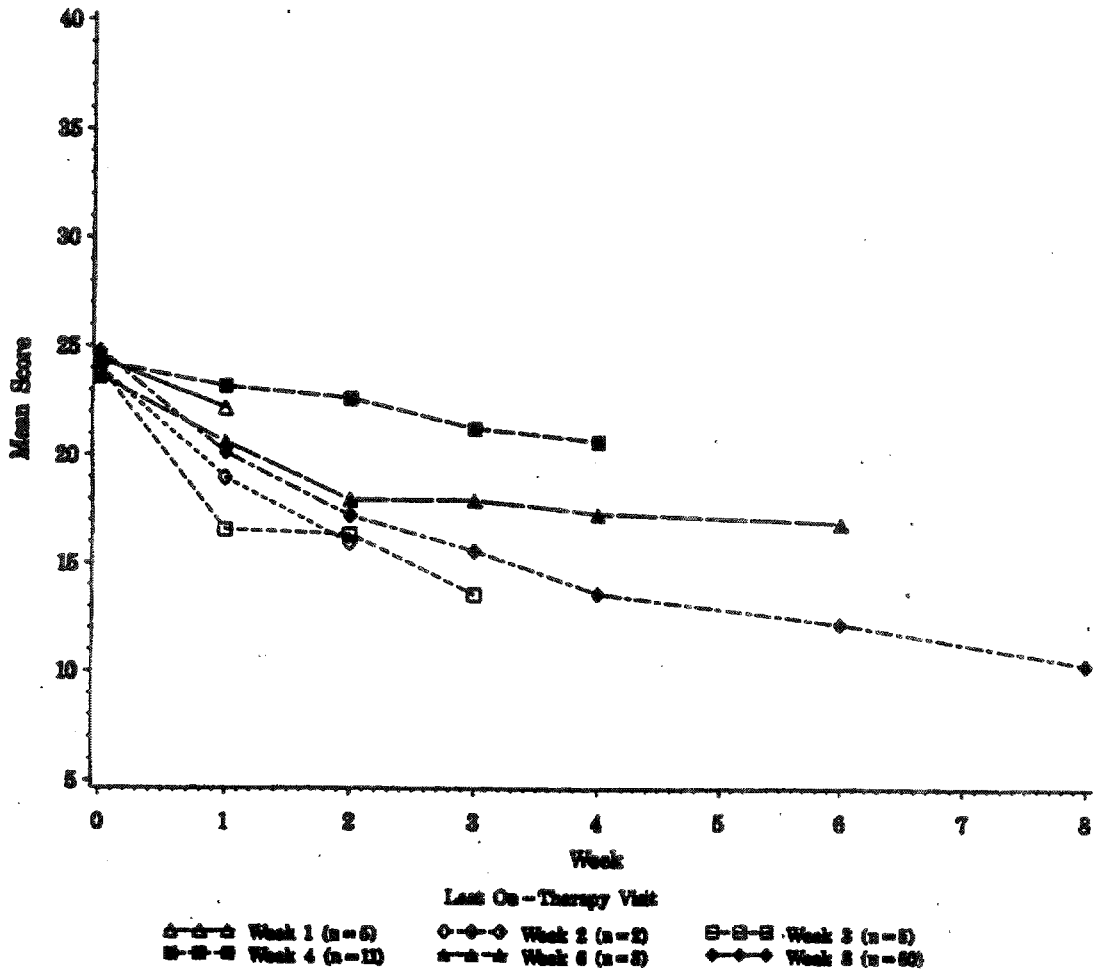Protocol 209
Therapy: Venlafaxine ER

TABLE 2.4.1

DEPRESSED MOOD ITEM - HAM-D
COMPARISON BETWEEN PBO AND VEN ER - LOCF VALUE ANALYSIS

Week on Therapy	Therapy Group	Number of Patients	Adj Change From Baseline	Adj Means (95% CL)	Diff Adj Means (95% CL) Pbo-Ven ER	F-test[a]
	Pbo	100	-0.42	2.38 (2.22,2.53)		
1	Ven ER	91	-0.60	2.19 (2.03,2.35)	0.19 (-0.03,0.41)	.09
	Pbo	100	-0.57	2.22 (2.03,2.40)		
2	Ven ER	91	-0.81	1.98 (1.79,2.18)	0.24 (-0.03,0.50)	.08
	Pbo	100	-0.71	2.08 (1.89,2.27)		
3	Ven ER	91	-1.03	1.76 (1.56,1.96)	0.32 (0.05,0.59)	.02
	Pbo	100	-0.72	2.07 (1.87,2.28)		
4	Ven ER	91	-1.15	1.65 (1.43,1.86)	0.43 (0.14,0.72)	.005
	Pbo	100	-0.83	1.96 (1.75,2.18)		
6	Ven ER	91	-1.32	1.47 (1.25,1.70)	0.49 (0.18,0.79)	.002
	Pbo	100	-0.74	2.05 (1.83,2.28)		
8	Ven ER	91	-1.50	1.29 (1.06,1.52)	0.76 (0.45,1.08)	<.001

a: p-Values for the F-test.

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FIGURE 2.4.3

HAM–D DEPRESSED MOOD ITEM VS TIME ON THERAPY
LOCF ANALYSIS
STUDY 209

* = p ≤ .05   ** = p ≤ .01   *** = p ≤ .001
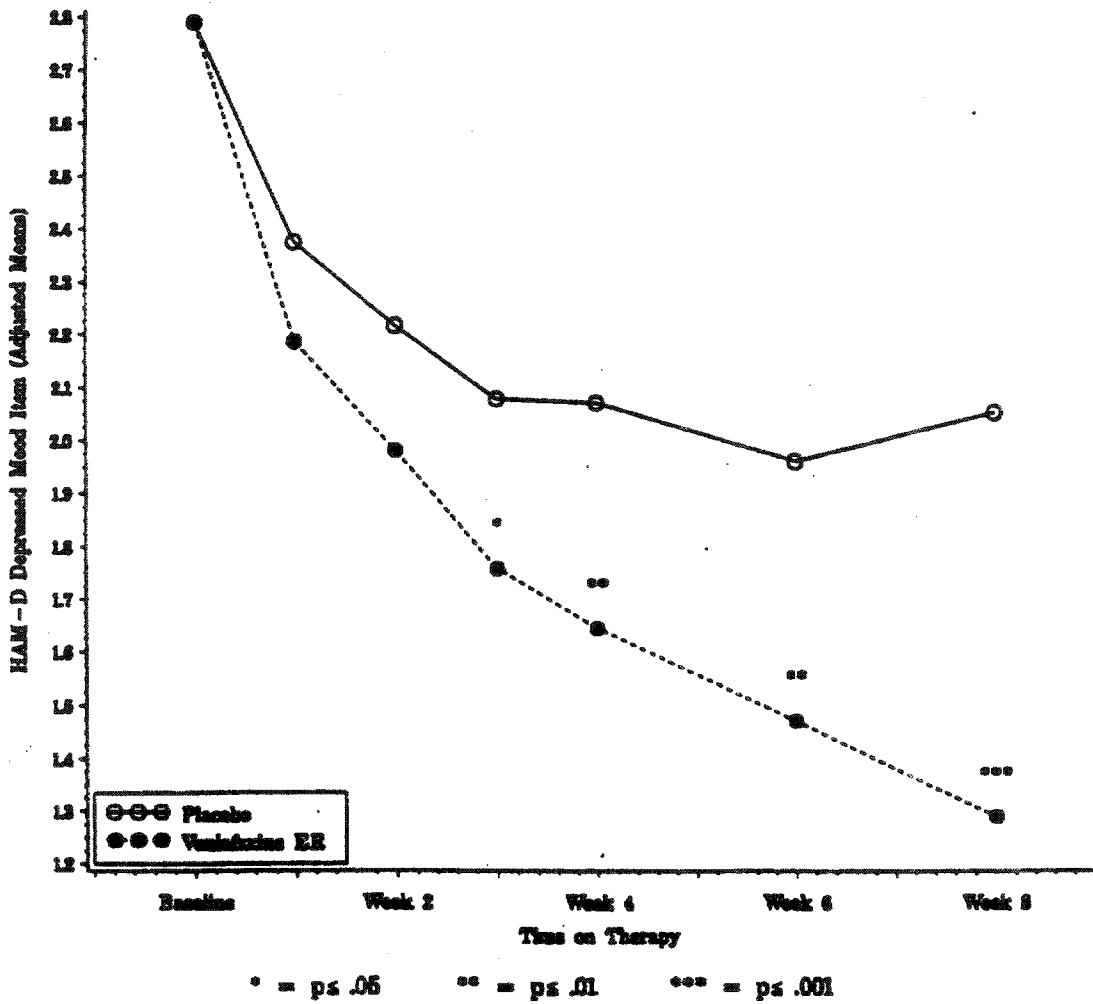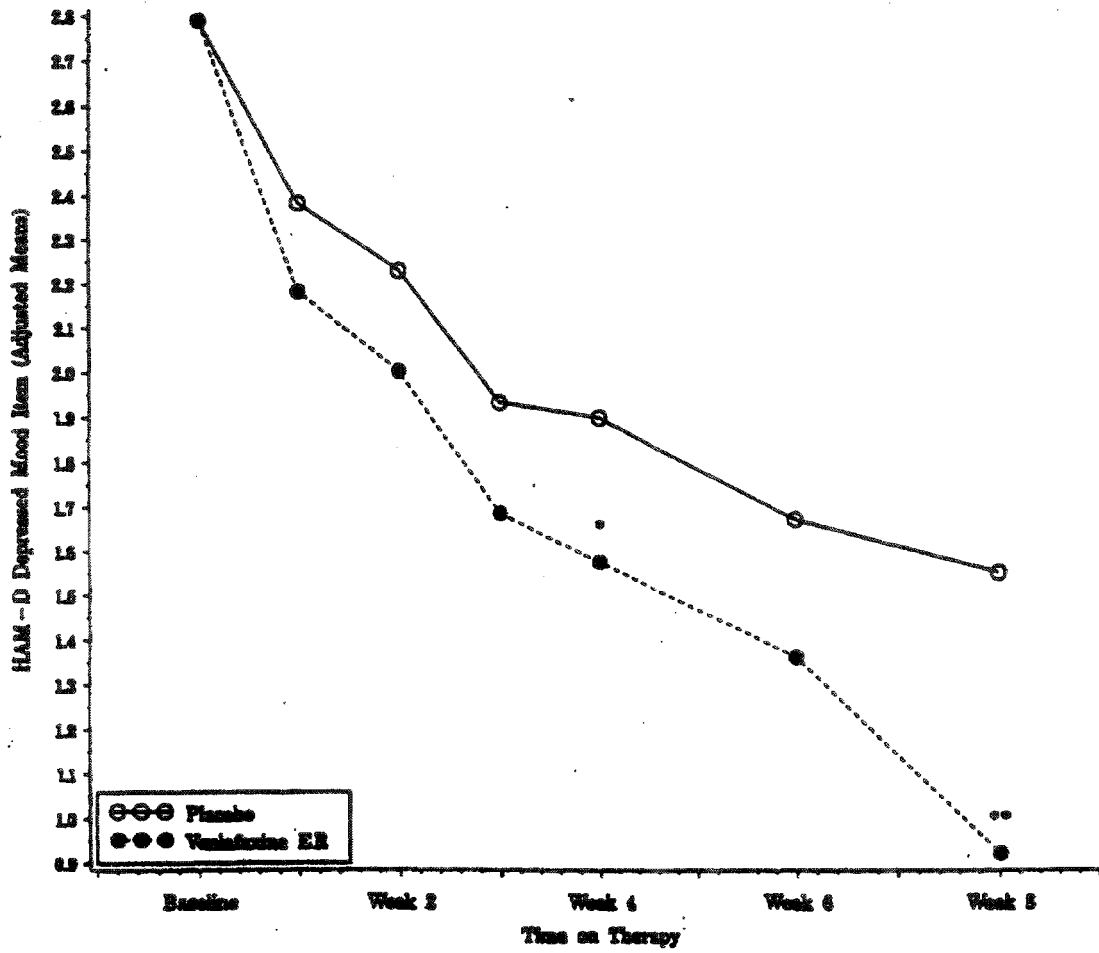
FIGURE 2.4.4

HAM–D DEPRESSED MOOD ITEM VS TIME ON THERAPY
OBSERVED ANALYSIS
STUDY 209

* = p ≤ .05   ** = p ≤ .01   *** = p ≤ .001

TABLE 2.5.1 CGI-SEVERITY 209-US
COMPARISON BETWEEN PBO AND VEN ER - LOCF VALUE ANALYSIS

Week on Therapy	Therapy Group	Number of Patients	Adj Change From Baseline	Adj Means (95% CL)	Diff Adj Means (95% CL) Pbo-Ven ER	F-test[a]
1	Pbo	100	-0.33	4.03 (3.90,4.16)		
	Ven ER	91	-0.28	4.08 (3.95,4.22)	-0.05 (-0.24,0.13)	.56
2	Pbo	100	-0.46	3.90 (3.74,4.06)		
	Ven ER	91	-0.72	3.64 (3.47,3.81)	0.26 (0.03,0.49)	.03
3	Pbo	100	-0.65	3.71 (3.52,3.90)		
	Ven ER	91	-0.95	3.41 (3.21,3.61)	0.30 (0.03,0.57)	.03
4	Pbo	100	-0.72	3.64 (3.44,3.84)		
	Ven ER	91	-1.14	3.22 (3.01,3.43)	0.42 (0.14,0.71)	.004
6	Pbo	100	-0.94	3.42 (3.18,3.65)		
	Ven ER	91	-1.44	2.93 (2.68,3.17)	0.49 (0.16,0.82)	.004
8	Pbo	100	-0.85	3.51 (3.27,3.76)		
	Ven ER	91	-1.55	2.81 (2.56,3.07)	0.70 (0.35,1.05)	<.001

a: p-Values for the F-test.

