# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20699

## STATISTICAL REVIEW(S)

Date:

Statistical Review and Evaluation

JAN 28 1997

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

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.

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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STUDY 208-US

HAMILTON DEPRESSION SCALE - 21-ITEM TOTAL

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 | -4.82 | 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

| | Effexor XR | | Effexor IR | | PLACEBO | | Effexor XR Vs Placebo | |
|---|---|---|---|---|---|---|---|---|
| WEEK | 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.

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CLINICAL GLOBAL IMPRESSIONS SCALE - SEVERITY OF ILLNESS

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 | -0.39 | 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

| | Effexor XR | | Effexor IR | | PLACEBO | | Effexor XR Vs Placebo | |
|---|---|---|---|---|---|---|---|---|
| WEEK | 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.

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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

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).

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STUDY 209-US

HAMILTON DEPRESSION SCALE - 21-ITEM TOTAL

LOCF

MEAN CHANGE FROM BASELINE

| WEEK | Effexor XR N | Effexor XR MEAN | PLACEBO N | PLACEBO MEAN | Effexor XR Vs Placebo Difference | Effexor XR Vs Placebo 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 N | Effexor XR MEAN | PLACEBO N | PLACEBO MEAN | Effexor XR Vs Placebo Difference | Effexor XR Vs Placebo 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.

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HAMILTON DEPRESSION SCALE - Depressed Mood Item

LOCF

MEAN CHANGE FROM BASELINE

| WEEK | Effexor XR N | Effexor XR MEAN | PLACEBO N | PLACEBO MEAN | Effexor XR Vs Placebo Difference | Effexor XR Vs Placebo 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

| WEEK | Effexor XR N | Effexor XR MEAN | PLACEBO N | PLACEBO MEAN | Effexor XR Vs Placebo Difference | Effexor XR Vs Placebo 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.

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CLINICAL GLOBAL IMPRESSIONS SCALE - SEVERITY OF ILLNESS

LOCF

MEAN CHANGE FROM BASELINE

| WEEK | Effexor XR N | Effexor XR MEAN | PLACEBO N | PLACEBO MEAN | Effexor XR Vs Placebo Difference | Effexor XR Vs Placebo 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 N | Effexor XR MEAN | PLACEBO N | PLACEBO MEAN | Effexor XR Vs Placebo Difference | Effexor XR Vs Placebo P-value |
|---|---|---|---|---|---|---|
| 1 | 89 | -0.29 | 99 | -0.31 | 0.02 | 0.58 |
| 2 | 82 | -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.

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MONTGOMERY/ASBERG SCALE - TOTAL SCORE

LOCF

MEAN CHANGE FROM BASELINE

| WEEK | Effexor XR N | Effexor XR MEAN | PLACEBO N | PLACEBO MEAN | Effexor XR Vs Placebo Difference | Effexor XR Vs Placebo 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 N | Effexor XR MEAN | PLACEBO N | PLACEBO MEAN | Effexor XR Vs Placebo Difference | Effexor XR Vs Placebo 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.

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

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.

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## 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.

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TABLE 0.1.1

**TABLE OF ALL CLINICAL STUDIES OF VENLAFAXINE ER IN NDA 20-699**

| Protocol Number-Report Number (Investigators) | Status Start-Stop Date | Site[a] | Study Design | Study Drugs[b] | Dose, Frequency, Route, Duration[c] | Batch No. Date-Plant[d] | Enrolled/ Safety/ ITT[e] | Gender[f,g] Ethnic Origin[h] | Age[i] (y) Range (Mean) | Location: Report/ Data Listings/ CRFs |
|---|---|---|---|---|---|---|---|---|---|---|
| **PLACEBO-CONTROLLED CLINICAL STUDIES - DEPRESSION INDICATION** | | | | | | | | | | |
| 600B-208-US<br>26165<br>(Baumel/ Cunninghan/ Diamond/Freeman/ Gibson/Kennedy/ Khan/Patrick/ Riesenberg/ Shrivastava/Stahl/ Weiss) | Completed<br>05/94 - 02/95 | US | Multicenter, randomized, double-blind, parallel group, placebo-controlled, active comparative | Pbo | 12 wks | ER-Pbo:<br>3TJC<br>01/94-RP<br>IR-Pbo:<br>1VXR<br>06/91-RP | 301 P/<br>293 P/<br>287 P | 41M/59F<br>2A/3B/1H/94W | 20 - 65<br>(40) | Item 6<br>1.46-1.54<br>Item 8<br>1.63-1.72<br>Item 10<br>1.113-1.122/<br>1.149-1.167/<br>1.222-1.223 |
| | | | | ER | flexible dose, 75 mg/day, 12 wks (after 2 wks, dose could be increased to 150 mg/day) | 3T11V<br>01/94-RP | | 37M/60F<br>1A/7B/2H/1Ot/86W | 18 - 70<br>(40) | |
| | | | | IR | flexible dose, 75 mg/day, 12 wks (after 2 wks, dose could be increased to 150 mg/day) | 2TMZ<br>12/92-RP | | 31M/65F<br>5B/4H/1Ot/86W | 19 - 72<br>(43) | |

(Table continues)

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TABLE 0.1.2

TABLE OF ALL CLINICAL STUDIES OF VENLAFAXINE ER IN NDA 20-699

| Protocol Number-Report Number (Investigators) | Status Start-Stop Date | Site[a] | Study Design | Study Drugs[b] | Dose, Frequency, Route, Duration[c] | Batch No. Date-Plant[d] | Enrolled/ Safety/ ITT[e] | Gender[f,g] Ethnic Origin[h] | Age[i] (y) Range (Mean) | Location: Report/ Data Listings/ CRFs |
|---|---|---|---|---|---|---|---|---|---|---|
| **PLACEBO-CONTROLLED CLINICAL STUDIES - DEPRESSION INDICATION (Continued)** | | | | | | | | | | |
| 600B-209-US<br>27258<br>(Carman/Charles/ Cohn/Farrell/Fava/ Feiger/Feighner/ Ferguson/Yonkers/ Goldstein/Thase/ Weisler) | Completed<br>12/94 - 08/95 | US | Multicenter, randomized, double-blind, parallel-group, placebo-controlled | Pbo | 8 wks | 3TJC<br>01/94-RP | 204 P/<br>197 P/<br>191 P | 41M/61F<br>1A/2B/1H/98W | 27-77<br>(42) | Item 8<br>1.73-1.79<br>Item 10<br>1.123-1.129/<br>1.168-1.181/<br>1.224 |
| | | | | ER | flexible dose:<br>75 mg/day, 8 wks<br>(dose could be increased after 2 wks to 150 mg/day; after 2 more wks to 225 mg/day) | A94D020/4TLC<br>and<br>A94D016/4TBL<br>12/93-RP & AWPI | | 35M/60F<br>3B/2H/90W | 18-66<br>(40) | |

(Table continues)

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TABLE 0.1.3

TABLE OF ALL CLINICAL STUDIES OF VENLAFAXINE ER IN NDA 20-699

| Protocol Number-Report Number (Investigators) | Status Start-Stop Date | Site[a] | Study Design | Study Drugs[b] | Dose, Frequency, Route, Duration[c] | Batch No. Date-Plant[d] | Enrolled/ Safety/ ITT[e] | Gender[f,g] Ethnic Origin[h] | Age[i] (y) Range (Mean) | Location: Report/ Data Listings/ CRFs |
|---|---|---|---|---|---|---|---|---|---|---|
| **PLACEBO-CONTROLLED CLINICAL STUDIES (WITH ACTIVE CONTROL) - DEPRESSION INDICATION** | | | | | | | | | | |
| 600B-367-EU<br>25782<br>(Bonnafoux/ Bourgeois/Chiaroni/ Cook/Danic/Dassa/ Daurignac/Denayer/ Dierick/Fengler/ Ferrero/Frei/ Geraud/Giavedoni/ Goron-Parry/ Gros-Gean/Hanus/ Hirsch/Hosie/Langdon/ LeClercq/Legoubey/ Letzelter/Mahapatra/ Martin/Martin/May/ Mesotten/N'Guyen/ Rance/Ravizza/ Realini/Thermoz/ Volterra/Young/ Whitby) | Completed<br>10/94 - 08/95 | BE<br>ST<br>FR<br>UK<br>IT | Multicenter, randomized, double-blind, parallel-group, placebo-controlled | Pbo (for ER)<br>Pbo (for Prx) | 8 wks | 3TJC<br>01/94-RP<br>3WJQ<br>12/92-Mont | 332 P/<br>329 P/<br>323 P | 26M/57F<br>1B/82W | 19-71<br>(45) | Item 8<br>1.80-1.84d Item 10<br>1.130-1.134D/<br>1.194-1.212/<br>1.228-1.231 |
| | | | | ER | fixed dose, 75 mg/day, 8 wks | 3THV<br>01/94-RP | | 25M/58F<br>2Ot/81W | 18-77<br>(45) | |
| | | | | ER | fixed, dose, 150 mg/day, 8 wk | 3THV<br>01/94-RP | | 29M/53F<br>1B/81W | 24-74<br>(45) | |
| | | | | Prx | fixed dose, 20 mg/day, 8 wks | 4TFB<br>07/94-RP<br>and<br>4WJL<br>05/94-Mont | | 37M/44F<br>2B/1Ot/78W | 24-75<br>(48) | |