50

FIGURE 2.5.3

CGI-SEVERITY SCORES VS TIME ON THERAPY
LOCF ANALYSIS
STUDY 209
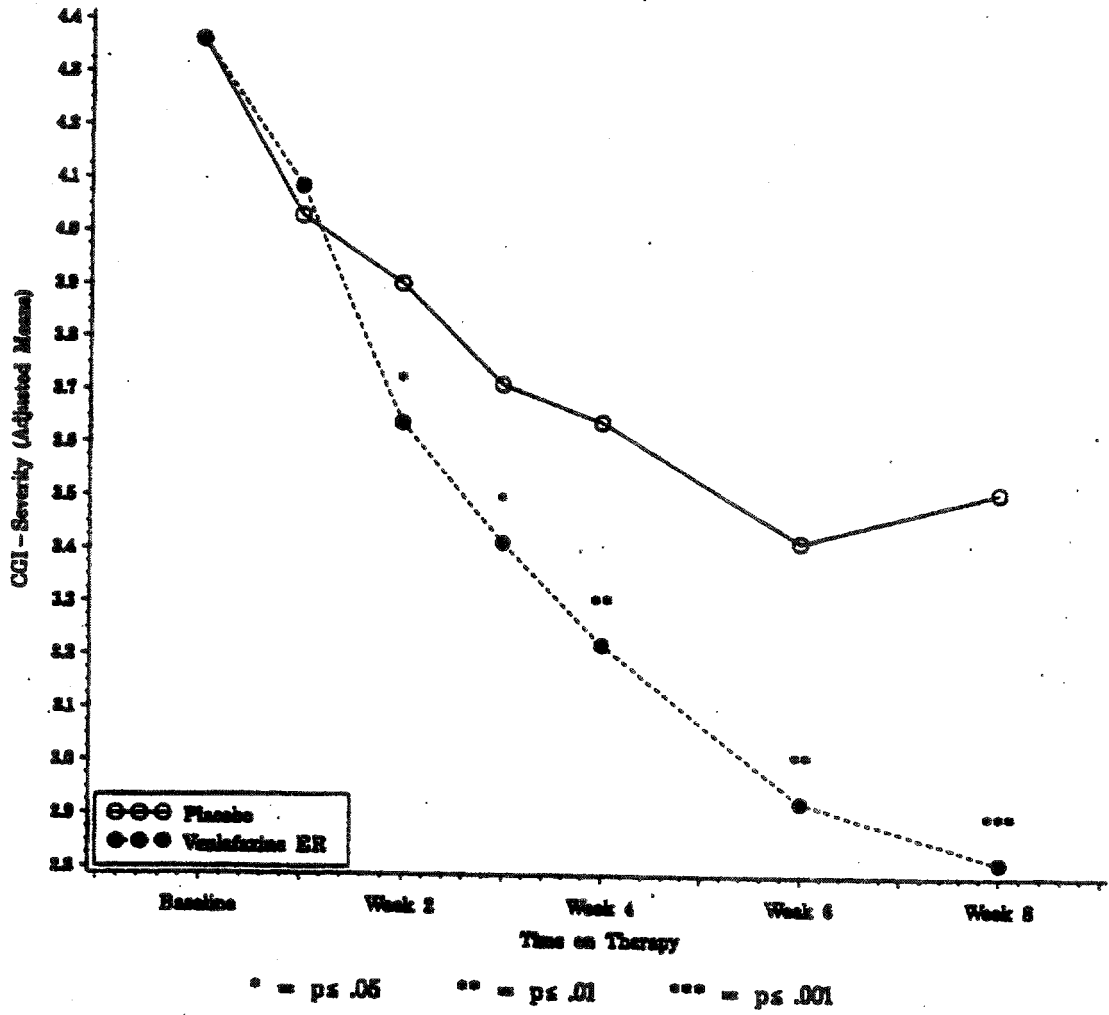
FIGURE 2.5.4

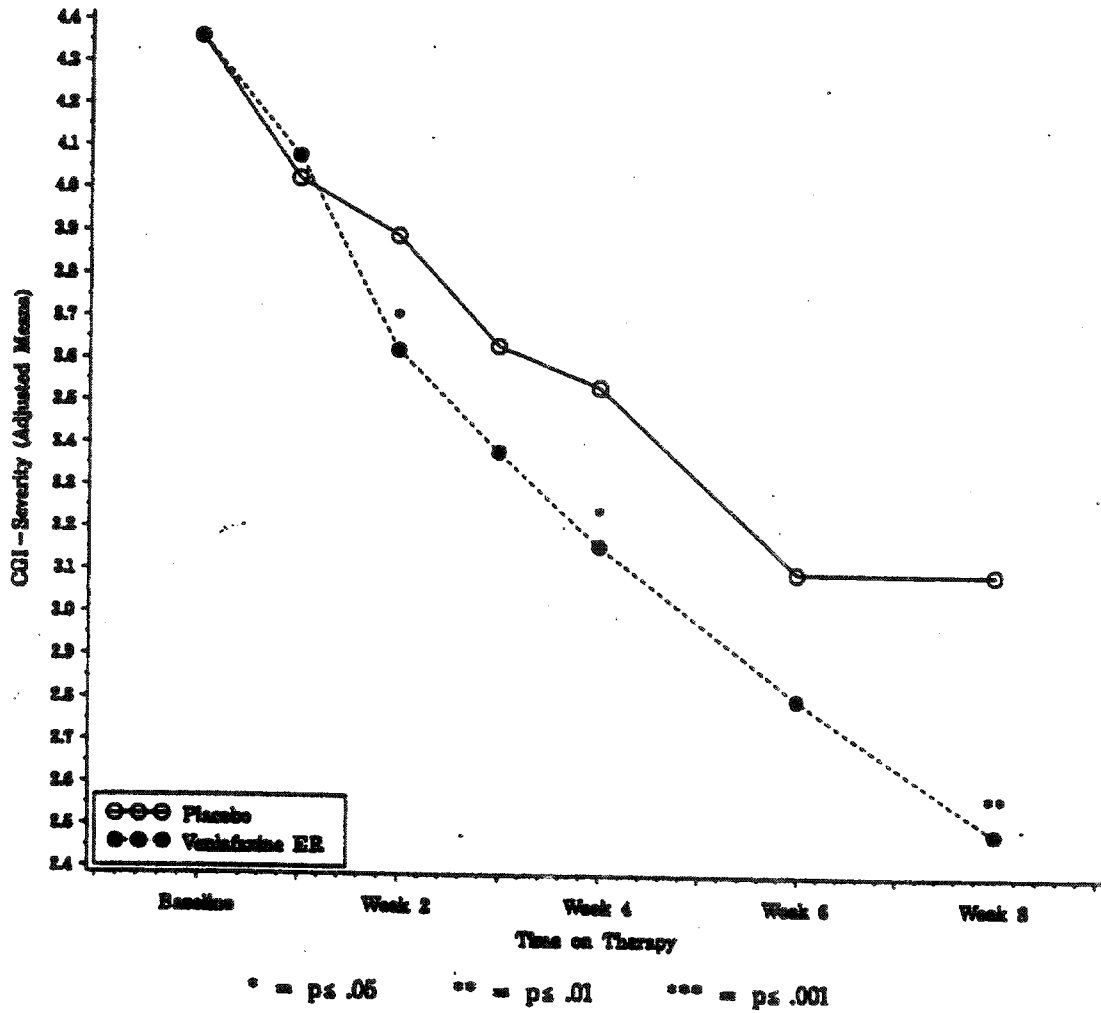CGI–SEVERITY SCORES VS TIME ON THERAPY
OBSERVED ANALYSIS
STUDY 209

* = p≤ .05   ** = p≤ .01   *** = p≤ .001

TABLE 2.6.1 MADRS TOTAL 209-US
COMPARISON BETWEEN PBO AND VEN ER - LOCF VALUE ANALYSIS

Week on Therapy	Therapy Group	Number of Patients	Adj Change From Baseline	Adj Means (95% CL)	Diff Adj Means (95% CL) Pbo-Ven ER	F-test[a]
1	Pbo	100	-4.66	23.21 (21.98.24.43)		
	Ven ER	91	-4.25	23.62 (22.33.24.90)	-0.41 (-2.15.1.33)	.64
2	Pbo	100	-5.39	22.48 (21.02.23.93)		
	Ven ER	91	-6.95	20.91 (19.38.22.43)	1.57 (-0.50.3.63)	.14
3	Pbo	100	-6.38	21.48 (19.85.23.12)		
	Ven ER	91	-8.33	19.53 (17.82.21.24)	1.95 (-0.36.4.27)	.10
4	Pbo	100	-6.51	21.35 (19.60.23.10)		
	Ven ER	91	-9.54	18.33 (16.49.20.16)	3.03 (0.54.5.51)	.02
6	Pbo	100	-8.62	19.25 (17.31.21.19)		
	Ven ER	91	-11.89	15.97 (13.94.18.01)	3.27 (0.52.6.03)	.02
8	Pbo	100	-7.27	20.59 (18.53.22.66)		
	Ven ER	91	-12.66	15.21 (13.04.17.37)	5.38 (2.45.8.31)	<.001

a: p-Values for the F-test.

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FIGURE 2.6.3

MADRS TOTAL VS TIME ON THERAPY
LOCF ANALYSIS
STUDY 209

* = p≤ .05   ** = p≤ .01   *** = p≤ .001
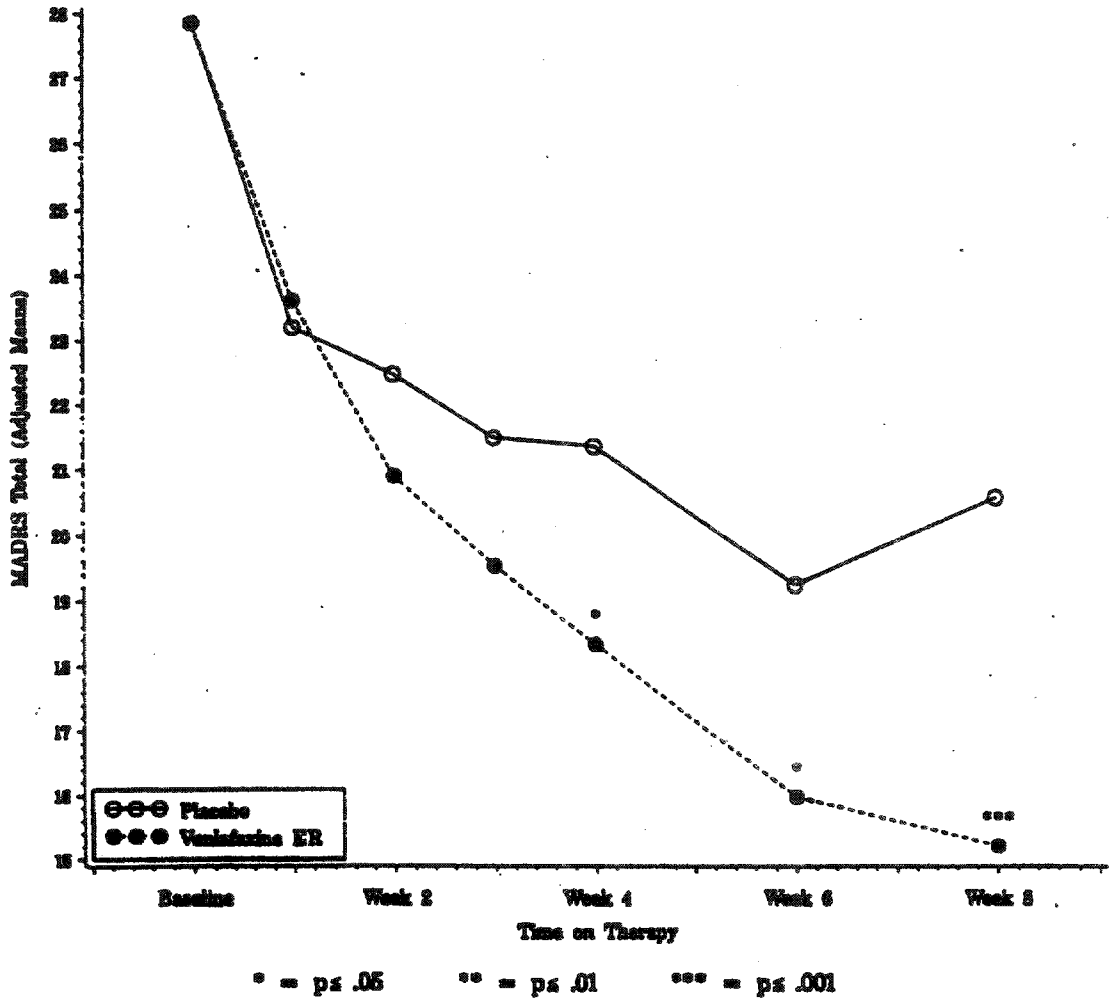
FIGURE 2.6.4

MADRS TOTAL VS TIME ON THERAPY
OBSERVED ANALYSIS
STUDY 209

* = p≤ .05   ** = p≤ .01   *** = p≤ .001
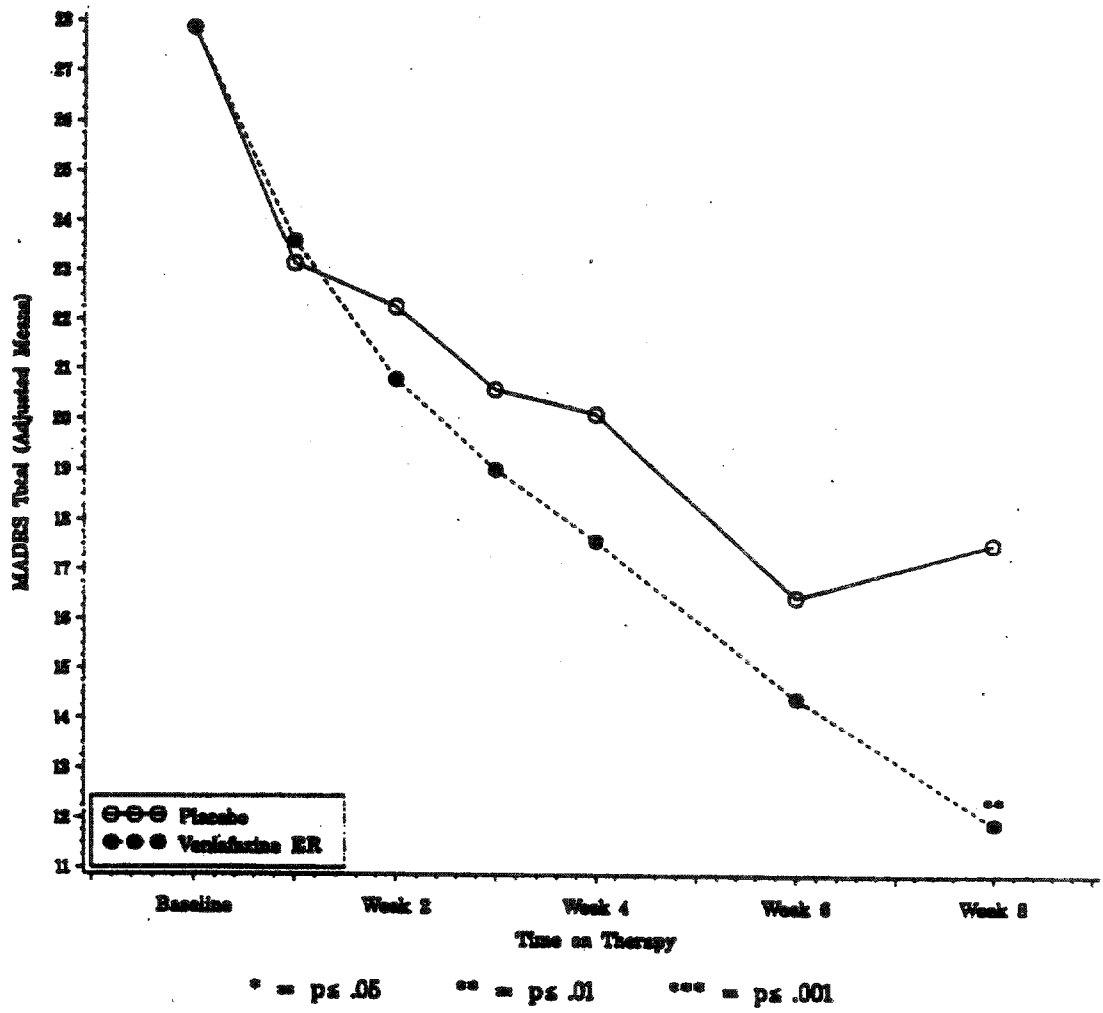
7.2.1.3   Study 367

Investigators/Locations

Principal investigators and locations of these foreign study sites are listed in Appendix 7.2.1.3.

Objectives

The primary objective of this study was to compare the safety and efficacy of two fixed doses of venlafaxine ER (75 and 150 mg/day) to placebo in depressed outpatients.

Population

A total of 332 outpatients with DSM-III-R major depression were enrolled. Other inclusion criteria included:

* minimum age of 18 years.
* symptoms of depression for at least one month.
* minimum prestudy 21-item HAM-D total score of 20, with no greater than a 20% decrease between screening and baseline visits.

Relevant exclusion criteria included the following:

* history or presence of any psychotic disorder not related to depression, bipolar disorder, or organic mental disorder.
* use of any investigational drug, antipsychotic drug, or ECT within 30 days; fluoxetine within 21 days; MAOI, paroxetine, or sertraline within 14 days; or any other antidepressant, anxiolytic, sedative-hypnotic, or other psychotropic agent within 7 days (except chloral hydrate).
* use of any drug with psychotropic effects within 7 days of the study unless a stable dose had been maintained for the past month.
* drug or alcohol dependence within 1 year.

Design

This was a randomized, double-blind, placebo- and active-controlled, double-dummy, parallel group, fixed dose study conducted at 35 sites in Europe. After a 7-10 day single-blind placebo run-in, which was intended to exclude early placebo responders, eligible patients were randomized to one of four treatment arms: venlafaxine ER 75 mg/day, venlafaxine ER 150 mg/day, placebo, or paroxetine 20 mg/day.

Double-blind treatment at the assigned fixed dose was continued for 8 weeks. Dosing during all 8 weeks was constant, with no titration to the assigned fixed dose. Patients took all study medication in the morning given as three capsules, two peach-

colored and one blue-colored: peach capsules contained
venlafaxine ER 75mg or placebo and blue capsules contained
paroxetine 20mg or placebo (double-dummy design). Any patient
intolerant of the assigned dose was dropped out.

During a subsequent 3 day taper period, all patients received
placebo except for patients who had taken venlafaxine ER 150mg,
who received venlafaxine ER 75mg during taper.

Study visits occurred at the end of weeks 1, 2, 4, 6, and 8
during double-blind treatment. Primary efficacy assessments were
performed at each visit and consisted of the HAM-D, MADRS, and
CGI.

Analysis

The efficacy intent-to-treat (ITT) population included all
patients who had been enrolled in double-blind therapy, had a
baseline evaluation on at least one primary variable (HAM-D,
MADRS, or CGI), took at least one dose of assigned medication,
and had at least one evaluation on one of the primary variables
either during therapy or within 3 days of last treatment. A
total of 323 patients comprised the efficacy ITT.

This review focused on a one-way analysis of variance (ANOVA),
with therapy as the factor, for the pairwise comparisons of raw
mean change from baseline at each visit in four key efficacy
variables: HAM-D and MADRS total scores, HAM-D depressed mood
item, and CGI-severity score. Analysis was performed on both
observed cases (OC) and last-observation-carried-forward (LOCF)
datasets. Statistical significance was defined at the $\alpha = 0.05$
level and all hypothesis testing was 2-sided. Although it could
be argued that the α level should be adjusted for multiple
comparisons, given comparisons of the two venlafaxine ER groups
versus placebo, it is clear from examination of the efficacy
results (see below) that such adjustment would not change the
overall efficacy conclusion from this study.

For purposes of analysis, the 35 study sites were pooled to
combine data from sites with small sample sizes; this resulted in
9 centers. This pooling, which was determined prior to breaking
the blind, is depicted in vol. 1.80 on page 20.

Baseline Demographics

Baseline demographic data is displayed by treatment group in
Appendix 7.2.1.3. There was no statistically significant
difference among groups with respect to age, sex, or race (p=
0.14, 0.20, and 0.54, respectively).

Baseline Severity of Illness

There were no statistically significant differences between groups with respect to baseline HAM-D total scores, HAM-D depressed mood item scores, MADRS total scores, or CGI-severity scores.

A large majority of patients in each group were rated at baseline as either "moderately ill" or "markedly ill" on the CGI-severity item: 79% of venlafaxine ER 75mg, 79% of venlafaxine ER 150mg, 81% of placebo, and 86% of paroxetine patients.

Patient Disposition

Of the 332 patients enrolled, 329 were randomized and 323 comprised the efficacy ITT, of which 83 were randomized to venlafaxine ER 75mg, 78 to 150mg, 82 to placebo, and 80 to paroxetine. The number of completers (i.e. patients with observed data for at least one of the four key efficacy variables), also expressed as a percentage of the efficacy ITT, at each visit is displayed in Appendix 7.2.1.3.

The percentages of patients who completed 8 weeks of double-blind treatment in each group is as follows:

Venlafaxine ER 75mg	64%	(53/83)
Venlafaxine ER 150mg	62%	(48/78)
Placebo	65%	(53/82)
Paroxetine	60%	(48/80)

The most frequent reason for dropout in each treatment group (% of the safety ITT) is as follows: inadequate response in the 75mg patients (7%), an adverse event in the 150mg patients (12%), inadequate response in the placebo group (16%) and inadequate response in the paroxetine group (16%).

Two paroxetine patients were withdrawn for protocol violations:

* patient 36729-016 - intake of alprazolam.
* patient 36739-003 - high transaminase value at baseline.

The visit at which at least two-thirds of the patients in both groups were still in-study and had observed efficacy data was week 6, with 70% of the 75mg group, 69% of the 150mg group, 70% of the placebo group, and 69% of the paroxetine group remaining at that timepoint.

Concomitant Medications

More than 50% of patients in each group received concomitant medication during the study. By far, the most commonly used drug class (between 40-45% of patients in each group) was "psycholeptics:" this consisted almost entirely of chloral hydrate and zolpidem; these drugs were permitted for sleep by

protocol. "Psychoanaleptics" (not defined by the sponsor) were used by 1% of placebo and 4% of paroxetine patients. It is not felt that the above concomitant drug use substantially influenced the study efficacy results.

Efficacy Results

This review focused on the raw change from baseline for the four key efficacy variables: the HAM-D total score, HAM-D depressed mood item (item #1), MADRS total score, and the CGI-severity score. Efficacy analysis results are displayed for the OC and the LOCF datasets in Appendix 7.2.1.3.

There were no consistent patterns of statistically significant differences between either venlafaxine ER group and placebo for any of the four key variables for either the LOCF or OC analyses, even without adjustment for multiple comparisons. There was one isolated significant difference: at the final visit, the 75mg group was superior to placebo for the observed cases dataset (p= 0.03).

There were no statistically significant differences between paroxetine and placebo at any timepoint, for any key variable, for either dataset in this study.

The sponsor assessed for a treatment-by-center interaction at each visit for the following measures: HAM-D total score, MADRS total score, and CGI improvement score (LOCF dataset): overall, there was no evidence of a consistent treatment-by-center interaction. However, the statistical reviewer did note that two sites (36717 and 36722) were atypical in that there was a 100% response rate with respect to the HAM-D total score (see below) across all treatment groups at these sites (combined N=27).

A responder analysis, with response defined as a ≥50% decrease from baseline in HAM-D or MADRS total scores or a CGI-improvement score of "much improved" or "very much improved," revealed no statistically significant differences for the overall comparisons of the proportions of responders among the four treatment groups.

Conclusions

Study 367 provided no persuasive evidence of antidepressant efficacy for venlafaxine ER. Comparison of week 8 change from baseline data for the key variables from this study with the corresponding data from studies 208 and 209 reveals the following patterns:

* the mean changes from baseline for the venlafaxine ER groups in 367 are generally greater than those of 208 and 209.

● the mean changes from baseline for the placebo group in 367 are generally greater, often considerably so, than those of 208 and 209.
● the absolute difference between the mean venlafaxine ER and placebo changes from baseline are generally considerably less in 367 compared to those in 208 and 209.

From these observations, it seems that a major reason for the lack of drug-placebo differences in this study is the large placebo response.

It is notable that paroxetine, which is a widely recognized antidepressant agent, also failed to demonstrate superiority over placebo. Of course, this begs the question of whether 20mg can be considered an effective dose in these patients; current labeling recommends antidepressant doses in the range 20-50 mg/day for most patients. In fact, several of the mean changes for placebo surpassed those of paroxetine, suggesting that paroxetine had a minimal effect for many of these patients, inconsistent with its reputation as an established antidepressant. The question of how many of these paroxetine patients would have responded at higher doses must remain unanswered. Nonetheless, since 20mg is deemed to be in the effective dose range, it is assumed that there existed poor assay sensitivity in this study and this study is considered failed.

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STUDY 367: PRINCIPAL INVESTIGATORS	
Investigator (Site #)	**Country**
J. Hosie, MD (36701)	United Kingdom
G.D.R. Martin, MD (36703)	United Kingdom
S. Mahapatra, MD (36705)	United Kingdom
H.D. N'Guyen, MD (36708)	Belgium
J. Gros-Gean, MD (36711)	Belgium
R. Whitby, MD (36702)	United Kingdom
C.L. Langdon, MD (36704)	United Kingdom
F. Ferrero, MD (36707)	Switzerland
P. Bourgeois, MD (36709)	Belgium
A. Denayer, MD (36712)	Belgium
M. Dierick, MD (36713)	Belgium
M. Frei, MD (36716)	Switzerland
D. Bonnafoux, MD (36719)	France
C. Danic, MD (36722)	France
B. Fengler, MD (36725)	France
M. Hanus, MD (36727)	France
R. Realini, MD (36715)	Switzerland
R. Cook, MD (36717)	United Kingdom
P. Chiaroni, MD (36720)	France
M. Daurignac, MD (36723)	France
C. Géraud, MD (36726)	France
P Leclerg, MD (36728)	France
P. Legoubey, MD (36729)	France
J.P. May, MD (36731)	France
F. Mesotten, MD (36734)	Belgium
L. Ravizza, MD (36737)	Italy
Goron-Parry, MD (36741)	France

APPENDIX 7.2.1.3

STUDY 367: PRINCIPAL INVESTIGATORS	
Investigator (Site #)	Country
J.M. Letzelter, MD (36746)	France
M. Martin, MD (36730)	France
P. Thermoz, MD (36733)	France
V. Volterra, MD (36736)	Italy
A. Giavedoni, MD (36739)	Italy
D. Dassa, MD (36742)	France
J.R. Rancé (36748)	France
E. Hirsch, MD (36749)	France

Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
STUDY 367: MEAN CHANGE FROM BASELINE IN HAM-D TOTAL SCORE												
LAST OBSERVATION CARRIED FORWARD ANALYSIS												
VEN 75	82	26.5	82	-5.4	82	-9.8	82	-12.5	82	-14.5	82	-15.6
VEN 150	75	27.1	75	-3.5	75	-9.2	75	-13.4	75	-14.4	75	-14.6
PLAC	81	26.6	81	-3.7	81	-8.2	81	-11.3	81	-12.5	81	-13.1
PAR	80	26.1	80	-3.5	80	-7.2	80	-9.8	80	-10.4	80	-11.3
2-sided p-values for pairwise comparisons												
75 vs. P	0.859		0.83		0.42		0.15		0.24		0.37	
150 vs. P	0.458		0.05		0.18		0.39		0.21		0.14	
PAR vs. P	0.471		0.86		0.41		0.33		0.20		0.27	
OBSERVED CASES ANALYSIS												
VEN 75	82	26.5	82	-5.4	79	-10.2	69	-13.8	58	-17.6	53	-18.6
VEN 150	75	27.1	75	-3.5	68	-10.0	60	-15.3	54	-17.3	48	-19.5
PLAC	81	26.6	81	-3.7	80	-8.3	66	-13.4	57	-15.8	53	-16.6
PAR	80	26.1	80	-3.5	73	-8.4	62	-12.3	55	-13.8	48	-16.5
2-sided p-values for pairwise comparisons												
75 vs. P	0.859		0.83		0.15		0.19		0.35		0.06	
150 vs. P	0.458		0.05		0.10		0.76		0.26		0.18	
PAR vs. P	0.471		0.86		0.92		0.46		0.20		0.95	

APPENDIX 7.2.1.3

Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
STUDY 367: MEAN CHANGE FROM BASELINE IN HAM-D DEPRESSED MOOD ITEM												
LAST OBSERVATION CARRIED FORWARD ANALYSIS												
VEN 75	82	2.9	82	-0.6	82	-1.2	82	-1.5	82	-1.7	82	-1.9
VEN 150	75	2.8	75	-0.4	75	-1.0	75	-1.5	75	-1.5	75	-1.6
PLAC	81	2.9	81	-0.5	81	-1.0	81	-1.3	81	-1.5	81	-1.6
PAR	80	2.8	80	-0.4	80	-0.9	80	-1.3	80	-1.4	80	-1.5
2-sided p-values for pairwise comparisons												
75 vs. P	0.509		0.31		0.94		0.43		0.93		0.81	
150 vs. P	0.417		0.27		0.09		0.43		0.29		0.16	
PAR vs. P	0.403		0.36		0.64		0.80		0.45		0.73	
OBSERVED CASES ANALYSIS												
VEN 75	82	2.9	82	-0.6	79	-1.3	69	-1.6	58	-2.1	53	-2.2
VEN 150	75	2.8	75	-0.4	68	-1.1	60	-1.6	54	-1.8	48	-2.2
PLAC	81	2.9	81	-0.5	80	-1.0	66	-1.5	57	-1.9	53	-1.9
PAR	80	2.8	80	-0.4	73	-1.0	62	-1.5	55	-1.7	48	-2.0
2-Sided p-values for pairwise comparisons												
75 vs. P	0.509		0.31		0.55		0.53		0.81		0.12	
150 vs. P	0.417		0.27		0.07		0.66		0.25		0.14	
PAR vs. P	0.403		0.36		0.87		0.93		0.31		0.67	

Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
STUDY 367: MEAN CHANGE FROM BASELINE IN MADRS TOTAL SCORE												
LAST OBSERVATION CARRIED FORWARD ANALYSIS												
VEN 75	82	29.7	82	-5.7	82	-11.1	82	-14.4	82	-16.5	82	-17.7
VEN 150	75	30.6	75	-3.3	75	-9.8	75	-15.5	75	-16.5	75	-16.8
PLAC	81	29.9	81	-4.4	81	-9.4	81	-13.0	81	-14.3	81	-14.9
PAR	79	29.3	79	-3.4	79	-7.9	79	-11.4	79	-12.3	79	-13.3
2-sided p-values for pairwise comparisons												
75 vs. P	0.816		0.28		0.77		0.15		0.26		0.36	
150 vs. P	0.442		0.18		0.20		0.42		0.25		0.17	
PAR vs. P	0.599		0.29		0.27		0.35		0.30		0.40	
OBSERVED CASES ANALYSIS												
VEN 75	82	29.7	82	-5.7	79	-11.5	69	-15.9	58	-20.1	53	-21.0
VEN 150	75	30.6	75	-3.3	68	-10.7	60	-17.6	54	-20.5	48	-22.9
PLAC	81	29.9	81	-4.4	80	-9.5	66	-15.5	57	-18.2	53	-18.9
PAR	79	29.3	79	-3.4	72	-8.9	62	-14.2	55	-16.2	48	-19.4
2-sided p-values for pairwise comparisons												
75 vs. P	0.816		0.28		0.39		0.21		0.23		0.03	
150 vs. P	0.442		0.18		0.13		0.77		0.32		0.22	
PAR vs. P	0.599		0.29		0.70		0.46		0.30		0.78	

STUDY 367: MEAN CHANGE FROM BASELINE IN CGI-SEVERITY SCORE												
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS												
VEN 75	82	4.7	82	−0.4	82	−1.2	82	−1.6	82	−1.9	82	−2.1
VEN 150	75	4.9	75	−0.3	75	−1.1	75	−1.8	75	−1.9	75	−2.1
PLAC	81	4.8	81	−0.3	81	−1.0	81	−1.5	81	−1.7	81	−1.9
PAR	79	4.7	79	−0.2	79	−0.7	79	−1.1	79	−1.4	79	−1.6
2-sided p-values for pairwise comparisons												
75 vs. P	0.541		0.99		0.42		0.14		0.41		0.62	
150 vs. P	0.585		0.34		0.23		0.66		0.47		0.47	
PAR vs. P	0.333		0.44		0.20		0.14		0.18		0.20	
OBSERVED CASES ANALYSIS												
VEN 75	82	4.7	82	−0.4	79	−1.3	69	−1.7	58	−2.3	53	−2.5
VEN 150	75	4.9	75	−0.3	68	−1.2	60	−2.2	54	−2.4	48	−2.8
PLAC	81	4.8	81	−0.3	80	−1.0	66	−1.7	57	−2.2	53	−2.4
PAR	79	4.7	79	−0.2	72	−0.8	62	−1.4	55	−1.8	48	−2.4
2-sided p-values for pairwise comparisons												
75 vs. P	0.541		0.99		0.23		0.09		0.40		0.25	
150 vs. P	0.585		0.34		0.18		0.99		0.63		0.79	
PAR vs. P	0.333		0.44		0.39		0.19		0.18		0.78	

Essential features of the study, including investigators, details of the Design and study conduct, (Patient) Population, Efficacy Assessment and Statistical Methods, Results, and Conclusions may be seen in the synopsis provided by the sponsor in the pages iii to v of the statistical vol. 1.130. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

3A. Objective

1) To compare the efficacy and safety of two fixed doses of venlafaxine XR (75 and 150 mg) versus placebo in depressed outpatients after 8 weeks of treatment.