(Table continues)

**FIGURE 0.2.1**

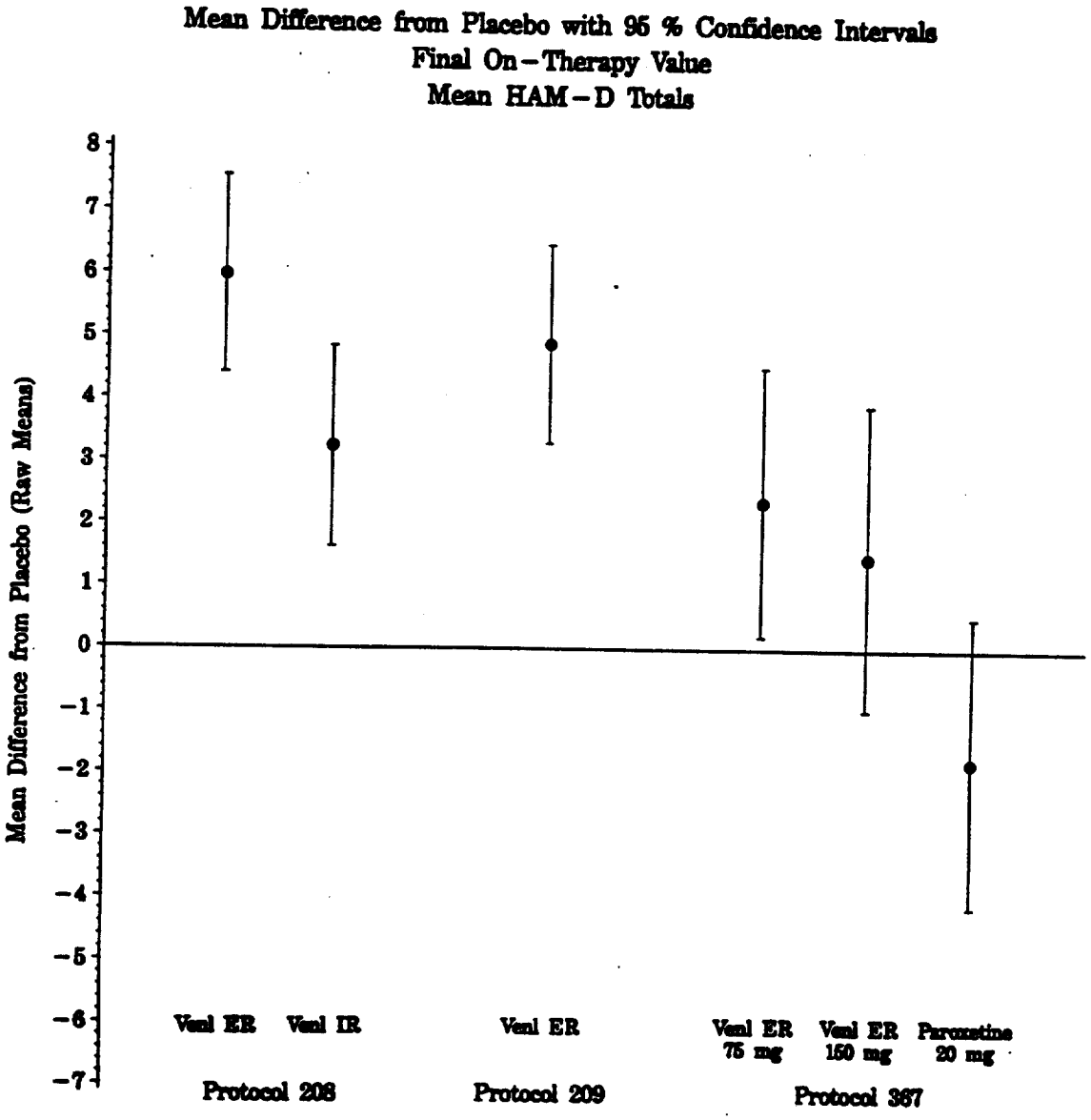

Mean Difference from Placebo with 95 % Confidence Intervals
Final On-Therapy Value
Mean HAM-D Totals
Mean Difference from Placebo (Raw Means)
8
7
6
5
4
3
2
1
0
−1
−2
−3
−4
−5
−6
−7
Venl ER
Venl IR
Venl ER
Venl ER 75 mg
Venl ER 150 mg
Paroxetine 20 mg
Protocol 208
Protocol 209
Protocol 367

**FIGURE** 0.2.2

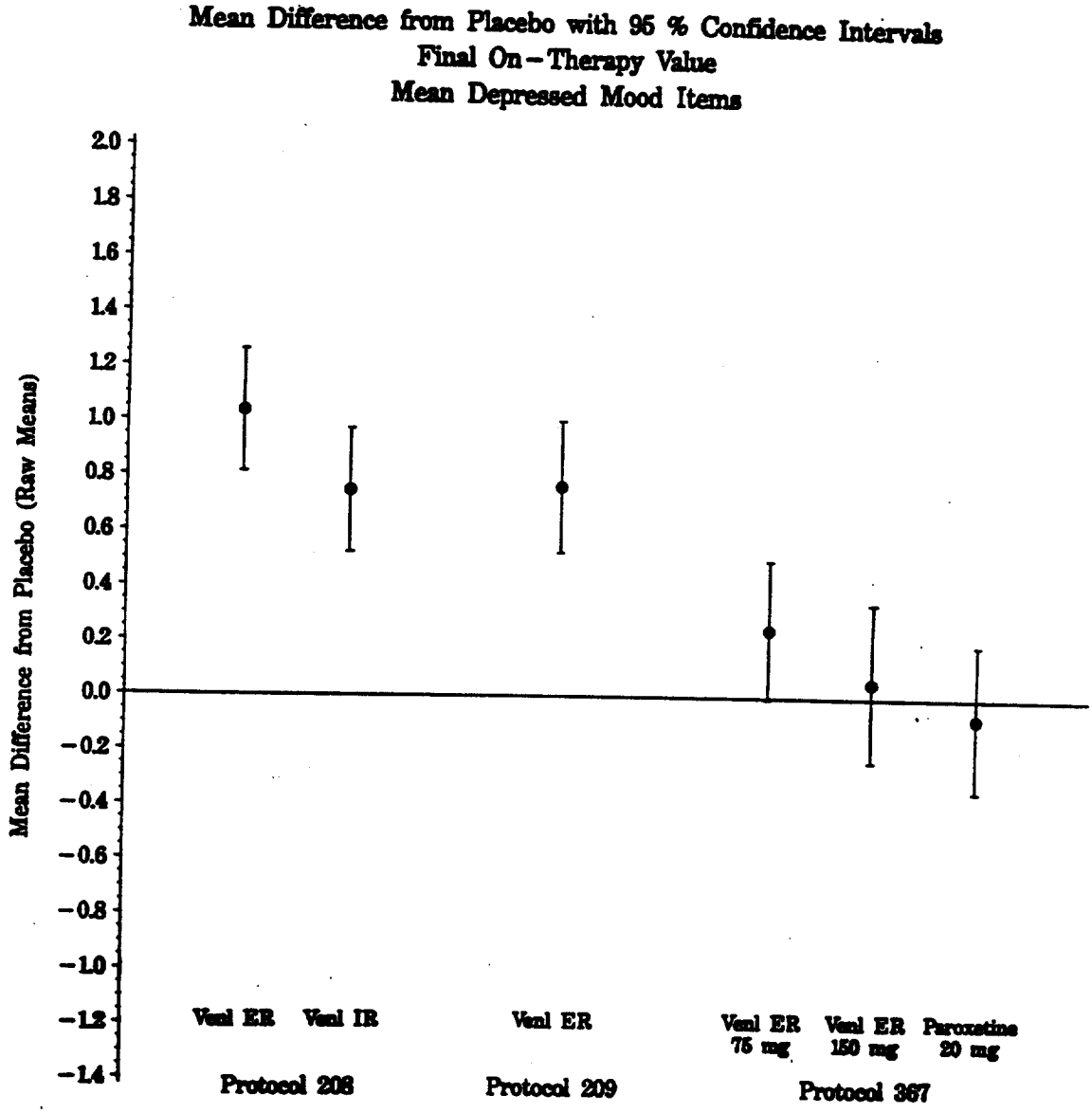

Mean Difference from Placebo with 95 % Confidence Intervals
Final On-Therapy Value
Mean Depressed Mood Items
Mean Difference from Placebo (Raw Means)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
Venl ER
Venl IR
Venl ER
Venl ER 75 mg
Venl ER 150 mg
Paroxetine 20 mg
Protocol 208
Protocol 209
Protocol 367

**FIGURE** 0.2.3

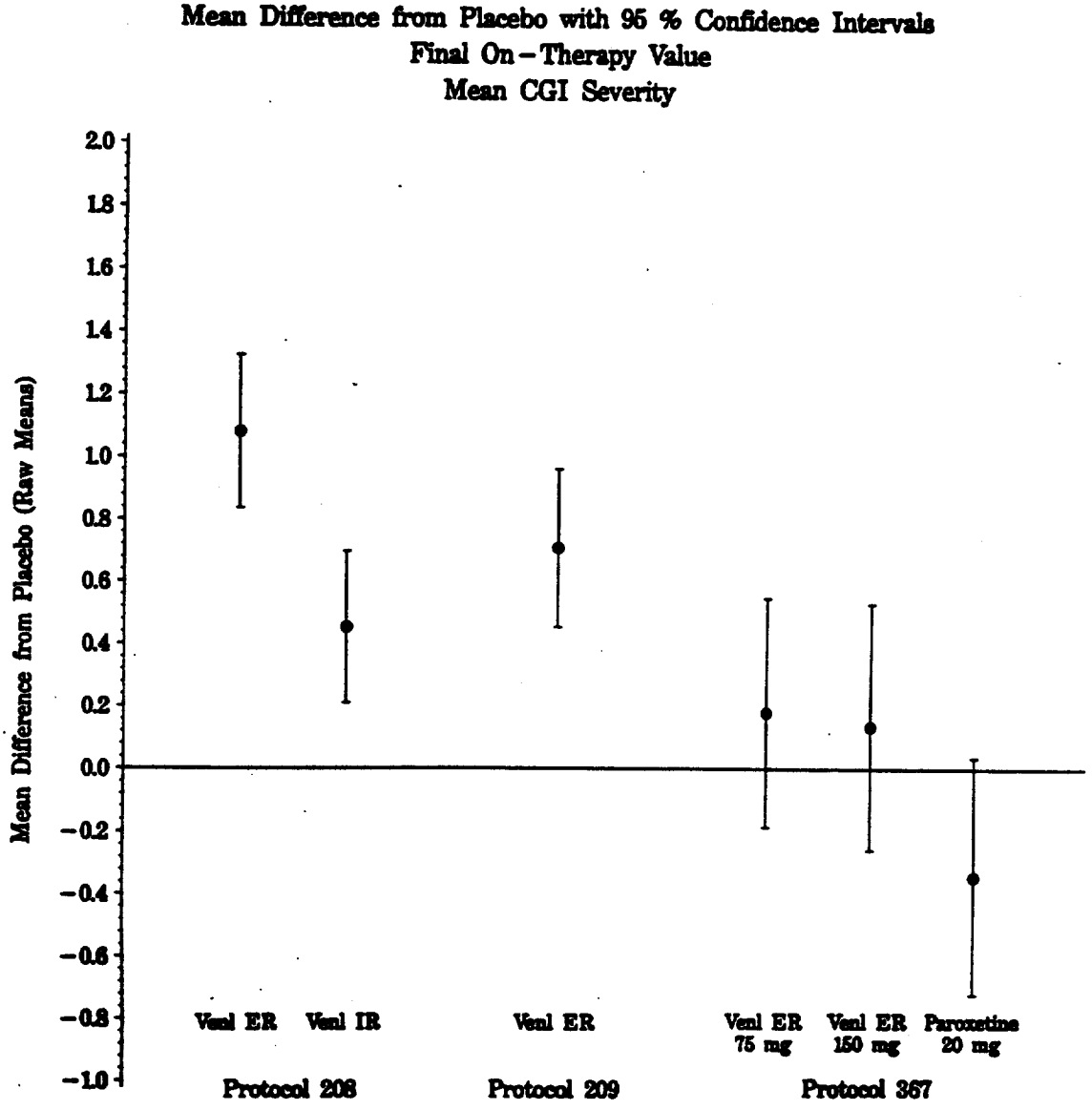

Mean Difference from Placebo with 95 % Confidence Intervals
Final On-Therapy Value
Mean CGI Severity
Mean Difference from Placebo (Raw Means)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
Venl ER
Venl IR
Venl ER
Venl ER 75 mg
Venl ER 150 mg
Paroxetine 20 mg
Protocol 208
Protocol 209
Protocol 367