2) To compare the efficacy and safety of venlafaxine XR (75 and 150 mg) versus paroxetine, and the efficacy and safety of paroxetine versus placebo in depressed outpatients after 8 weeks of treatment.

3B. Disposition of Patients

Various types of information related with Patient Disposition are presented as the attached Tables 3.1.1 to 3.1.3. Figure 3.1.4 of Percentage of Patients Continuing Over Time involves only those patients for whom efficacy measures were accepted for analysis in those weeks.

Six of the 329 patients who received randomly assigned study medication did not satisfy the criteria for being included in the intent-to-treat efficacy analysis. Four of these 6 patients were from the venlafaxine XR 150 mg group, one from the placebo group, and the remaining one from the paroxetine 20 mg group.

The percentages of patients completing the study were 71%, 80%, 65%, and 65% respectively for the placebo, Effexor XR 75 mg, Effexor XR 150 mg, and paroxetine groups.

"Adverse Event" occurred the most in the Effexor XR 150 mg group(12%). "Unsatisfactory Response/Efficacy" occurred most in the placebo (16%) and paroxetine(16%) groups (the most at Weeks 3-4 with respect to Time).

3C. Gender Composition of the Study Population

In the Intent-to-Treat patients set, the percentage of females varied as: 67% (placebo), 70% (Effexor XR 75 mg), 61% (Effexor XR 150 mg), and 54% (paroxetine).

3D. Efficacy Results (Sponsor's Analyses)

The analyses of Raw Means (with pairwise comparison p-values) are attached as Tables 3.3.1 and 3.3.2 (HAM-D Total), 3.4.1 and 3.4.2 (HAM-D Depressed Mood Item), 3.5.1 and 3.5.2 (CGI Severity of Illness), and 3.6.1 and 3.6.2 (MADRS). The analyses of Adjusted Means are attached as Tables 3.3.3 and 3.3.4 (HAMD-Total), (Detailed HAM-D Depressed Mood Item analyses were not provided), 3.5.3 and 3.5.4 (CGI Improvement, CGI Severity of Illness not provided), and 3.6.3 and 3.6.4 (MADRS). In the Tables for RAW MEANS, the column labeling under the -- P-VALUES -- were wrong. The correct order is V75 MG V150 MG PARO.

Overall, this was a failed study; even paroxetine did not show efficacy. Even without multiple comparison adjustments, there were very few significant p-values. Venlafaxine groups showed numerical superiority to other treatment groups.

3E. Reviewer's Comments and Conclusions on Study 367-EU

1. This was a failed study - neither negative nor positive. However, venlafaxine groups showed numerical superiority to other treatment groups.

2. Sample size per treatment arm was around 80 in this study, while in the other two studies discussed before, it was, generally, above 90 and approximately 100 in a few cases.

3. The sponsor stated, "A large placebo response rate was observed in the efficacy results, ranging from 57% to 81%. This may account for the lack of clear differentiation of the active treatment groups, particularly the paroxetine treatment group, from placebo."

4. There were two atypical centers (36717 and 36722) in which a 100% response rate (in HAM-D) across all treatments was observed, in contrast to a maximum of 75% in all other centers. These two centers had enrolled 27 patients.

The primary efficacy variables were reanalyzed after excluding the

FIGURE 0.2.6

Cumulative Percent Vs HAM−D Total Scores
Study 367
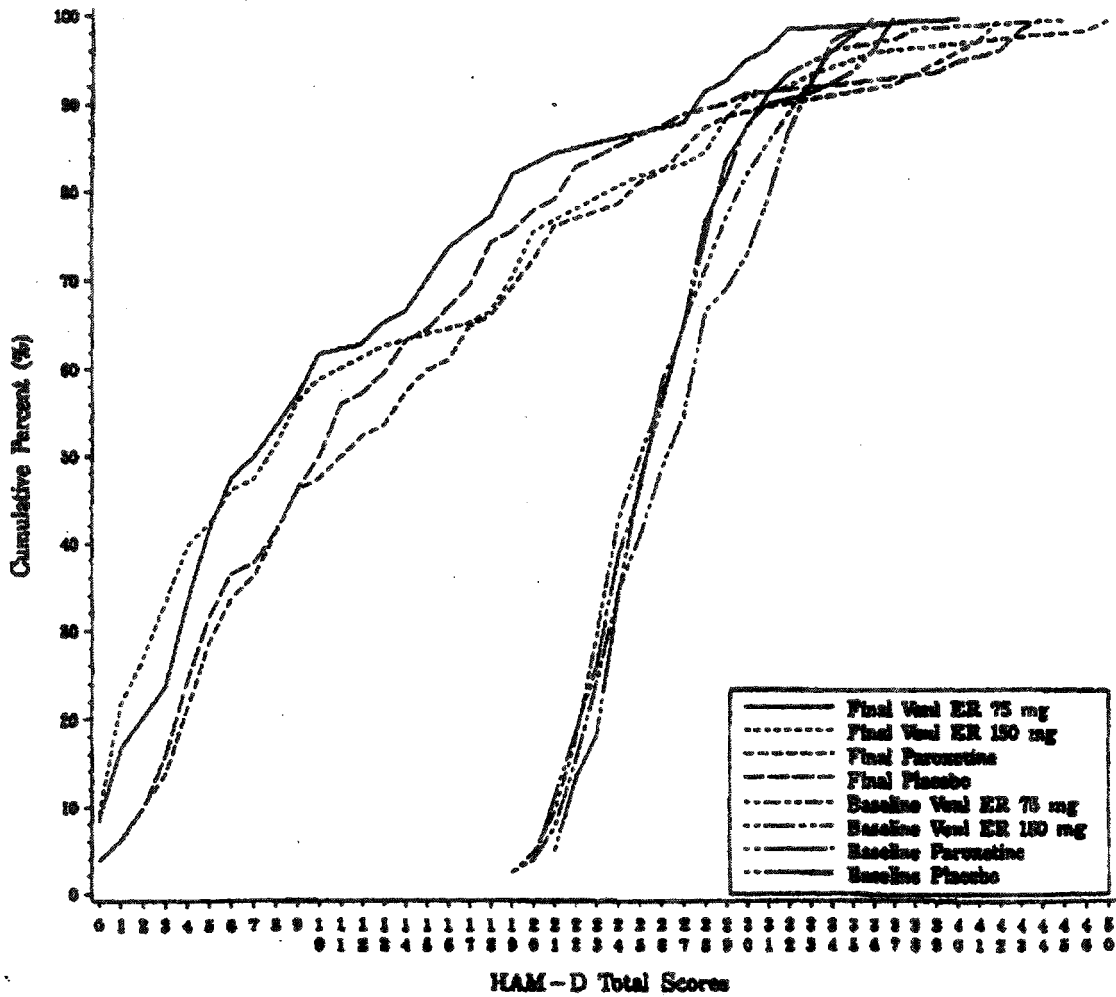
FIGURE 0.2.9

Mean Difference Between Therapy and Placebo with 95% Confidence Intervals
Using HAM-D Total Change from Baseline Scores from
Final On-Therapy Values for Protocol 367
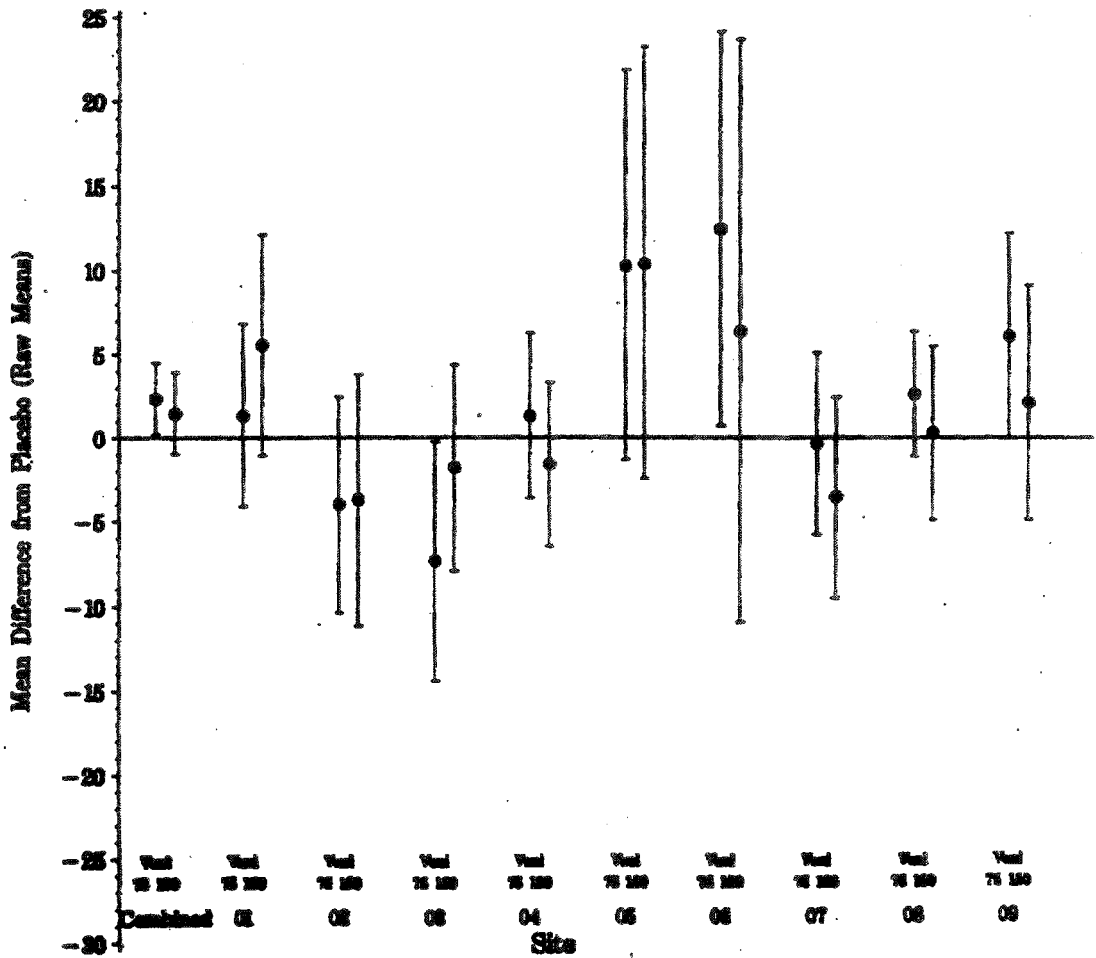
TABLE 3.1.1 PATIENT DISPOSITION   367-EU

	Screening			1-7		8-14		15-28		29-42		43-56		>56		Taper	
	R	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
Placebo	83	83	0	83	0	79	4	70	13	65	18	60	23	59	24	47	24
V 75 mg	83	83	0	82	1	81	2	69	14	69	14	67	16	66	17	57	17
V 150 mg	82	82	0	75	7	73	9	65	17	60	22	55	27	53	29	46	29
Paroxetine	81	81	0	78	3	74	7	66	15	59	22	53	28	53	28	44	28

R: Number of randomized patients
C: Number of patients completing the time interval
D: Cumulative number of patients discontinuing

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TABLE 3.1.2 NUMBER (%) OF PATIENTS WHO WITHDREW BY PRIMARY REASONS 367-EU

Reasons	Placebo (n=83)	V 75 mg (n=83)	V 150 mg (n=82)	Paroxetine (n=81)	p-Value[a]
Any Reasons	24 (29)	17 (20)	29 (35)	28 (35)	0.13
Adverse reaction	3 (4)	5 (6)	10 (12)	7 (9)	0.20
Failed to return	4 (5)	3 (4)	5 (6)	0 (0)	0.15
Patient/subject request	3 (4)	1 (1)	3 (4)	4 (5)	0.59
Unsatisfactory response - efficacy	13 (16)	6 (7)	9 (11)	13 (16)	0.25
Protocol violation	0 (0)	0 (0)	0 (0)	2 (2)	0.060
Other medical event	1 (1)	2 (2)	0 (0)	1 (1)	0.81
Other non-medical event	0 (0)	0 (0)	2 (2)	1 (1)	0.24

a: Fischer's exact test

TABLE 3.1.3　　　　　367-EU

PRIMARY REASONS FOR DISCONTINUATION OVER TIME
NUMBER (%) OF PATIENTS

REASONS	TREATMENT	TIME (days)						
		1-7	8-14	15-28	29-42	43-56	>56	Total
Any reasons	Placebo	0 (0)	4 (5)	9 (11)	5 (6)	5 (6)	1 (1)	24 (29)
	V 75 mg	1 (1)	1 (1)	12(14)	0 (0)	2 (2)	1 (1)	17 (20)
	V 150 mg	7 (9)	2 (2)	8 (10)	5 (6)	5 (6)	2 (2)	29 (35)
	Paroxetine	3 (4)	4 (5)	8 (10)	7 (9)	6 (7)	0 (0)	28 (35)
Adverse reaction	Placebo	0 (0)	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)	3 (4)
	V 75 mg	1 (1)	1 (1)	3 (4)	0 (0)	0 (0)	0 (0)	5 (6)
	V 150 mg	5 (6)	0 (0)	3 (4)	0 (0)	2 (2)	0 (0)	10 (12)
	Paroxetine	2 (2)	2 (2)	2 (2)	0 (0)	1 (1)	0 (0)	7 (9)
Failed to return	Placebo	0 (0)	0 (0)	0 (0)	3 (4)	1 (1)	0 (0)	4 (5)
	V 75 mg	0 (0)	0 (0)	2 (2)	0 (0)	1 (1)	0 (0)	3 (4)
	V 150 mg	1 (1)	0 (0)	2 (2)	0 (0)	1 (1)	1 (1)	5 (6)
	Paroxetine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Patient/subject request	Placebo	0 (0)	0 (0)	1 (1)	1 (1)	1 (1)	0 (0)	3 (4)
	V 75 mg	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
	V 150 mg	1 (1)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	3 (4)
	Paroxetine	0 (0)	1 (1)	0 (0)	2 (2)	1 (1)	0 (0)	4 (5)
Unsatisfactory response -efficacy	Placebo	0 (0)	3 (4)	6 (7)	1 (1)	2 (2)	1 (1)	13 (16)
	V 75 mg	0 (0)	0 (0)	5 (6)	0 (0)	1 (1)	0 (0)	6 (7)
	V 150 mg	0 (0)	2 (2)	2 (2)	3 (4)	1 (1)	1 (1)	9 (11)
	Paroxetine	0 (0)	1 (1)	6 (7)	3 (4)	3 (4)	0 (0)	13 (16)
Protocol violation	Placebo	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	V 75 mg	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	V 150 mg	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Paroxetine	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	2 (2)
Other medical event	Placebo	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
	V 75 mg	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)
	V 150 mg	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Paroxetine	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Other non-medical event	Placebo	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	V 75 mg	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	V 150 mg	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	2 (2)
	Paroxetine	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)

FIGURE 3.1.4

PERCENTAGE OF PATIENTS OVER TIME
STUDY 367

TABLE 3.3.1

VENLAFAXINE ER STUDY 600B-367

HAM-D TOTAL: INTENT-TO-TREAT COMPARISON BETWEEN THERAPY GROUPS - LOCF ANALYSIS (RAW MEANS)

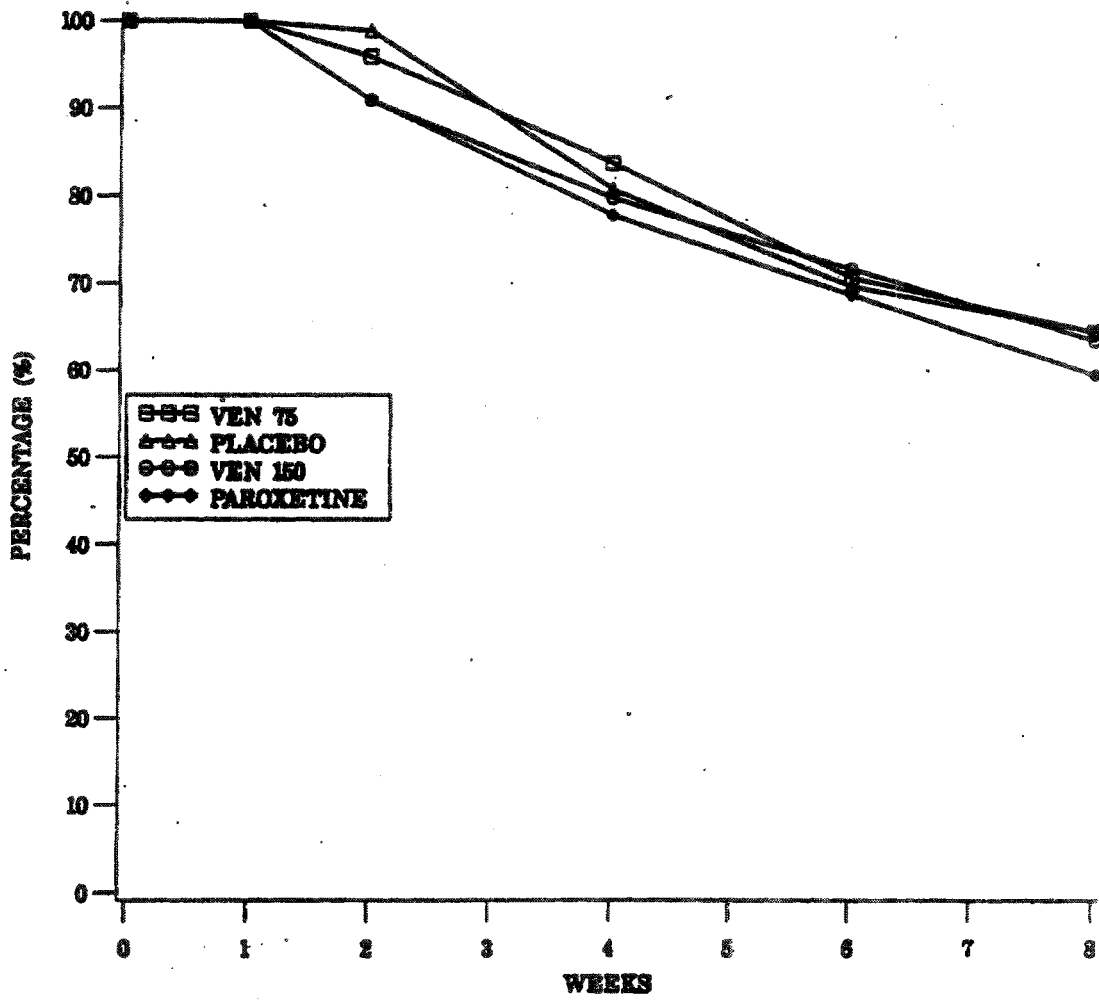| WEEK ON THERAPY	THERAPY GROUP	NUMBER OF PATIENTS	BASELINE MEAN	RAW CHANGE FROM BASELINE	F-TEST	------P-VALUES------		
						V150 MG	V75 MG	PARO
WEEK 1	PLACEBO	81	26.60	-3.65	.09	.05	.83	.86
	V 75 MG	82	26.49	-5.37			.03	.03
	V 150 MG	75	27.11	-3.67				.97
	PAROXETINE	80	26.13	-3.50				
WEEK 2	PLACEBO	81	26.60	-8.20	.15	.18	.42	.41
	V 75 MG	82	26.49	-9.79			.61	.03
	V 150 MG	75	27.11	-9.17				.11
	PAROXETINE	80	26.13	-7.21				
WEEK 4	PLACEBO	81	26.60	-11.26	.09	.39	.15	.33
	V 75 MG	82	26.49	-12.51			.56	.07
	V 150 MG	75	27.11	-13.37				.02
	PAROXETINE	80	26.13	-9.84				
WEEK 6	PLACEBO	81	26.60	-12.48	.04	.21	.24	.20
	V 75 MG	82	26.49	-14.48			.96	.01
	V 150 MG	75	27.11	-14.40				.02
	PAROXETINE	80	26.13	-10.40				
WEEK 8	PLACEBO	81	26.60	-13.10	.06	.14	.37	.27
	V 75 MG	82	26.49	-15.59			.57	.01
	V 150 MG	75	27.11	-14.63				.05
	PAROXETINE	80	26.13	-11.26				

TABLE 3.3.2

VENLAFAXINE ER STUDY 600B-367

HAM-D TOTAL: INTENT-TO-TREAT COMPARISON BETWEEN THERAPY GROUPS - OBSERVED CASES ANALYSIS (RAW MEANS)

WEEK ON THERAPY	THERAPY GROUP	NUMBER OF PATIENTS	BASELINE MEAN	RAW CHANGE FROM BASELINE	F-TEST	P-VALUES V150 MG	V75 MG	PARO
WEEK 1	PLACEBO	81	26.60	-3.65	.09	.05	.83	.86
	V 75 MG	82	26.49	-5.37			.03	.03
	V 150 MG	75	27.11	-3.47				.97
	PAROXETINE	80	26.13	-3.50				
WEEK 2	PLACEBO	80	26.49	-8.25	.22	.10	.15	.92
	V 75 MG	79	26.61	-10.16			.88	.13
	V 150 MG	68	27.13	-9.99				.19
	PAROXETINE	73	25.97	-8.37				
WEEK 4	PLACEBO	66	25.92	-13.36	.24	.76	.19	.46
	V 75 MG	69	26.36	-13.78			.30	.30
	V 150 MG	60	26.82	-15.27				.04
	PAROXETINE	62	25.69	-12.31				
WEEK 6	PLACEBO	57	26.07	-15.84	.07	.26	.35	.20
	V 75 MG	58	26.31	-17.59			.85	.02
	V 150 MG	54	26.39	-17.30				.03
	PAROXETINE	55	25.05	-13.82				
WEEK 8	PLACEBO	53	25.66	-16.64	.13	.18	.06	.95
	V 75 MG	53	26.06	-18.58			.55	.17
	V 150 MG	48	26.46	-19.48				.05
	PAROXETINE	48	25.21	-16.54				

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TABLE 3.3.3   367–EU

PRIMARY EFFICACY VARIABLES: PAIRWISE COMPARISONS OF ADJUSTED MEANS
LOCF ANALYSIS

Time	Comparison			Difference[a]	SEM	95% CL	F-test p-Value	Pairwise p-Value[b]
HAM-D TOTAL SCORE								
Week 1	Placebo	vs	V 75 mg	1.7	0.8	(0.1, 3.4)	0.057	0.035
	Placebo	vs	V 150 mg	-0.3	0.9	(-2.0, 1.4)		0.74
	Placebo	vs	Paroxetine	-0.0	0.8	(-1.7, 1.6)		0.96
	V 75 mg	vs	V 150 mg	-2.0	0.9	(-3.7, -0.4)		0.018
	V 75 mg	vs	Paroxetine	-1.8	0.8	(-3.4, -0.2)		0.033
	V 150 mg vs		Paroxetine	0.2	0.9	(-1.5, 1.9)		0.78
Week 2	Placebo	vs	V 75 mg	1.8	1.1	(-0.5, 4.0)	0.097	0.13
	Placebo	vs	V 150 mg	0.9	1.2	(-1.4, 3.3)		0.44
	Placebo	vs	Paroxetine	-1.0	1.2	(-3.3, 1.3)		0.38
	V 75 mg	vs	V 150 mg	-0.8	1.2	(-3.2, 1.5)		0.48
	V 75 mg	vs	Paroxetine	-2.8	1.2	(-5.1, -0.5)		0.017
	V 150 mg vs		Paroxetine	-1.9	1.2	(-4.3, 0.4)		0.11
Week 4	Placebo	vs	V 75 mg	1.4	1.4	(-1.4, 4.2)	0.059	0.32
	Placebo	vs	V 150 mg	2.1	1.5	(-0.8, 5.0)		0.16
	Placebo	vs	Paroxetine	-1.6	1.4	(-4.4, 1.2)		0.26
	V 75 mg	vs	V 150 mg	0.7	1.5	(-2.2, 3.6)		0.64
	V 75 mg	vs	Paroxetine	-3.0	1.4	(-5.8, -0.2)		0.035
	V 150 mg vs		Paroxetine	-3.7	1.5	(-6.6, -0.8)		0.013
Week 6	Placebo	vs	V 75 mg	2.1	1.6	(-1.1, 5.2)	0.024	0.20
	Placebo	vs	V 150 mg	1.9	1.7	(-1.3, 5.2)		0.24
	Placebo	vs	Paroxetine	-2.4	1.6	(-5.6, 0.8)		0.15
	V 75 mg	vs	V 150 mg	-0.1	1.7	(-3.4, 3.1)		0.94
	V 75 mg	vs	Paroxetine	-4.4	1.6	(-7.6, -1.3)		0.006
	V 150 mg vs		Paroxetine	-4.3	1.7	(-7.6, -1.0)		0.011
Week 8	Placebo	vs	V 75 mg	2.5	1.7	(-0.7, 5.8)	0.032	0.13
	Placebo	vs	V 150 mg	1.6	1.7	(-1.8, 5.0)		0.35
	Placebo	vs	Paroxetine	-2.1	1.7	(-5.4, 1.2)		0.20
	V 75 mg	vs	V 150 mg	-0.9	1.7	(-4.3, 2.4)		0.59
	V 75 mg	vs	Paroxetine	-4.7	1.7	(-8.0, -1.4)		0.005
	V 150 mg vs		Paroxetine	-3.8	1.7	(-7.2, -0.3)		0.032
Final on-therapy	Placebo	vs	V 75 mg	2.6	1.7	(-0.6, 5.9)	0.029	0.11
	Placebo	vs	V 150 mg	1.6	1.7	(-1.8, 4.9)		0.37
	Placebo	vs	Paroxetine	-2.2	1.7	(-5.5, 1.2)		0.20
	V 75 mg	vs	V 150 mg	-1.1	1.7	(-4.4, 2.3)		0.53
	V 75 mg	vs	Paroxetine	-4.8	1.7	(-8.0, -1.5)		0.005
	V 150 mg vs		Paroxetine	-3.7	1.7	(-7.1, -0.3)		0.034

a: An advantage of the second treatment group over the first is indicated by a positive difference.

b: A pairwise comparison is significant if the p-value of the F-test and the p-value of the comparison are both <= 0.05.

TABLE 3.3.4   367–EU

PRIMARY EFFICACY VARIABLES PAIRWISE COMPARISONS OF ADJUSTED MEANS
OBSERVED CASES ANALYSIS

Time	Comparison			Difference[a]	SEM	95% CL	F-Test p-Value	Pairwise p-Value[b]
HAM-D TOTAL SCORE								
Week 1	Placebo	vs	V 75 mg	1.7	0.8	(0.1, 3.4)	0.057	0.035
	Placebo	vs	V 150 mg	-0.3	0.9	(-2.0, 1.4)		0.74
	Placebo	vs	Paroxetine	-0.0	0.8	(-1.7, 1.6)		0.96
	V 75 mg	vs	V 150 mg	-2.0	0.9	(-3.7, -0.4)		0.018
	V 75 mg	vs	Paroxetine	-1.8	0.8	(-3.4, -0.2)		0.033
	V 150 mg vs		Paroxetine	0.2	0.9	(-1.5, 1.9)		0.78
Week 2	Placebo	vs	V 75 mg	2.0	1.1	(-0.2, 4.3)	0.12	0.070
	Placebo	vs	V 150 mg	1.6	1.2	(-0.7, 3.9)		0.18
	Placebo	vs	Paroxetine	-0.3	1.2	(-2.6, 2.0)		0.81
	V 75 mg	vs	V 150 mg	-0.4	1.2	(-2.8, 1.9)		0.71
	V 75 mg	vs	Paroxetine	-2.3	1.2	(-4.6, -0.0)		0.047
	V 150 mg vs		Paroxetine	-1.9	1.2	(-4.3, 0.5)		0.13
Week 4	Placebo	vs	V 75 mg	0.3	1.4	(-2.4, 3.0)	0.19	0.82
	Placebo	vs	V 150 mg	1.5	1.5	(-1.4, 4.3)		0.32
	Placebo	vs	Paroxetine	-1.8	1.4	(-4.6, 1.1)		0.22
	V 75 mg	vs	V 150 mg	1.1	1.4	(-1.7, 4.0)		0.43
	V 75 mg	vs	Paroxetine	-2.1	1.4	(-4.9, 0.7)		0.14
	V 150 mg vs		Paroxetine	-3.2	1.5	(-6.2, -0.3)		0.033
Week 6	Placebo	vs	V 75 mg	1.1	1.6	(-2.0, 4.3)	0.15	0.47
	Placebo	vs	V 150 mg	0.2	1.6	(-3.0, 3.4)		0.90
	Placebo	vs	Paroxetine	-2.5	1.7	(-5.8, 0.7)		0.13
	V 75 mg	vs	V 150 mg	-0.9	1.6	(-4.0, 2.2)		0.56
	V 75 mg	vs	Paroxetine	-3.7	1.6	(-6.9, -0.5)		0.025
	V 150 mg vs		Paroxetine	-2.7	1.7	(-6.0, 0.5)		0.10
Week 8	Placebo	vs	V 75 mg	2.0	1.5	(-1.0, 5.0)	0.28	0.18
	Placebo	vs	V 150 mg	2.9	1.5	(-0.1, 5.9)		0.060
	Placebo	vs	Paroxetine	1.2	1.7	(-2.1, 4.6)		0.47
	V 75 mg	vs	V 150 mg	0.9	1.5	(-2.0, 3.8)		0.54
	V 75 mg	vs	Paroxetine	-0.8	1.6	(-4.0, 2.4)		0.64
	V 150 mg vs		Paroxetine	-1.7	1.7	(-4.9, 1.6)		0.32

a: An advantage of the second treatment group over the first is indicated by a positive difference.
b: A pairwise comparison is significant if the p-value of the F-test and the p-value of the comparison are both <= 0.05.