FIGURE 0.2.4

Cumulative Percent Vs HAM-D Total Scores

Study 208

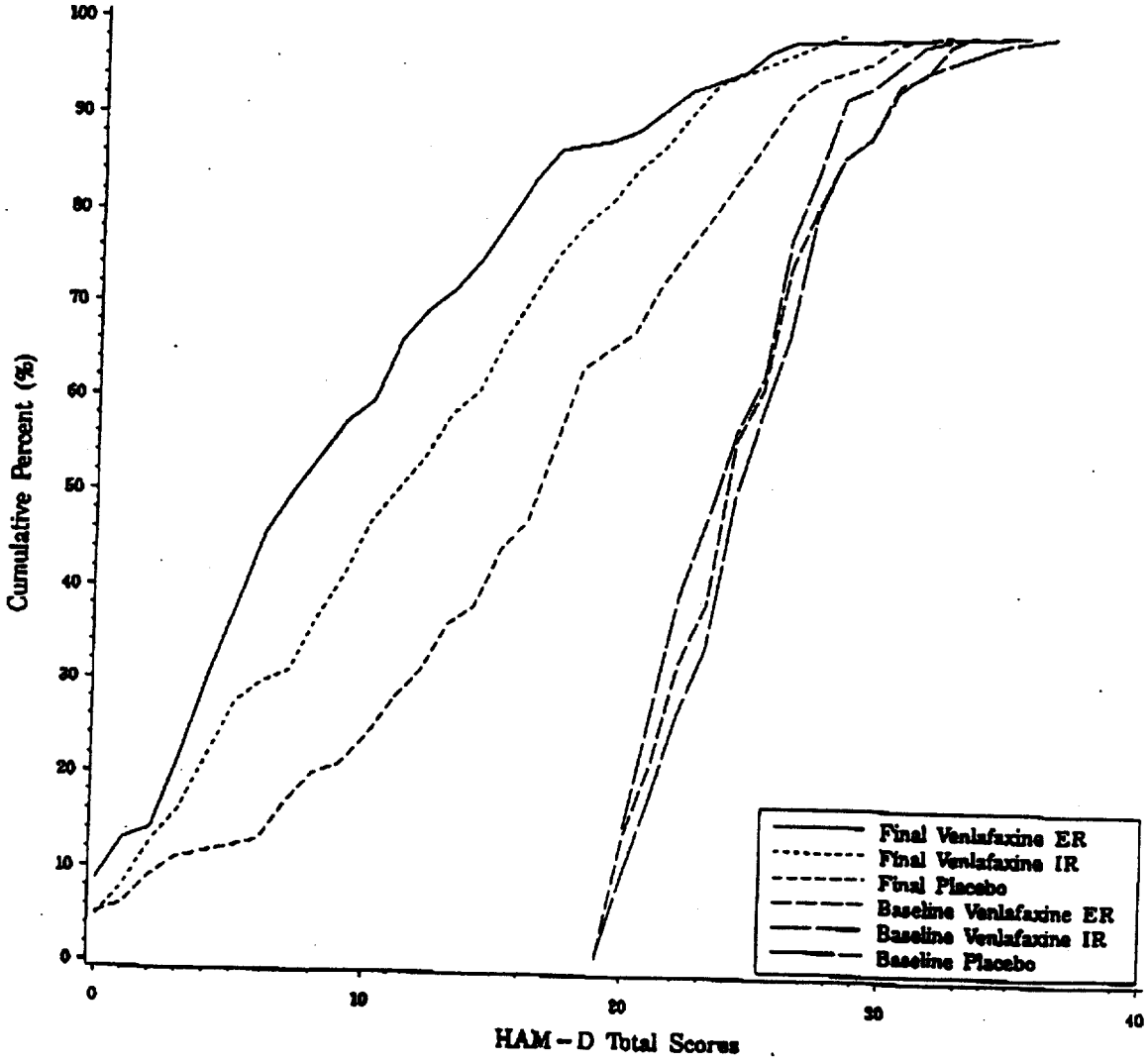


FIGURE 0.2.5

Cumulative Percent Vs HAM-D Total Scores
Study 209

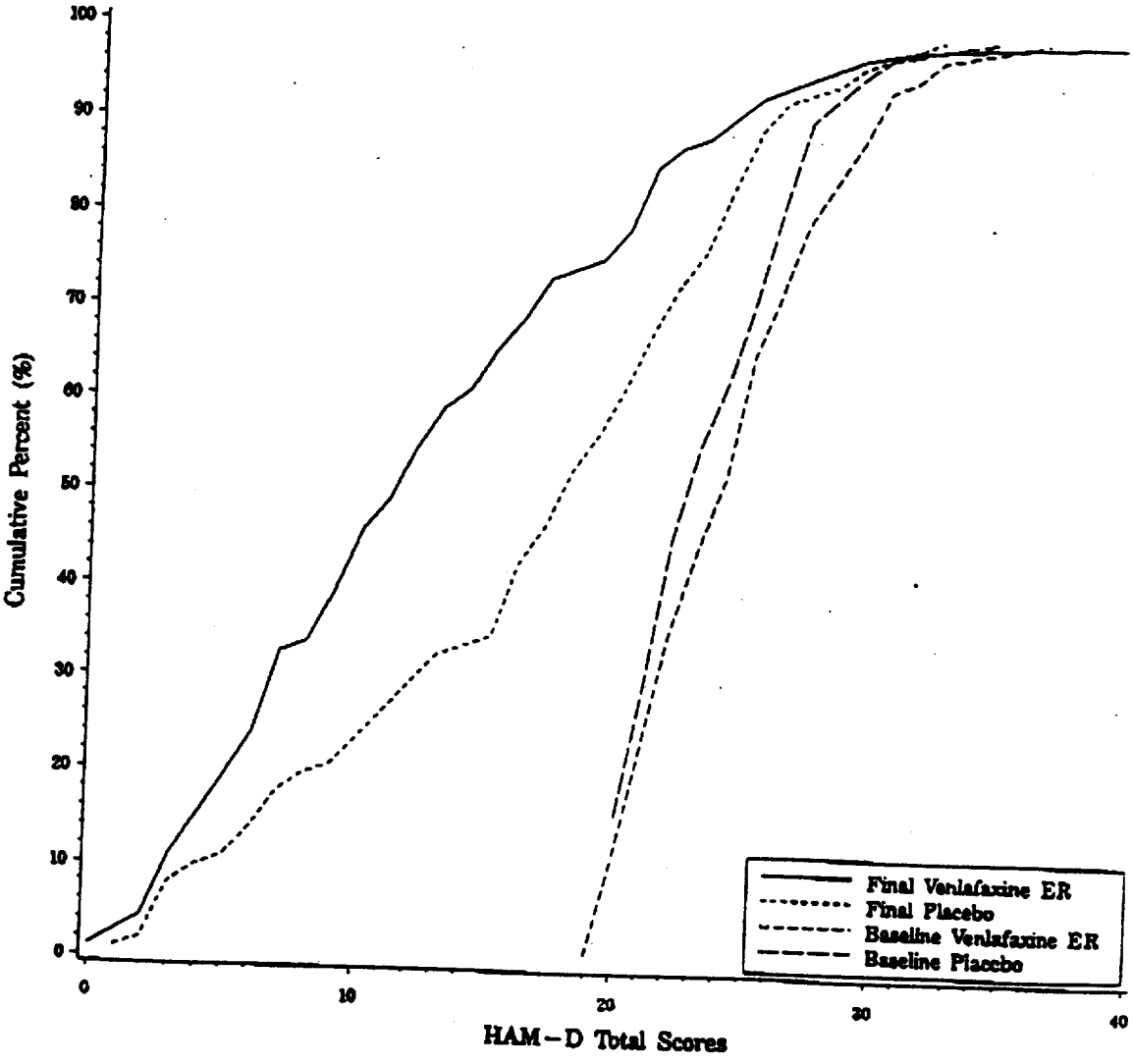


FIGURE 0.2.6

**Cumulative Percent Vs HAM−D Total Scores**
**Study 367**

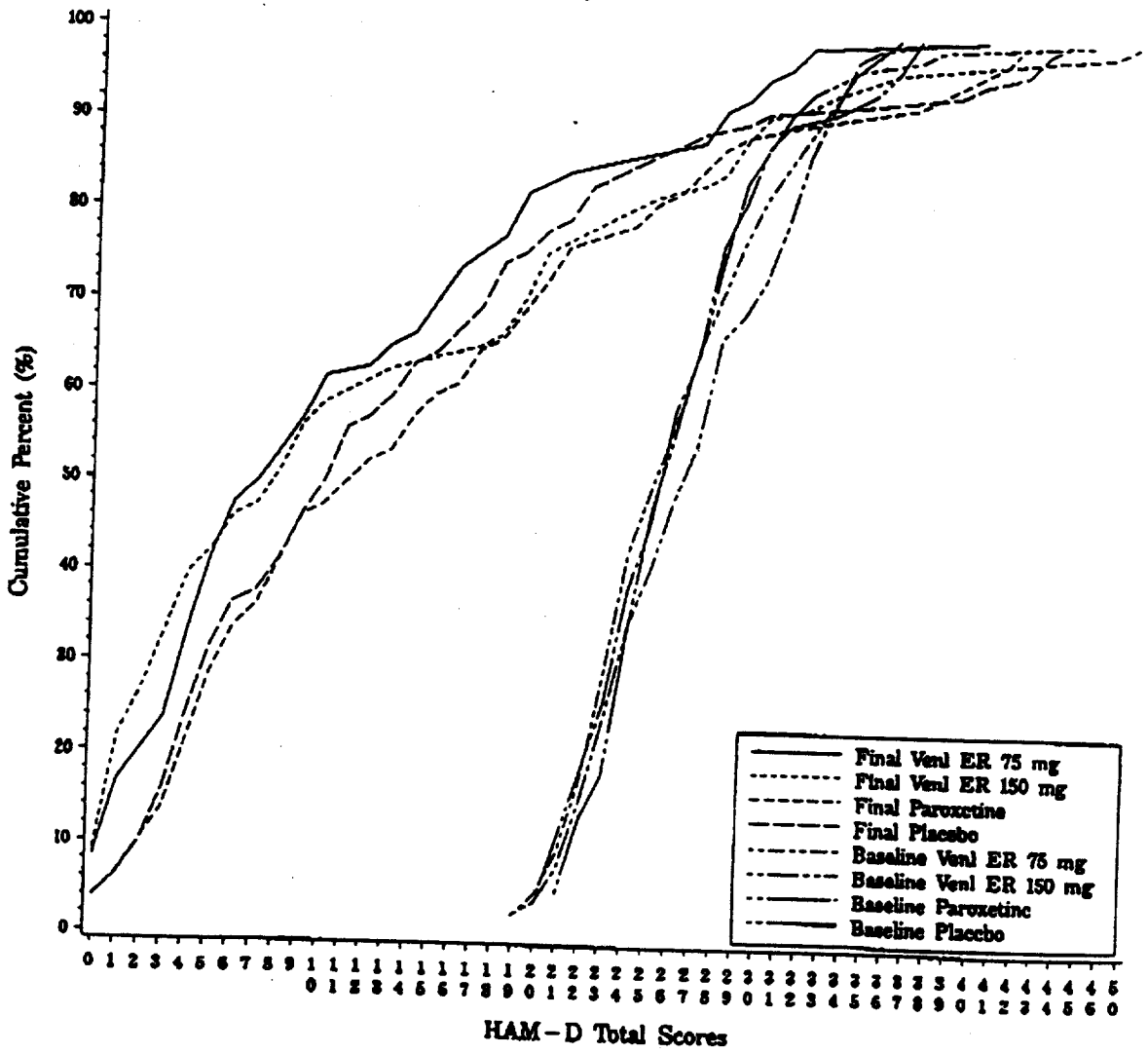


**FIGURE** 0.2.7

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

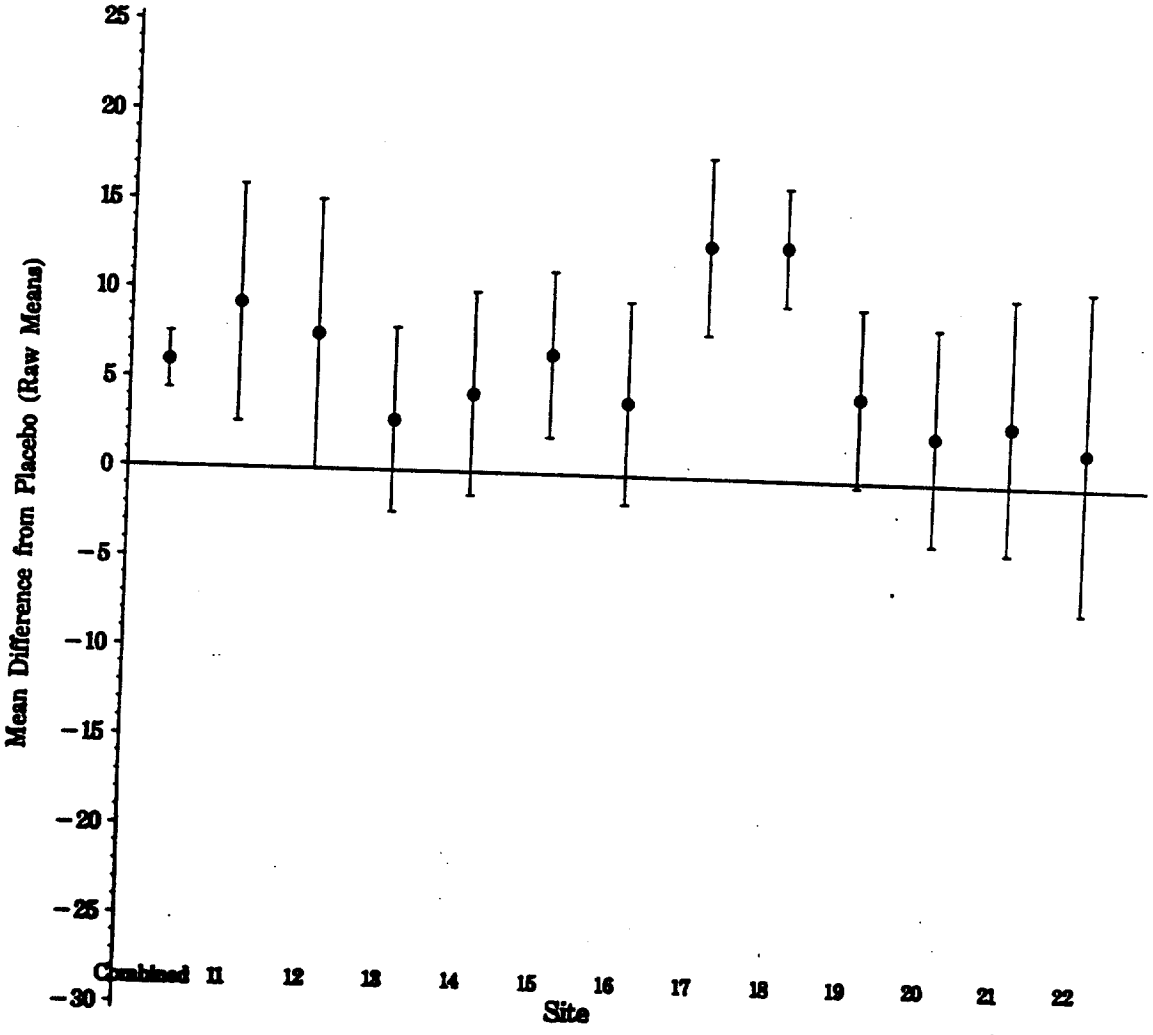


**FIGURE 10.2.8**

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

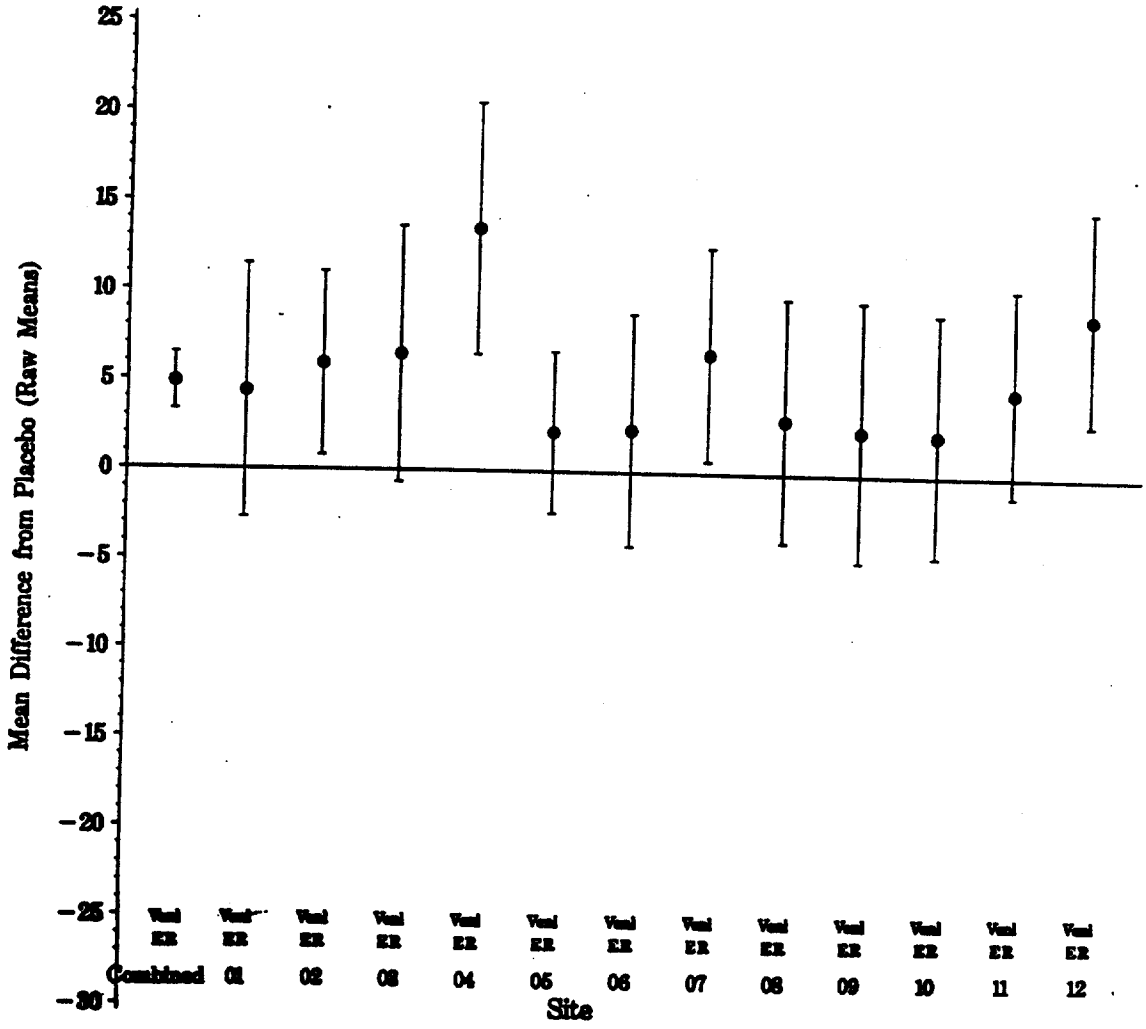


**FIGURE** 0.2.9

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

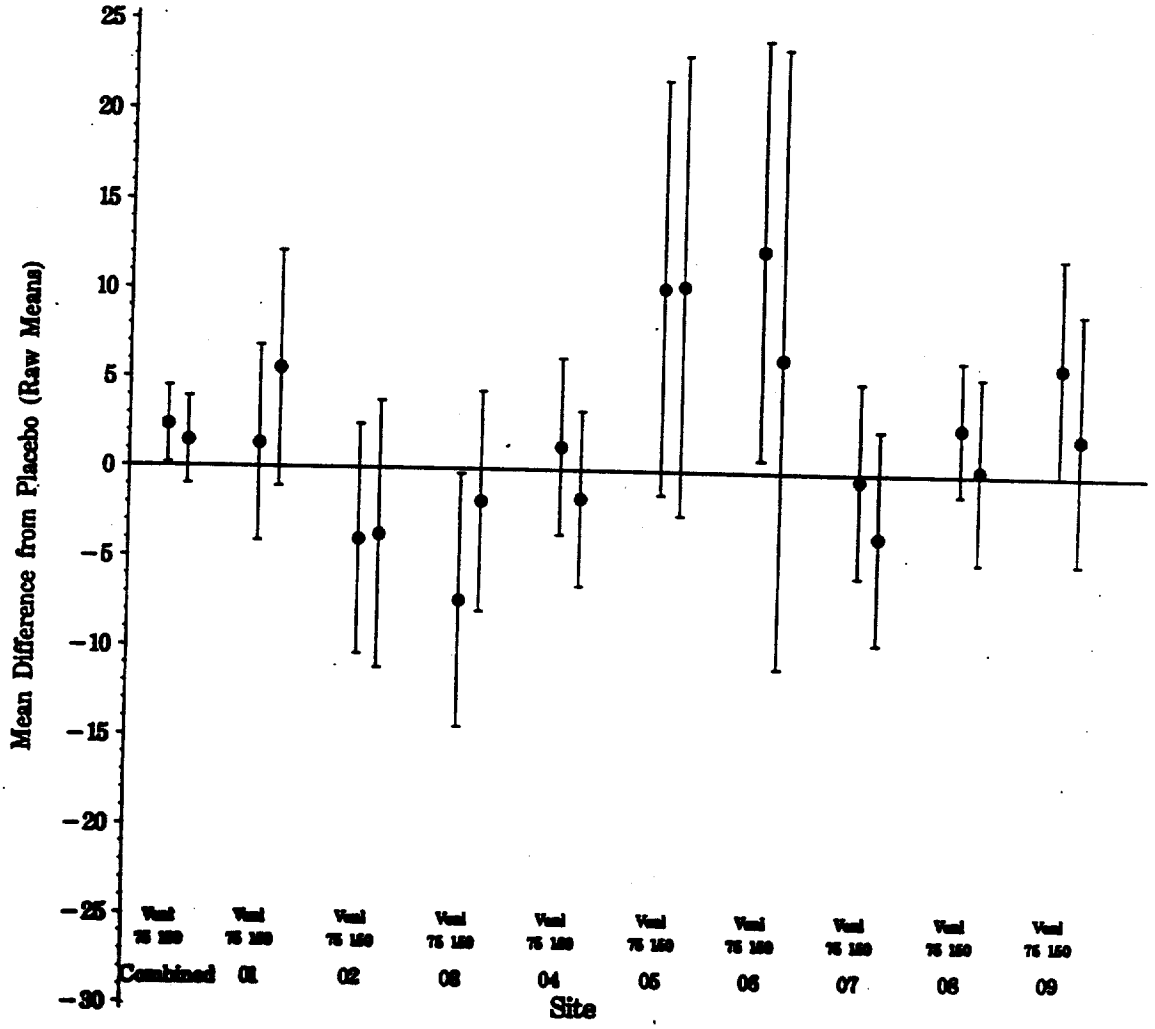


TABLE 1.1.1

208-US

PATIENT STATUS OVER TIME FOR ALL RANDOMIZED PATIENTS WITH DATA: NUMBER OF PATIENTS

| Time (week) | ---------Placebo-------- | | | | -----Venlafaxine ER------ | | | | -------Venlafaxine IR----- | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | C[a] | D[b] | CD[c] | No. | C | D | CD | No. | C | D | CD |
| Randomized patients with data | 100 | | | | 97 | | | | 96 | | | |
| Intent-to-treat patients[d] | 99 | | | | 92 | | | | 87 | | | |
| 1 | | 94 | 6 | 6 | | 90 | 7 | 7 | | 83 | 13 | 13 |