TABLE 3.4.1

VENLAFAXINE ER STUDY 600B-367

HAM-D DEPRESSED MOOD ITEM: INTENT-TO-TREAT COMPARISON BETWEEN THERAPY GROUPS - LOCF ANALYSIS (RAW MEANS)

WEEK ON THERAPY	THERAPY GROUP	NUMBER OF PATIENTS	BASELINE MEAN	RAW CHANGE FROM BASELINE	F-TEST	------P-VALUES------ V150 MG	V75 MG	PARO
WEEK 1	PLACEBO	81	2.88	-0.49	.12	.27	.31	.36
	V 75 MG	82	2.93	-0.62			.04	.04
	V 150 MG	75	2.81	-0.37				.90
	PAROXETINE	80	2.81	-0.39				
WEEK 2	PLACEBO	81	2.88	-0.98	.16	.09	.94	.64
	V 75 MG	82	2.93	-1.24			.12	.03
	V 150 MG	75	2.81	-0.99				.60
	PAROXETINE	80	2.81	-0.90				
WEEK 4	PLACEBO	81	2.88	-1.32	.63	.43	.43	.80
	V 75 MG	82	2.93	-1.46			.99	.30
	V 150 MG	75	2.81	-1.47				.30
	PAROXETINE	80	2.81	-1.28				
WEEK 6	PLACEBO	81	2.88	-1.53	.34	.29	.93	.45
	V 75 MG	82	2.93	-1.73			.34	.07
	V 150 MG	75	2.81	-1.55				.41
	PAROXETINE	80	2.81	-1.39				
WEEK 8	PLACEBO	81	2.88	-1.59	.33	.16	.81	.73
	V 75 MG	82	2.93	-1.87			.25	.08
	V 150 MG	75	2.81	-1.64				.56
	PAROXETINE	80	2.81	-1.53				

TABLE 3.5.3 PRIMARY EFFICACY VARIABLES (CONTINUED)   367—EU
PAIRWISE COMPARISONS OF ADJUSTED MEANS LOCF ANALYSIS

Time	Comparison			Difference[a]	SEM	95% CL	F-Test p-Value	Pairwise p-Value[b]
CGI IMPROVEMENT								
Week 1	Placebo	vs	V 75 mg	0.1	0.2	(-0.2, 0.4)	0.026	0.59
	Placebo	vs	V 150 mg	-0.3	0.2	(-0.6, 0.0)		0.052
	Placebo	vs	Paroxetine	-0.3	0.2	(-0.6, 0.0)		0.084
	V 75 mg	vs	V 150 mg	-0.4	0.2	(-0.7, -0.1)		0.013
	V 75 mg	vs	Paroxetine	-0.4	0.2	(-0.7, -0.1)		0.023
	V 150 mg	vs	Paroxetine	0.0	0.2	(-0.3, 0.4)		0.82
Week 2	Placebo	vs	V 75 mg	0.2	0.2	(-0.2, 0.6)	0.15	0.26
	Placebo	vs	V 150 mg	0.2	0.2	(-0.2, 0.6)		0.34
	Placebo	vs	Paroxetine	-0.2	0.2	(-0.6, 0.2)		0.36
	V 75 mg	vs	V 150 mg	-0.0	0.2	(-0.4, 0.4)		0.88
	V 75 mg	vs	Paroxetine	-0.4	0.2	(-0.8, -0.0)		0.042
	V 150 mg	vs	Paroxetine	-0.4	0.2	(-0.8, 0.0)		0.065
Week 4	Placebo	vs	V 75 mg	0.2	0.2	(-0.2, 0.7)	0.061	0.29
	Placebo	vs	V 150 mg	0.4	0.2	(-0.1, 0.8)		0.13
	Placebo	vs	Paroxetine	-0.2	0.2	(-0.7, 0.2)		0.33
	V 75 mg	vs	V 150 mg	0.1	0.2	(-0.3, 0.6)		0.61
	V 75 mg	vs	Paroxetine	-0.5	0.2	(-0.9, -0.0)		0.042
	V 150 mg	vs	Paroxetine	-0.6	0.2	(-1.0, -0.1)		0.013
Week 6	Placebo	vs	V 75 mg	0.3	0.2	(-0.2, 0.7)	0.24	0.28
	Placebo	vs	V 150 mg	0.2	0.2	(-0.3, 0.7)		0.40
	Placebo	vs	Paroxetine	-0.2	0.2	(-0.7, 0.3)		0.45
	V 75 mg	vs	V 150 mg	-0.1	0.2	(-0.5, 0.4)		0.82
	V 75 mg	vs	Paroxetine	-0.4	0.2	(-0.9, 0.0)		0.067
	V 150 mg	vs	Paroxetine	-0.4	0.2	(-0.9, 0.1)		0.12
Week 8	Placebo	vs	V 75 mg	0.3	0.2	(-0.2, 0.8)	0.12	0.23
	Placebo	vs	V 150 mg	0.0	0.2	(-0.5, 0.5)		0.89
	Placebo	vs	Paroxetine	-0.3	0.2	(-0.8, 0.2)		0.23
	V 75 mg	vs	V 150 mg	-0.3	0.2	(-0.7, 0.2)		0.29
	V 75 mg	vs	Paroxetine	-0.6	0.2	(-1.1,- 0.1)		0.016
	V 150 mg	vs	Paroxetine	-0.3	0.3	(-0.8, 0.2)		0.19
Final on-therapy	Placebo	vs	V 75 mg	0.3	0.2	(-0.2, 0.8)	0.082	0.18
	Placebo	vs	V 150 mg	0.0	0.2	(-0.5, 0.5)		0.90
	Placebo	vs	Paroxetine	-0.3	0.2	(-0.8, 0.2)		0.21
	V 75 mg	vs	V 150 mg	-0.3	0.2	(-0.8, 0.2)		0.24
	V 75 mg	vs	Paroxetine	-0.6	0.2	(-1.1, -0.2)		0.010
	V 150 mg	vs	Paroxetine	-0.3	0.3	(-0.8, 0.1)		0.17

a: An advantage of the second treatment group over the first is indicated by a positive difference.

b::   A pairwise comparison is significant if the p-value of the F-test and the p-value of the comparison are both <= 0.05.

Time	Comparison			Difference[a]	SEM	95% CL	F-Test p-Value	Pairwise p-Value[b]
CGI IMPROVEMENT								
Week 1	Placebo	vs	V 75 mg	0.1	0.2	(-0.2, 0.4)	0.026	0.59
	Placebo	vs	V 150 mg	-0.3	0.2	(-0.6, 0.0)		0.052
	Placebo	vs	Paroxetine	-0.3	0.2	(-0.6, 0.0)		0.084
	V 75 mg	vs	V 150 mg	-0.4	0.2	(-0.7, -0.1)		0.013
	V 75 mg	vs	Paroxetine	-0.4	0.2	(-0.7, -0.1)		0.023
	V 150 mg.vs		Paroxetine	0.0	0.2	(-0.3, 0.4)		0.82
Week 2	Placebo	vs	V 75 mg	0.3	0.2	(-0.1, 0.6)	0.18	0.17
	Placebo	vs	V 150 mg	0.3	0.2	(-0.1, 0.7)		0.20
	Placebo	vs	Paroxetine	-0.1	0.2	(-0.5, 0.3)		0.64
	V 75 mg	vs	V 150 mg	-0.0	0.2	(-0.4, 0.4)		0.99
	V 75 mg	vs	Paroxetine	-0.4	0.2	(-0.7, 0.0)		0.073
	V150 mg	vs	Paroxetine	-0.4	0.2	(-0.8, 0.1)		0.089
Week 4	Placebo	vs	V 75 mg	-0.0	0.2	(-0.4, 0.4)	0.055	0.99
	Placebo	vs	V 150 mg	0.3	0.2	(-0.2, 0.7)		0.25
	Placebo	vs	Paroxetine	-0.4	0.2	(-0.8, 0.1)		0.095
	V 75 mg	vs	V 150 mg	0.3	0.2	(-0.2, 0.7)		0.23
	V 75 mg	vs	Paroxetine	-0.4	0.2	(-0.8, 0.1)		0.091
	V 150 mg	vs	Paroxetine	-0.7	0.2	(-1.1, -0.2)		0.006
Week 6	Placebo	vs	V 75 mg	0.1	0.2	(-0.3, 0.5)	0.75	0.63
	Placebo	vs	V 150 mg	0.0	0.2	(-0.4, 0.5)		0.93
	Placebo	vs	Paroxetine	-0.1	0.2	(-0.6, 0.3)		0.55
	V 75 mg	vs	V 150 mg	-0.1	0.2	(-0.5, 0.3)		0.69
	V 75 mg	vs	Paroxetine	-0.2	0.2	(-0.7, 0.2)		0.28
	V 150 mg	vs	Paroxetine	-0.2	0.2	(-0.6, 0.3)		0.49
Week 8	Placebo	vs	V 75 mg	0.1	0.2	(-0.3, 0.5)	0.83	0.47
	Placebo	vs	V 150 mg	0.2	0.2	(-0.3, 0.6)		0.46
	Placebo	vs	Paroxetine	0.0	0.2	(-0.4, 0.5)		0.93
	V 75 mg	vs	V 150 mg	0.0	0.2	(-0.4, 0.4)		0.97
	V 75 mg	vs	Paroxetine	-0.1	0.2	(-0.6, 0.3)		0.57
	V 150 mg	vs	Paroxetine	-0.1	0.2	(-0.6, 0.3)		0.55

a: An advantage of the second treatment group over the first is indicated by a positive difference.
b: A pairwise comparison is significant if the p-value of the F-test and the p-value of the comparison are both <= 0.05.

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Time	Comparison			Difference[a]	SEM	95% CL	F-Test p-Value	Pairwise p-Value[b]
MADRS TOTAL SCORE								
Week 1	Placebo	vs	V 75 mg	1.5	0.9	(-0.3, 3.3)	0.020	0.11
	Placebo	vs	V 150 mg	-1.0	1.0	(-2.9, 0.9)		0.31
	Placebo	vs	Paroxetine	-1.2	0.9	(-3.1, 0.7)		0.21
	V 75 mg	vs	V 150 mg	-2.4	1.0	(-4.3, -0.6)		0.011
	V 75 mg	vs	Paroxetine	-2.6	0.9	(-4.5, -0.8)		0.005
	V 150 mg vs		Paroxetine	-0.2	1.0	(-2.1, 1.7)		0.83
Week 2	Placebo	vs	V 75 mg	1.8	1.3	(-0.8, 4.4)	0.064	0.16
	Placebo	vs	V 150 mg	0.3	1.4	(-2.4, 3.0)		0.85
	Placebo	vs	Paroxetine	-1.8	1.4	(-4.5, 0.9)		0.18
	V 75 mg	vs	V 150 mg	-1.6	1.4	(-4.2, 1.1)		0.25
	V 75 mg	vs	Paroxetine	-3.6	1.3	(-6.3, -1.0)		0.007
	V 150 mg vs		Paroxetine	-2.1	1.4	(-4.8, 0.7)		0.14
Week 4	Placebo	vs	V 75 mg	1.6	1.7	(-1.7, 4.9)	0.068	0.34
	Placebo	vs	V 150 mg	2.2	1.7	(-1.2, 5.6)		0.21
	Placebo	vs	Paroxetine	-2.1	1.7	(-5.5, 1.3)		0.22
	V 75 mg	vs	V 150 mg	0.6	1.7	(-2.8, 4.0)		0.73
	V 75 mg	vs	Paroxetine	-3.7	1.7	(-7.0, -0.3)		0.031
	V 150 mg vs		Paroxetine	-4.3	1.8	(-7.8, -0.8)		0.016
Week 6	Placebo	vs	V 75 mg	2.4	1.9	(-1.3, 6.1)	0.054	0.21
	Placebo	vs	V 150 mg	2.1	2.0	(-1.8, 5.9)		0.29
	Placebo	vs	Paroxetine	-2.4	1.9	(-6.2, 1.4)		0.21
	V 75 mg	vs	V 150 mg	-0.3	1.9	(-4.1, 3.5)		0.88
	V 75 mg	vs	Paroxetine	-4.8	1.9	(-8.6, -1.0)		0.013
	V 150 mg vs		Paroxetine	-4.5	2.0	(-8.4, -0.6)		0.026
Week 8	Placebo	vs	V 75 mg	3.0	2.0	(-0.9, 6.8)	0.073	0.13
	Placebo	vs	V 150 mg	1.8	2.0	(-2.2, 5.9)		0.37
	Placebo	vs	Paroxetine	-2.0	2.0	(-6.0, 2.0)		0.32
	V 75 mg	vs	V 150 mg	-1.1	2.0	(-5.1, 2.9)		0.58
	V 75 mg	vs	Paroxetine	-5.0	2.0	(-8.9, -1.0)		0.013
	V 150 mg vs		Paroxetine	-3.9	2.1	(-8.0, 0.2)		0.065
Final on-therapy	Placebo	vs	V 75 mg	3.4	2.0	(-0.5, 7.2)	0.054	0.087
	Placebo	vs	V 150 mg	1.9	2.0	(-2.2, 5.9)		0.36
	Placebo	vs	Paroxetine	-1.9	2.0	(-5.9, 2.1)		0.35
	V 75 mg	vs	V 150 mg	-1.5	2.0	(-5.5, 2.5)		0.46
	V 75 mg	vs	Paroxetine	-5.3	2.0	(-9.2, -1.3)		0.009
	V 150 mg vs		Paroxetine	-3.8	2.1	(-7.9, 0.4)		0.073

a: An advantage of the second treatment group over the first is indicated by a positive difference.

b: A pairwise comparison is significant if the p-value of the F-test and the p-value of the comparison are both <= 0.05.

Time	Comparison			Difference[a]	SEM	95% CL	F-Test p-Value	Pairwise p-Value[b]
MADRS TOTAL SCORE								
Week 1	Placebo	vs	V 75 mg	1.5	0.9	(-0.3, 3.3)	0.020	0.11
	Placebo	vs	V 150 mg	-1.0	1.0	(-2.9, 0.9)		0.31
	Placebo	vs	Paroxetine	-1.2	0.9	(-3.1, 0.7)		0.21
	V 75 mg	vs	V 150 mg	-2.4	1.0	(-4.3, -0.6)		0.011
	V 75 mg	vs	Paroxetine	-2.6	0.9	(-4.5, -0.8)		0.005
	V 150 mg	vs	Paroxetine	-0.2	1.0	(-2.1, 1.7)		0.83
Week 2	Placebo	vs	V 75 mg	2.1	1.3	(-0.5, 4.7)	0.12	0.12
	Placebo	vs	V 150 mg	0.9	1.4	(-1.8, 3.6)		0.52
	Placebo	vs	Paroxetine	-1.1	1.4	(-3.9, 1.6)		0.41
	V 75 mg	vs	V 150 mg	-1.2	1.4	(-3.9, 1.6)		0.39
	V 75 mg	vs	Paroxetine	-3.2	1.4	(-6.0, -0.5)		0.021
	V 150 mg	vs	Paroxetine	-2.1	1.5	(-4.9, 0.8)		0.16
Week 4	Placebo	vs	V 75 mg	0.1	1.6	(-3.1, 3.3)	0.29	0.95
	Placebo	vs	V 150 mg	1.2	1.7	(-2.2, 4.7)		0.48
	Placebo	vs	Paroxetine	-2.1	1.7	(-5.5, 1.2)		0.22
	V 75 mg	vs	V 150 mg	1.1	1.7	(-2.2, 4.5)		0.51
	V 75 mg	vs	Paroxetine	-2.2	1.7	(-5.5, 1.1)		0.18
	V 150 mg	vs	Paroxetine	-3.4	1.8	(-6.9, 0.2)		0.062
Week 6	Placebo	vs	V 75 mg	0.6	1.9	(-3.0, 4.3)	0.24	0.73
	Placebo	vs	V 150 mg	-0.1	1.9	(-3.9, 3.6)		0.95
	Placebo	vs	Paroxetine	-3.0	1.9	(-6.9, 0.8)		0.12
	V 75 mg	vs	V 150 mg	-0.8	1.9	(-4.4, 2.9)		0.68
	V 75 mg	vs	Paroxetine	-3.7	1.9	(-7.4, 0.1)		0.055
	V 150 mg	vs	Paroxetine	-2.9	1.9	(-6.8, 0.9)		0.13
Week 8	Placebo	vs	V 75 mg	2.1	1.8	(-1.4, 5.6)	0.34	0.24
	Placebo	vs	V 150 mg	3.3	1.8	(-0.3, 6.9)		0.070
	Placebo	vs	Paroxetine	1.6	2.0	(-2.4, 5.5)		0.43
	V 75 mg	vs	V 150 mg	1.3	1.7	(-2.1, 4.6)		0.47
	V 75 mg	vs	Paroxetine	-0.5	1.9	(-4.3, 3.3)		0.79
	V 150 mg	vs	Paroxetine	-1.8	1.9	(-5.6, 2.1)		0.36

a: An advantage of the second treatment group over the first is indicated by a positive difference.
b: A pairwise comparison is significant if the p-value of the F-test and the p-value of the comparison are both <= 0.05.