| 2 | | 88 | 6 | 12 | | 86 | 4 | 11 | | 80 | 3 | 16 |
| 3 | | 87 | 1 | 13 | | 82 | 4 | 15 | | 76 | 4 | 20 |
| 4 | | 82 | 5 | 18 | | 81 | 1 | 16 | | 72 | 4 | 24 |
| 5 | | 79 | 3 | 21 | | 80 | 1 | 17 | | 71 | 1 | 25 |
| 6 | | 74 | 5 | 26 | | 77 | 3 | 20 | | 66 | 5 | 30 |
| 7 | | 73 | 1 | 27 | | 77 | 0 | 20 | | 65 | 1 | 31 |
| 8 | | 72 | 1 | 28 | | 73 | 4 | 24 | | 63 | 2 | 33 |
| 9 | | 70 | 2 | 30 | | 73 | 0 | 24 | | 62 | 1 | 34 |
| 10 | | 65 | 5 | 35 | | 73 | 0 | 24 | | 59 | 3 | 37 |
| 11 | | 63 | 2 | 37 | | 71 | 2 | 26 | | 59 | 0 | 37 |
| 12 | | 60 | 3 | 40 | | 70 | 1 | 27 | | 58 | 1 | 38 |
| >12 | | 59 | 1 | 41 | | 69 | 1 | 28 | | 58 | 0 | 38 |
| Total | | | - | 41 | | | - | 28 | | | - | 38 |

a: Number of patietns 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.
d: The 1 placebo-treated, 9 venlafaxine IR-treated, and 5 venlafaxine ER-treated patients who did not qualify as intent-to-treat patients (ie, did not have at least one primary evaluation while on therapy) are included in the number of patients who discontinued during week 1.

TABLE 1.1.2



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.

TABLE 1.1.3



NUMBER OF PATIENTS WHO DISCONTINUED PREMATURELY DURING EACH WEEK BY CATEGORY

| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 | | | Week 5 | | | Week 6-12 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reason | Pbo | ER | IR | Pbo | ER | IR | Pbo | ER | IR | Pbo | ER | IR | Pbo | ER | IR | Pbo | ER | IR |
| Adverse Event | 0 | 4 | 8 | 1 | 2 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 3 | 1 |
| Failed to Return | 2 | 1 | 4 | 2 | 0 | 1 | 1 | 2 | 1 | 2 | 1 | 1 | 1 | 0 | 0 | 8 | 5 | 7 |
| Patient Request | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Unsatisfactory Response/ Efficacy | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 1 | 0 | 0 | 7 | 1 | 4 |
| Protocol Violation | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Other medical event | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| Other non-medical event | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 | 0 | 0 |
| Total | 6 | 7 | 13 | 6 | 4 | 3 | 1 | 4 | 4 | 5 | 1 | 4 | 3 | 1 | 1 | 20 | 11 | 13 |

FIGURE 1-1,4

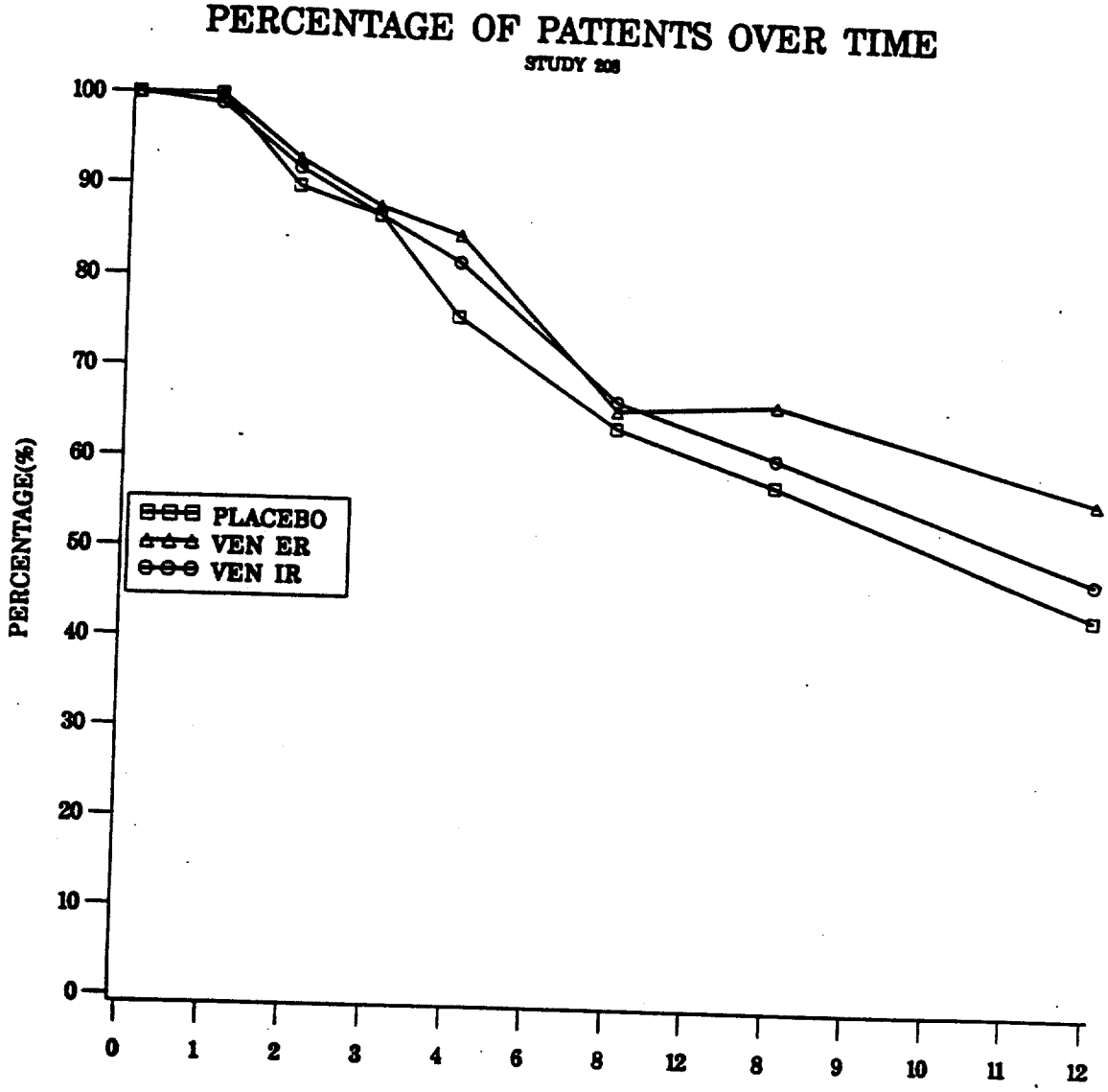

PERCENTAGE OF PATIENTS OVER TIME
STUDY 208
PERCENTAGE(%)
100
90
80
70
60
50
40
30
20
10
0
PLACEBO
VEN ER
VEN IR
0
1
2
3
4
6
8
12
8
9
10
11
12