APPENDIX 5.1.1.1 Table of All Studies

Phase 1: Pharmacokinetic Studies	
600B-127-US 23446	Open-label, crossover, randomized, single dose comparative bioavailability trial; normal male volunteers (n=16); venlafaxine ER dose (75 mg), venlafaxine IR dose (37.5 mg q 12 hours)
600B-134-US 24775	Open-label, crossover, randomized, 4 day comparative bioavailability trial; normal male volunteers (n=18); venlafaxine ER dose (75 mg QD), venlafaxine IR dose (37.5 mg BID)
600B-136-US 26141	Open-label, crossover, randomized, 4 day multiple dose relative bioavailability study; normal male and female volunteers (n=24); venlafaxine ER doses (75 mg BID and 150 mg QD); venlafaxine IR 3 day titration on 37.5 mg BID and 75 mg BID
600B-138-US 25771	Open-label, randomized, crossover; single dose food effect (fed/fast); normal male volunteers (n=12); venlafaxine ER dose (75 mg)
600B-143-UK 26760	Open-label, randomized, crossover, single-dose bioavailability study; normal male and female volunteers (n=24); venlafaxine ER doses (2x75 mg and 1x150 mg), venlafaxine IR dose (50 mg)
600B-144-FR 26761	Double-blind, randomized, placebo-controlled, crossover, single dose, absolute bioavailability study; normal male volunteers (n=16); venlafaxine ER dose (75 mg), venlafaxine IR dose (50 mg), venlafaxine IV dose (10 mg)
600B-145-US 26787	Open-label, randomized, crossover, single-dose, food effect (fed/fast); normal male and female volunteers (n=16); venlafaxine ER dose (150 mg)
600B-139-US 25880	Open-label, randomized, 4-day crossover; AM vs PM; normal male volunteers (n=18); venlafaxine ER dose (75 mg/day AM dose; 75 mg/day PM dose)
600B-101-JA-ER Progress report in submission	Double-blind, placebo-controlled, ascending single dose tolerance and pharmacokinetics; normal subjects (n=32 planned); venlafaxine ER doses (37.5 mg, 75 mg, 150 mg, 225 mg)
Phase 3 Studies - Controlled Studies in Depression	
600B-208-US	Multicenter, 12-week, randomized, double-blind, parallel group, flexible dose; male and female depressed patients (n=293); venlafaxine ER dose (75 mg QD which could increase after 2 weeks to 150 mg QD), venlafaxine IR dose (75 mg QD which could increase after 2 weeks to 150 mg QD)
600B-209-US 27256	Multicenter, randomized, double-blind, parallel group; flexible dose x 8 weeks, depressed male and female patients (n=197); venlafaxine ER dose (75 mg QD which could increase to 150 mg QD after 2 weeks and to 225 mg QD after 2 more weeks)

600B-367-EU	Multicenter, randomized, 8 week, double-blind, parallel group, fixed dose; male and female depressed patients (n=329); venlafaxine ER doses (75 mg QD and 150 mg QD), paroxetine (20 mg QD)
600B-211-US Progress report in submission	Multicenter, randomized, 8-week, double-blind, parallel-group, flexible dose; depressed patients (n=300 planned); venlafaxine ER dose (75 mg QD which may be increased to 150 mg QD after 2 weeks and 225 mg QD after 4 weeks); fluoxetine dose (20 mg QD which may be increased to 40 mg QD after 2 weeks and 60 mg QD after 4 weeks)
600B-360-CA Progress report in submission	Multicenter, randomized, 12-week, double-blind, parallel-group, flexible dose; depressed patients (n=336 planned); venlafaxine ER dose (75 mg QD which could increase to 150mg QD after 2 weeks and 225 mg QD after 4 weeks), fluoxetine dose (20 mg QD which could increase to 40 mg QD after 2 weeks and 60 mg QD after 4 weeks)
Phase 3: Uncontrolled Studies in Depression	
600B-365-EU	Multicenter, open-label, flexible dose, 6-12 month long-term safety evaluation; male and female depressed patients (n=251); venlafaxine ER dose (75 mg QD which can increase to 150 mg QD after 2 weeks)
600B-369-US	Multicenter, open-label, flexible dose, 6-12 month long-term safety evaluation; male and female depressed patients (n=120); venlafaxine ER dose (75 mg QD which can increase to 150 mg QD after 2 weeks, and after 4 weeks dose may be increased in 75 mg increments to a maximum of 375 mg QD at no less than 4 day intervals)
Phase 3: Studies in Generalized Anxiety Disorder	
600B-210-US Progress report in submission	Multicenter, randomized, 8-week, double-blind, dose-finding study; generalized anxiety disorder patients (n=400 planned); venlafaxine ER doses (75 mg QD fixed dose, 75 mg QD x 1 week increased to 150 mg QD for 7 weeks, and 75 mg QD for 1 week increased to 150 mg QD for 1 week, then to 225 mg QD for 6 weeks)

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7.2.2   Other Trials Pertinent to the Efficacy Evaluation

As noted mentioned in the overview to the efficacy section, there are two long-term, open label, uncontrolled studies of venlafaxine ER in depressed outpatients: studies 365 and 369. Interim reports, to include interim efficacy data, for these studies were included in the original submission and will be summarized below.

Study 365 was a six month study, with the possibility of six additional months of treatment if clinically indicated, which was conducted at 37 European centers. Patients who completed study 367 and were in need of further antidepressant treatment could be enrolled; however, other patients with DSM-III-R major depression could be enrolled as well. The cutoff date for the interim report was August 31, 1995. Efficacy variables included the HAM-D total score and CGI-severity score. In the LOCF analysis (N=244), the mean raw changes from baseline in the HAM-D total score from months 4 to 10 were consistently in the range of -10 to -11, with 95% CI's of about -9 to -12. There was substantial attrition after month 4 but, up to that timepoint, OC results were similar. CGI-severity score raw changes from baseline from months 4 to 10 were in the range -1.6 to -1.8 (95% CI's about -1.4 to -2.0) in the LOCF analysis. At month 4, OC results were similar. The sponsor reports a significant therapy-by-center interaction in this study: at some centers, there was no significant change from baseline while substantial improvement was noted at other sites. This was attributed by the sponsor to wide differences at baseline in illness severity. The sponsor also performed a responder analysis, with response defined as a decrease in HAM-D total score of at least 50% OR a CGI-improvement score of "1" (very much improved) or "2" (much improved). In the LOCF dataset, at least 45% of patients met response criteria on visits at months 2, 4, and 6, with slightly higher corresponding rates in the OC dataset.

Study 369 was a six month study, with the possibility of six additional months of treatment if clinically warranted, which was conducted at 10 U.S. sites. The cutoff date for the interim report was September 30, 1995.   The primary objective of this study was to collect long-term safety data; therefore, only limited efficacy data are available. Efficacy assessment was based on CGI scores. LOCF mean changes from baseline for the CGI-severity score (N=111) were in the range -1.35 (month 2) to -1.92 (month 6); for the OC analysis, mean changes were slightly higher, probably as a result of selection bias during the course of the study. The sponsor also performed a responder analysis, with response defined as a CGI-improvement score of "1" (very much improved) or "2" (much improved). In the LOCF dataset, at least two-thirds (67%) of patients met response criteria on visits at months 2, 3, 4, 5, and 6, with similar results in the OC dataset.

Efficacy results from these uncontrolled studies cannot provide persuasive evidence of efficacy but do suggest the hypothesis that venlafaxine ER has long-term efficacy. This hypothesis should be tested using an appropriately designed trial (e.g. a relapse prevention study).

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1   Predictors of Response

Subset analyses based on age (<60 or ≥60), sex (male or female), and baseline HAM-D score (<27 or ≥27) were performed for the pool of studies 208 and 209. An analysis based on race was not considered due to the small number of patients in non-white ethnic groups in these two studies.

The adjusted mean change from baseline in HAM-D total score at week 8 for venlafaxine ER patients under 60 (N=176) was -12.6 versus -10.4 for those 60 and older (N=7); mean changes in the placebo subgroups were -8.1 (N=187) and -8.0 (N=12), respectively. This difference in means is not felt to be clinically remarkable. However, given the relatively small number of older patients, this data must be interpreted with caution; no statistical testing was done by the sponsor.

In this pool of studies, females outnumbered males almost 2:1 in the venlafaxine ER, venlafaxine IR, and placebo treatment groups. For the gender subgroups, analysis of the adjusted mean changes from baseline to week 8 for the LOCF datasets with respect to the HAM-D total score, HAM-D depressed mood item, MADRS total score, and CGI-severity score across the three treatment groups revealed no consistently significant gender effects (α=0.10).

About two-thirds of the patients in each of the three treatment groups in this study pool had less severe depression (HAM-D score <27) at baseline. Baseline severity subgroup analysis was performed with respect to the HAM-D total score, HAM-D depressed mood item, MADRS total score, and CGI-severity score. For each severity subset, there was consistent statistical superiority of venlafaxine ER over placebo at weeks 4, 6, and 8 for all variables. However, for the venlafaxine ER patients, the adjusted mean changes from baseline at week 8 were numerically greater for patients with more severe depression versus less severe depression at baseline.

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[1]The poolability of the three efficacy trials (208, 209, and 367) was tested using the Inverse-Chi-Square method for the HAM-D total scores at week 8: the combined null hypothesis of no significant protocol effect with respect to treatment differences was rejected.

Overall, there was no evidence to suggest a significant effect of age, sex, or baseline illness severity on therapeutic outcome.

No information was provided to support a plasma concentration-response relationship for venlafaxine ER.

7.3.2   Size of Treatment Effect

It is difficult to characterize the treatment effect size for an antidepressant agent. Additionally, any comparison of treatment effects across studies must be interpreted with a huge grain of salt, given the multiplicity of potential confounding variables. With this in mind, the placebo-adjusted effect sizes[2] on each of the four key variables at week 6 from the observed cases analysis are depicted in Table 7.3.2 below for:

* study 208 (venlafaxine ER and IR),
* study 301 (the most robust flexible dose efficacy study in the original venlafaxine NDA 20,151, using a dose range of 75-225 mg/day), and
* study 003-022 (the strongest flexible dose efficacy study in NDA 20,415 for mirtazepine, the most recently approved antidepressant).

All drug-placebo differences were statistically significant (α= 0.05). All studies used the 21-item version of the HAM-D.

Table 7.3.2: Placebo-Adjusted Mean Changes from Baseline at Week 6 (OC) in Flexible Dose Antidepressant Trials				
	208		301	003-022
	Ven ER	Ven IR	Ven IR	Mirtazepine
HAM-D total	-4.6	-3.8	-6.0	-8.4
HAM-D item #1	-0.9	-0.8	-0.7	-0.7
MADRS total	-5.5	-5.3	-7.2	-9.2
CGI-severity	-0.6	-0.5	-0.7	-1.1

The results from study 209 are not displayed in this table because, at week 6, venlafaxine ER/placebo differences were not statistically significant; however, at week 8, venlafaxine ER was statistically superior, with effect sizes roughly comparable to

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[2]Scores = (mean drug change from baseline) minus (mean placebo change from baseline). Thus, negative numbers imply drug superiority over placebo.

those in study 208: HAM-D total= -5.1, HAM-D item #1= -0.7,
MADRS total= -5.9, and CGI-severity= -0.7.

Probably the most reliable comparison is between venlafaxine ER
and IR within study 208, since these two treatment groups can be
assumed to be reasonably balanced with respect to potential
confounders. From this comparison, it is seen that the mean
effect sizes for venlafaxine ER are slightly higher than those
for venlafaxine IR, an approved antidepressant.

7.3.3   Choice of Dose

Data from study 367, the fixed dose trial, did not provide solid
evidence of efficacy for either the 75mg or 150mg dose of
venlafaxine. Thus, an evaluation of dose-response from this
study is not feasible. Dose-response cannot be reliably assessed
in flexible dose trials.

The sponsor proposes to indicate in labeling that the usual
therapeutic dose of Effexor XR is 75 mg/day and that, for further
clinical effect, the dose may be increased to a maximum of 300
mg/day.

In support, the sponsor provides the results of an analysis of
those patients from the pool of the two positive studies (208 and
209) who remained at 75 mg/day (i.e. those for whom dose
increases were not deemed to be necessary to improve efficacy):
this subset comprised 43% (79/183) of the venlafaxine patients.
A comparison group was the placebo patients in this pool who did
not require an increase in the number of study capsules.
Pairwise comparisons of mean change from baseline in the four key
variables at weeks 2, 3, 4, 6, and 8 between these two subsets
revealed statistically significant superiority of venlafaxine ER
over placebo (LOCF dataset). A similar analysis using those
patients who required an increase in study medication dose did
not indicate consistent statistical superiority for venlafaxine
ER until week 8. Additionally, a responder analysis based on
CGI-improvement scores utilizing these same subgroups of
venlafaxine ER and placebo patients revealed clear superiority
(p≤0.001) of drug at week 8 (LOCF).

It is reasonable to ask whether those patients who required a
dose increase above 75mg experienced an enhanced therapeutic
effect compared to those who remained at the low dose: an
examination of placebo-adjusted response rates at week 8
indicates a slightly higher response rate among patients who
needed no dose increase (approximately 35% vs. 25%); this finding
is supported by larger placebo-adjusted mean changes from
baseline in HAM-D total and CGI-severity scores among low dose
patients (-6.2 vs. -3.7 and -1 vs. -0.6, respectively). Thus,
the sponsor concludes that the 75mg dose is effective for a large
portion of depressed patients and these patients tend to

experience improvement in depression similar to that observed in patients who require a dose increase.

It must be commented that the 75mg patients do not represent a randomized sample but rather a group selected on the basis of response to that dose; it is likely that patients who are relatively treatment-resistant are overrepresented in the group that required dose escalation to either 150mg or 225mg. Thus, efficacy comparisons between the low and higher dose patients must be viewed skeptically. Nonetheless, assuming that 1) these patients, as a whole, reasonably represent the general target population with respect to therapeutic responsiveness and 2) the flexible dosing used in these trials reflect how venlafaxine ER is likely to be used in clinical practice, it is reasonable to conclude that a large proportion of patients will respond to a 75 mg/day dose. Both assumptions are plausible.

The proposed maximum dose is 300 mg/day. However, the maximum daily dose studied in the clinical efficacy trials was 225 mg/day (study 209). The mean doses were about 138 mg/day and 176 mg/day in studies 208 and 209, respectively. It was considered that the higher proposed maximum dose may be based on extrapolation from the efficacy database for Effexor (NDA 20,151).

Two Effexor trials demonstrated efficacy at doses above 225 mg/day: a flexible dose study (206) in depressed, melancholic inpatients using a mean dose of about 350 mg/day (max. 375 mg/day) and a fixed dose study (203) in depressed outpatients, which showed superiority over placebo for 75, 225, and 375 mg/day but without evidence that the highest dose had any advantage over the two lower doses. Given the increased risk of hypertension with higher doses, it was felt that there would be no benefit, but increased risk, to use a dose higher than 225 mg/day in most patients. Therefore, Effexor labeling indicates no evidence of usefulness of doses greater than 225 mg/day for moderately depressed patients but adds that severely depressed inpatients responded to a mean dose of 350 mg/day; in the latter group, doses up to 375 mg/day may be helpful, generally in three divided doses.

This fails to explain why an Effexor XR dose up to 300 mg/day should be proposed for general use. In the absence of a compelling rationale for using a higher maximum dose, it is recommended that a maximum dose of 225 mg/day be labeled.

Finally, it is not clear why a starting dose of 37.5 mg/day was chosen. In the three controlled trials with Effexor XR, venlafaxine was started at doses of 75 mg/day (208, 209, and low dose patients in 367) and 150 mg/day (high dose patients in 367). It does not appear that these starting doses were poorly tolerated and there does not appear to be any advantage to delaying titration to the usual therapeutic dose. Thus, a

starting dose for most patients should be the usual therapeutic dose, 75 mg/day.

7.3.4   Duration of Treatment

The effectiveness of venlafaxine ER for more than 12 weeks has not been systematically evaluated in controlled studies.

7.4 Conclusions Regarding Efficacy

Table 7.4 summarizes the efficacy results for the three controlled efficacy trials at week 4, the timepoint at which at least 70% of the ITT sample for each treatment group remained in study.

These data, in conjunction with the more detailed efficacy data displayed in the Appendices and discussed previously, clearly show a significant drug effect favoring venlafaxine ER over placebo in studies 208 and 209.

No effect was evident in study 367, even without adjustment of the alpha level due to placebo comparisons with two dose groups. Since no effect was observed for the active comparator, paroxetine, this study is best considered failed, probably in large part due to a substantial placebo response.

Considering these studies as a whole, it is concluded that convincing evidence of antidepressant activity for venlafaxine ER has been demonstrated.

Date:

Statistical Review and Evaluation

NDA #: 20-699/ Drug Class 3S

Applicant: Wyeth-Ayerst Laboratories, Inc.