TABLE 1.3.1

208-US

HAM-D TOTAL/COMPARISON BETWEEN THERAPY GROUPS/LOCF ANALYSIS

| Week On Therapy | Therapy Group | Number of Patients | Adj Change From Baseline | Adj Means (95% CL) | Diff Adj Means (95% CL) Pbo-Therapy | Diff Adj Means (95% CL) Ven ER-Therapy | ----P-VALUES---- F-test | ER[a] | IR[a] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | PBO | 99 | -4.07 | 20.44(19.49 21.40) | | | .60 | .32 | .78 |
| | VEN ER | 92 | -4.76 | 19.75(18.77,20.74) | 0.69(-0.68,2.06) | | | | .50 |
| | VEN IR | 87 | -4.27 | 20.24(19.21,21.27) | 0.20(-1.21,1.61) | -0.49(-1.92,0.93) | | | |
| 2 | PBO | 99 | -5.24 | 19.27(18.09,20.45) | | | .02 | .02 | .01 |
| | VEN ER | 92 | -7.27 | 17.24(16.02,18.46) | 2.03(0.33,3.72) | | | | .85 |
| | VEN IR | 87 | -7.44 | 17.07(15.80,18.35) | 2.20(0.46,3.94) | 0.17(-1.59,1.94) | | | |
| 3 | PBO | 99 | -7.41 | 17.11(15.86,18.35) | | | .14 | .05 | .20 |
| | VEN ER | 92 | -9.20 | 15.31(14.02,16.60) | 1.79(0.00,3.59) | | | | .54 |
| | VEN IR | 87 | -8.62 | 15.89(14.54,17.24) | 1.22(-0.63,3.06) | -0.58(-2.45,1.29) | | | |
| 4 | PBO | 99 | -8.48 | 16.03(14.71,17.36) | | | .003 | <.001 | .03 |
| | VEN ER | 92 | -11.79 | 12.72(11.35,14.09) | 3.31(1.40,5.22) | | | | .25 |
| | VEN IR | 87 | -10.63 | 13.88(12.45,15.32) | 2.15(0.19,4.11) | -1.16(-3.14,0.83) | | | |
| 6 | PBO | 99 | -8.85 | 15.66(14.35,16.98) | | | <.001 | <.001 | .003 |
| | VEN ER | 92 | -13.15 | 11.36(10.00,12.72) | 4.30(2.42,6.19) | | | | .17 |
| | VEN IR | 87 | -11.77 | 12.74(11.32,14.16) | 2.92(0.98,4.86) | -1.38(-3.55,0.58) | | | |
| 8 | PBO | 99 | -8.99 | 15.52(14.19,16.85) | | | <.001 | <.001 | .01 |
| | VEN ER | 92 | -13.67 | 10.84(9.46,12.22) | 4.68(2.76,6.59) | | | | .04 |
| | VEN IR | 87 | -11.61 | 12.90(11.46,14.34) | 2.62(0.65,4.58) | -2.06(-4.05,-0.07) | | | |
| 12 | PBO | 99 | -8.71 | 15.80(14.37,17.23) | | | <.001 | <.001 | .001 |
| | VEN ER | 92 | -15.11 | 9.40(7.92,10.88) | 6.40(4.34,8.45) | | | | .009 |
| | VEN IR | 87 | -12.25 | 12.26(10.71,13.80) | 3.54(1.43,5.65) | -2.86(-4.99,-0.72) | | | |

[a] pairwise comparison of therapies

BEST POSSIBLE COPY



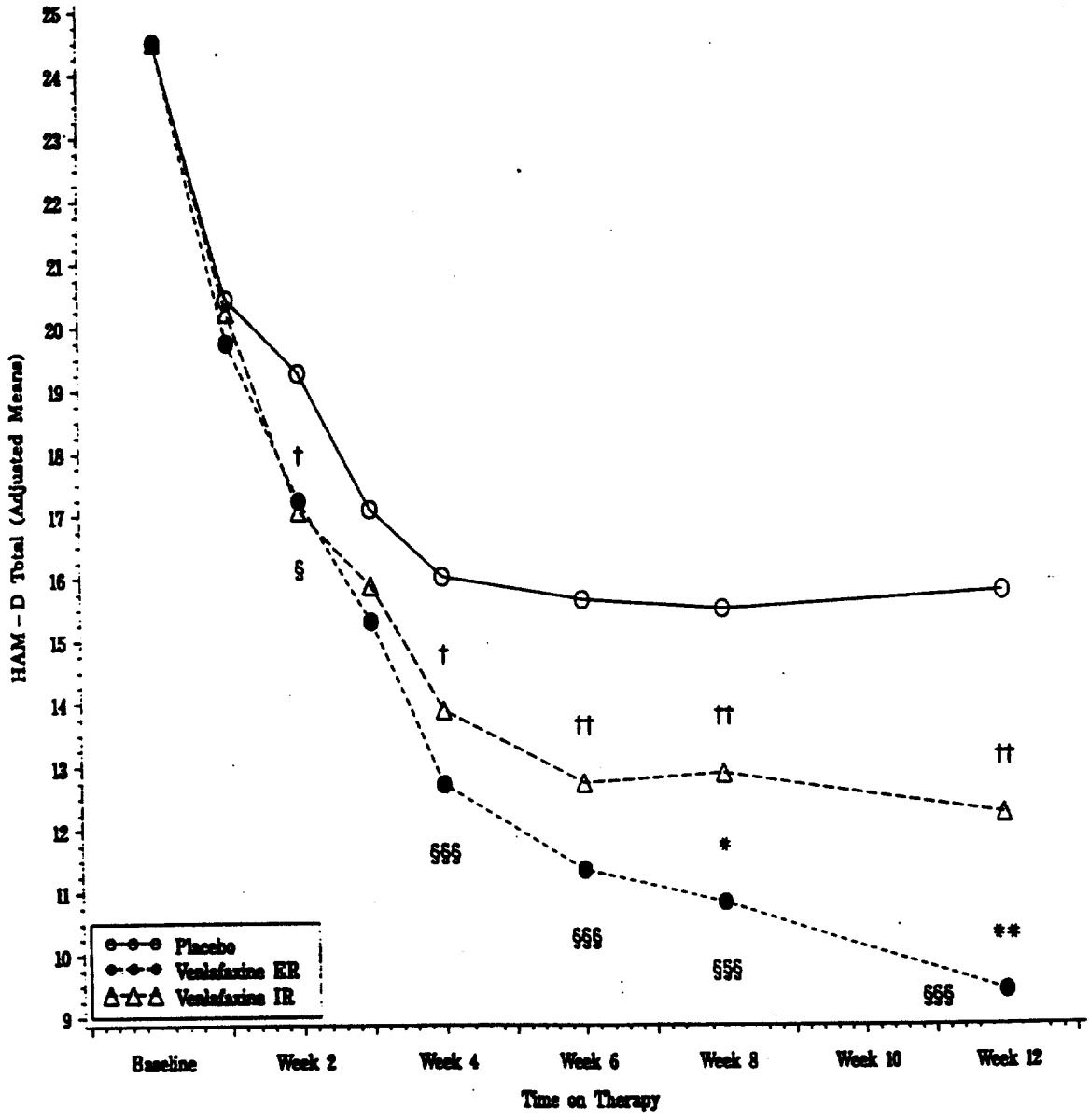
SUPPORTIVE TABLE 1.3.2 208-US

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

| Week On Therapy | Therapy Group | Number Of Patients | Adj Change From Baseline | Adj Means (95% CL) | Adj Means (95% CL) Plcb-Therapy | Adj Means (95% CL) Venl ER-Therapy | ----P-VALUES---- P-test | ER* | IR* |
|---|---|---|---|---|---|---|---|---|---|
| WEEK 1 | PLACEBO | 99 | -4.06 | 20.44 (19.48,21.39) | | | .61 | .32 | .72 |
| | VENLAFAXINE ER | 92 | -4.75 | 19.74 (18.76,20.73) | 0.69 (-0.68,2.06) | | | | .56 |
| | VENLAFAXINE IR | 86 | -4.32 | 20.18 (19.12,21.23) | 0.26 (-1.17,1.69) | -0.43 (-1.88,1.01) | | | |
| WEEK 2 | PLACEBO | 89 | -5.71 | 18.80 (17.56,20.04) | | | .08 | .08 | .04 |
| | VENLAFAXINE ER | 86 | -7.29 | 17.22 (15.95,18.48) | 1.58 (-0.19,3.35) | | | | .70 |
| | VENLAFAXINE IR | 80 | -7.65 | 16.86 (15.54,18.18) | 1.94 (0.12,3.75) | 0.36 (-1.47,2.19) | | | |
| WEEK 3 | PLACEBO | 86 | -8.08 | 16.34 (15.06,17.63) | | | .22 | .11 | .19 |
| | VENLAFAXINE ER | 81 | -9.63 | 14.79 (13.43,16.15) | 1.55 (-0.32,3.42) | | | | .78 |
| | VENLAFAXINE IR | 76 | -9.35 | 15.07 (13.67,16.47) | 1.27 (-0.63,3.18) | -0.28 (-2.23,1.67) | | | |
| WEEK 4 | PLACEBO | 75 | -9.39 | 15.09 (13.63,16.55) | | | .005 | .001 | .04 |
| | VENLAFAXINE ER | 78 | -12.80 | 11.68 (10.26,13.10) | 3.41 (1.37,5.44) | | | | .28 |
| | VENLAFAXINE IR | 71 | -11.65 | 12.83 (11.30,14.35) | 2.26 (0.15,4.37) | -1.15 (-3.23,0.93) | | | |
| WEEK 6 | PLACEBO | 63 | -9.73 | 14.62 (13.21,16.03) | | | <.001 | <.001 | <.001 |
| | VENLAFAXINE ER | 61 | -14.73 | 9.62 (8.09,11.14) | 5.00 (2.93,7.08) | | | | .57 |
| | VENLAFAXINE IR | 58 | -14.08 | 10.27 (8.61,11.93) | 4.35 (2.17,6.53) | -0.65 (-2.91,1.60) | | | |
| WEEK 8 | PLACEBO | 57 | -9.83 | 14.73 (13.16,16.31) | | | <.001 | <.001 | .002 |
| | VENLAFAXINE ER | 62 | -15.38 | 9.18 (7.64,10.72) | 5.55 (3.34,7.77) | | | | .20 |
| | VENLAFAXINE IR | 53 | -13.79 | 10.77 (8.91,12.62) | 3.97 (1.53,6.41) | -1.59 (-4.00,0.83) | | | |
| WEEK 12 | PLACEBO | 44 | -10.97 | 13.60 (11.45,15.74) | | | <.001 | <.001 | .01 |
| | VENLAFAXINE ER | 52 | -17.10 | 7.47 (5.70,9.23) | 6.13 (3.35,8.91) | | | | .20 |
| | VENLAFAXINE IR | 42 | -15.16 | 9.41 (7.07,11.75) | 4.19 (1.00,7.37) | -1.94 (-4.88,0.99) | | | |