Name of the Drug: Effexor XR® (venlafaxine hydrochloride)
               Extended Release Capsules

Indication: Treatment of Depression

Documents Reviewed: Volumes 1.1, 1.110 to 1.112, 1.112A to
               1.112Y, 1.113 to 1.135, amendments dated 8-
               14-96, 9-6-96, 9-18-96, 10-17-96, 11-12-96,
               12-20-96, 1-6-97

Clinical Reviewer: Gregory Dubitsky, M.D. (HFD-120)

The issues in this review have been discussed with the reviewing
medical officer, Dr. Gregory Dubitsky, M.D. (HFD-120).

Various Sections of this review are:

      I. Background/Introduction
     II. Clinical Studies
         1. Study 0600B-208-US
         2. Study 0600B-209-US
         3. Study 0600B-367-EU
    III. Overall Reviewer's Comments
     IV. Overall Conclusion

I.   **Background/Introduction**

The immediate-release (IR)dosage form of venlafaxine, Effexor, is
already approved (NDA No.20-151) for the treatment of depression.
It has also been registered in over 30 countries with approvals
pending in approximately   countries.

Venlafaxine XR (or ER) has been developed to provide a formulation of venlafaxine that requires only once a day administration. It has not been marketed in any country, and no registration applications are pending at the time of this NDA submission. It has been evaluated in controlled clinical studies. The sponsor states that two phase III studies, 208-US and 209-US provide the primary evidence of safety and efficacy. The third phase III study, 367-EU is supportive. Summary information of these three studies is attached as Tables 0.1.1 to o.1.3[1].

Study 208-US was double-blind, flexible-dose, twelve-week efficacy study in U.S.A. of 75-150 mg Effexor XR, 75-150 mg Effexor, and placebo in outpatients (301 enrolled and 287 ITT patients) with major depression.

Study 209-US was double-blind, flexible-dose, eight-week efficacy study in U.S.A. of 75-225 mg venlafaxine XR and placebo in outpatients (204 enrolled and 191 ITT patients) with major depression.

Study 367-EU was double-blind, fixed-dose, eight-week efficacy study in Europe of 75 and 150 mg venlafaxine XR, 20 mg Paxil, and placebo in outpatients (332 enrolled and 323 ITT patients) with major depression.

II. Clinical Studies

All analyses referred to in this report are the sponsor's analyses, except where specifically mentioned to be done by this reviewer.

In the Tables providing Raw Means, sometimes, the p-values are the same as those in the Tables providing adjusted means and, sometimes, they are not. When same, they are from 2-way ANOVA mentioned in the protocol. When not same, the p-values for the Raw Means were calculated by the 1-way ANOVA and those for Adjusted Means were always done by the 2-way ANOVA (telephone confirmation on 11-21-96).

Both parametric (in all the Tables included in this report) and non-parametric (no Tables included in this report) analyses

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[1] In the Table (or Appendix or Figure; no separate numbering systems have been created for these) number i.j.k, i stands for the serial number of the study in the list of studies above (except that 0 indicates overall or "common to all"), j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section.

data from these two atypical centers. These subset-analyses provided stronger results but were not yet capable of claiming consistently statistically significant evidence.

III. Overall Reviewer's Comments

Study 208-US provided strong statistical evidence, Study 209-US provided reasonable statistical evidence, and Study 367-EU provided no statistical evidence but numerical superiority, in favor of the efficacy of venlafaxine XR. The venlafaxine XR 150 mg dose performed no better than the venlafaxine XR 75 mg dose.

Ninety-five percent confidence intervals for the main studies, side-by-side, are presented in Graphs 0.2.1 to 0.2.3. These graphs provide a reasonably acceptable picture about the efficacy of venlafaxine XR, although Study 367 did not provide (adequately) statistically significant evidence in its favor. Also, these graphs provide some idea about the probable margins of error.

Cumulative distribution functions with respect to HAM-D Total, for the three studies, are attached as Figures 0.2.4 to 0.2.6. Regarding the separation of treatment groups, these functions with respect to CGI Severity and HAM-D Depressed Mood Item are similar. Separation between venlafaxine XR and placebo at Endpoint is the widest in Study 208, medium in Study 209, and narrowest and negligible in Study 367. This is consistent with all other results.

Through discussion with the Clinical Reviewer, this reviewer did not receive any safety statistical issues to consider.

Placebo patients, generally, dropped more after Week 3. In Study 367, paroxetine patients dropped the most; however, the difference in the rate of dropout was not substantial.

Consistency Across Sites

The sponsor stated, "The potential significance of the treatment-by-investigator interactions was also examined as part of the statistical analyses for each multicenter study. These analyses also demonstrated that it was appropriate to pool the data within each study."

The Treatment by Center interaction p-values have been provided in the NDA (vol. 1.116 p.11; vol. 1.125 p.12; vol. 1.133 p.14). A few significant p-values out of nearly 200 are negligible.

Ninety five percent confidence intervals for the sites side-by-side and the overall study (pooled) are presented in Figures 0.2.7 to 0.2.9, for the Mean Difference between venlafaxine XR and placebo with respect to Mean Change from Baseline in HAM-D Total. Although there was a moderate amount of inconsistency, almost all sites in studies 208 and 209 showed positive effects of venlafaxine XR. Center 18 in Study 208 showed outstandingly strong evidence in favor of venlafaxine XR; the intervals for this site and the Combined (pooled-sites) were non-overlapping. Site 04 of Study 209 showed a similar trend; however, it was only with respect to HAM-D Total and not other efficacy variables.

In Study 367, in addition to inconsistency, unacceptability of the evidence as positive is apparent. Final on-therapy Treatment by center interaction p-value (.057) for HAM-D Total was nominally significant but had to be neglected because of multiple comparisons.

Subgroup Analyses (Race, Gender, Age, Baseline HAM-D Total)

Subgroup analyses were performed after pooling data from the flexible-dose, double-blind, placebo-controlled studies performed under protocols 600B-208 and -209.

The sponsor stated, "A subset analysis based on race was not considered because the number of patients in non-white ethnic groups in these two studies was small."

Gender

These subgroup analyses were presented on pages 89, 134, and 135 of Vol. 1.111. Out of 24 interaction p-values, there were only 3 significant ones at the 15% level of significance. All of these 3 were with respect to the HAM-D Depressed Mood Item, where the females showed better efficacy than the males. With respect to other important efficacy variables also, females, generally, showed slightly better efficacy than the males.

Therapy p-values were almost always significant (i.e., after eliminating the effect of Gender).

Age

There were only 19 patients older than 60 years in the placebo and venlafaxine XR groups together, in the studies 208 and 209 combined. Therefore, the reduced efficacy (venlafaxine XR vs placebo mean difference) by an amount 2.1 in Change from Baseline in HAM-D Total in the older patients is statistically non-interpretable.

Baseline HAM-D Total Score

The sponsor investigated the effects of baseline level of severity on response. Level of severity was defined as a baseline HAM-D Total score of less than 27 for patients with less severe depression and greater than or equal to 27 for patients with more severe depression.

These subgroup analyses were presented on pages 90 to 94 and 136 to 143 of vol. 1.111.

The sponsor stated, "For both of the severity subgroups, patients treated with venlafaxine XR and venlafaxine IR had significantly greater improvement on all of the efficacy parameters at the final evaluation than did the respective placebo-treated patients. For venlafaxine XR or venlafaxine IR, but not for placebo, the adjusted mean changes from baseline were greater for the patients with more severe depression compared with those with less severe depression at baseline."

Patients With Associated Anxiety

In the Integrated Efficacy Summary, the sponsor seems to emphasize relieving the symptoms of anxiety, and stated, "In addition, positive results were found for venlafaxine XR treatment compared with placebo treatment of depressed patients with associated anxiety; venlafaxine XR was effective in both relieving the symptoms of anxiety and treating the depression in these patients."

This was not included in the objectives, factors for stratification, or pre-identified subgroups (in the protocol). However, the sponsor stated, "These subset analyses were planned before studies 600B-208 and -209 were completed or unblinded." The rationale for these analyses were the findings from previous studies.

**APPEARS THIS WAY
ON ORIGINAL**

IV. Overall Conclusion

Overall, there is reasonably acceptable statistical evidence in favor of the efficacy of venlafaxine XR. The venlafaxine XR 150 mg dose performed no better than the venlafaxine XR 75 mg dose.

This reviewer is not sure if it would be worthy of investigation why paroxetine did so poorly (Study 367-EU).

Japo Choudhury 1-16-97

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot   *JTS 1-17-97*

Dr. Chi *Chi 1/28/97*

CC:
Archival NDA 20-699

HFD-120/Dr. Leber
HFD-120/Dr. Laughren
HFD-120/Dr. Dubitsky
HFD-120/Mr. Purvis
HFD-120/Mr. David
HFD-344/Dr. Lisook
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/Dr. Choudhury
HFD-710/Chron
J.Choudhury:x71518:DB I: 01/16/97

This review consists of 22 pages of text and 75 pages of Tables, Figures, etc.

FIGURE 0.2.1

Mean Difference from Placebo with 95 % Confidence Intervals
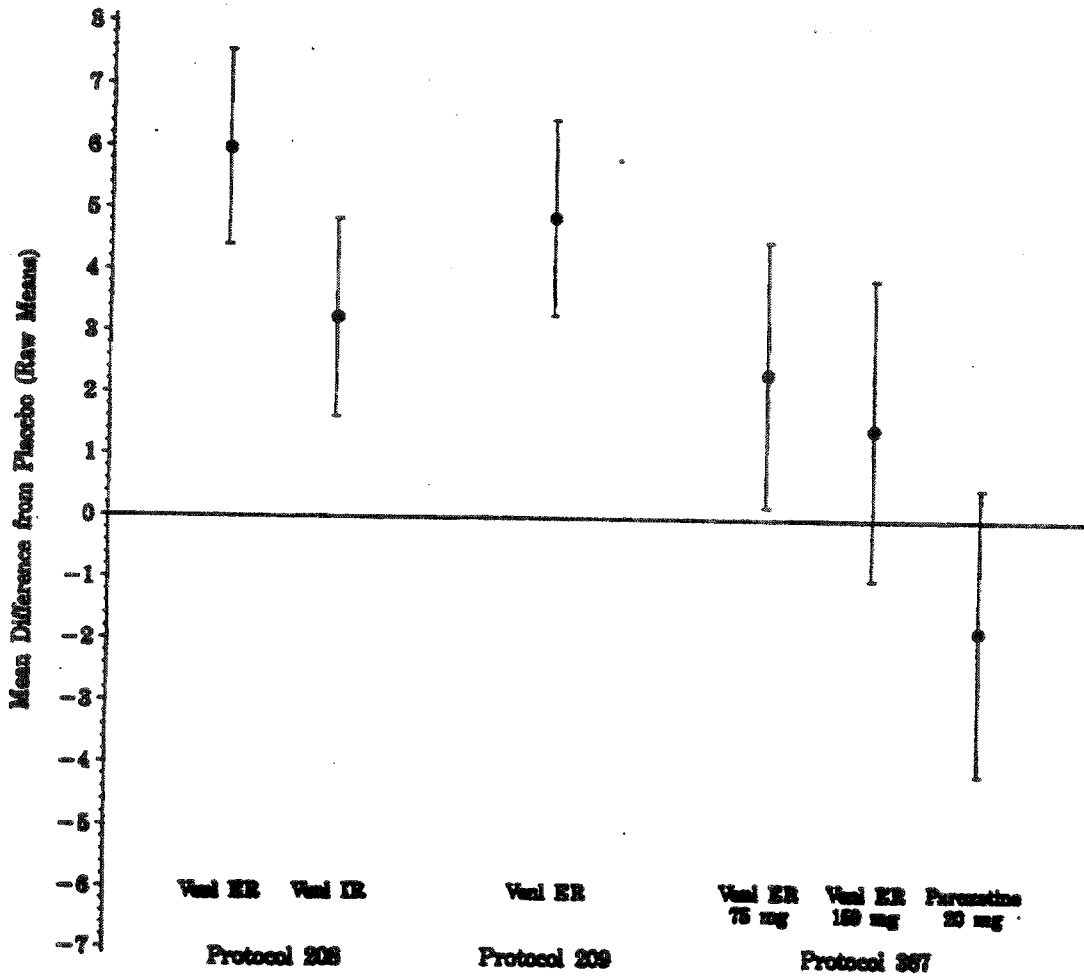Final On–Therapy Value
Mean HAM–D Totals

FIGURE 0.2.2

Mean Difference from Placebo with 95 % Confidence Intervals
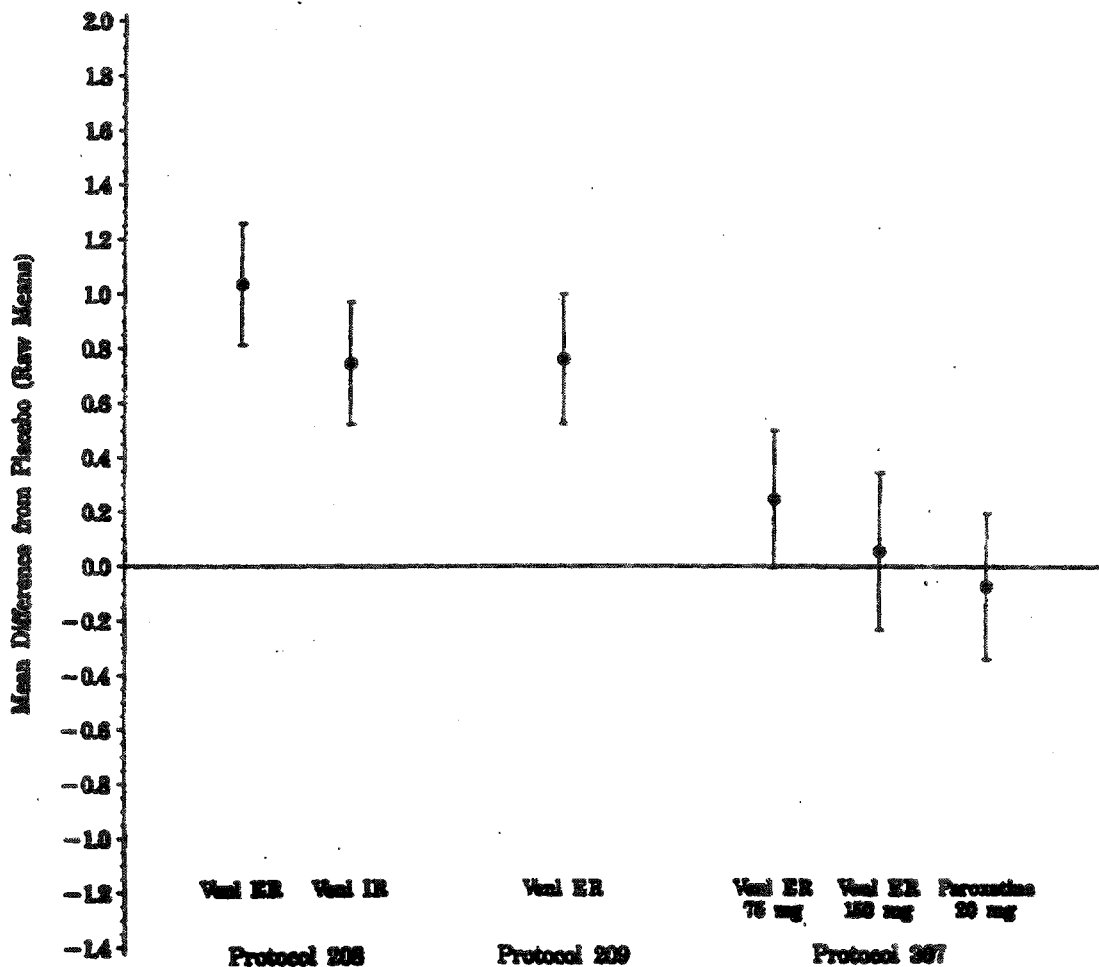Final On-Therapy Value
Mean Depressed Mood Items

FIGURE 0.2.3

Mean Difference from Placebo with 95 % Confidence Intervals
Final On-Therapy Value
Mean CGI Severity