FIGURE 1.3.3

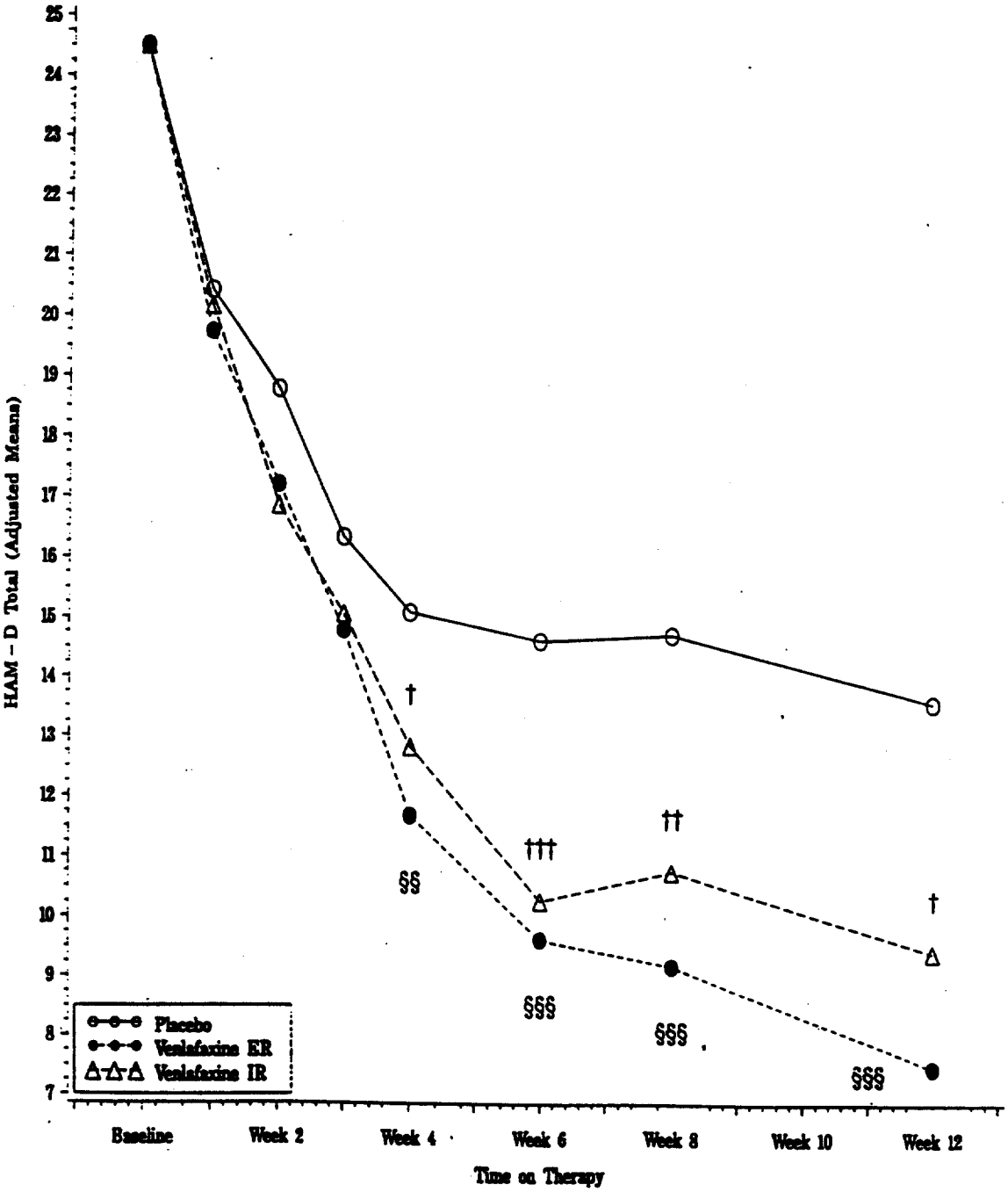
HAM-D TOTAL VS TIME ON THERAPY
LOCF ANALYSIS
STUDY 208




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 1.3.4

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 |

FIGURE 1.3.5

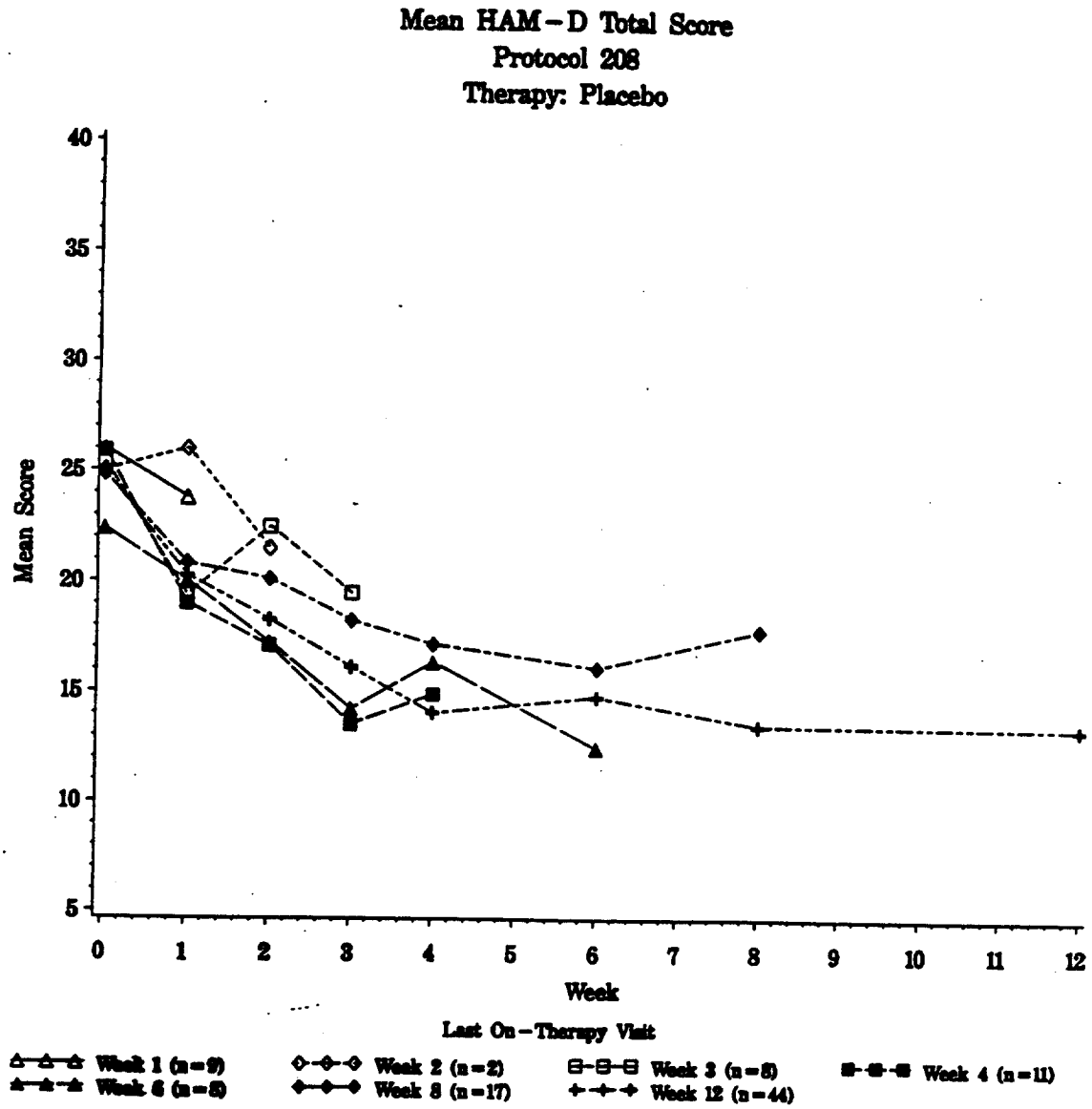

Mean HAM-D Total Score
Protocol 208
Therapy: Placebo
Mean Score
40
35
30
25
20
15
10
5
0
1
2
3
4
5
6
7
8
9
10
11
12
Week
Last On-Therapy Visit
Week 1 (n=9)
Week 2 (n=2)
Week 3 (n=8)
Week 4 (n=11)
Week 6 (n=8)
Week 8 (n=17)
Week 12 (n=44)

**FIGURE 1.3.6**

**Mean HAM-D Total Score**
**Protocol 208**
**Therapy: Venlafaxine ER**

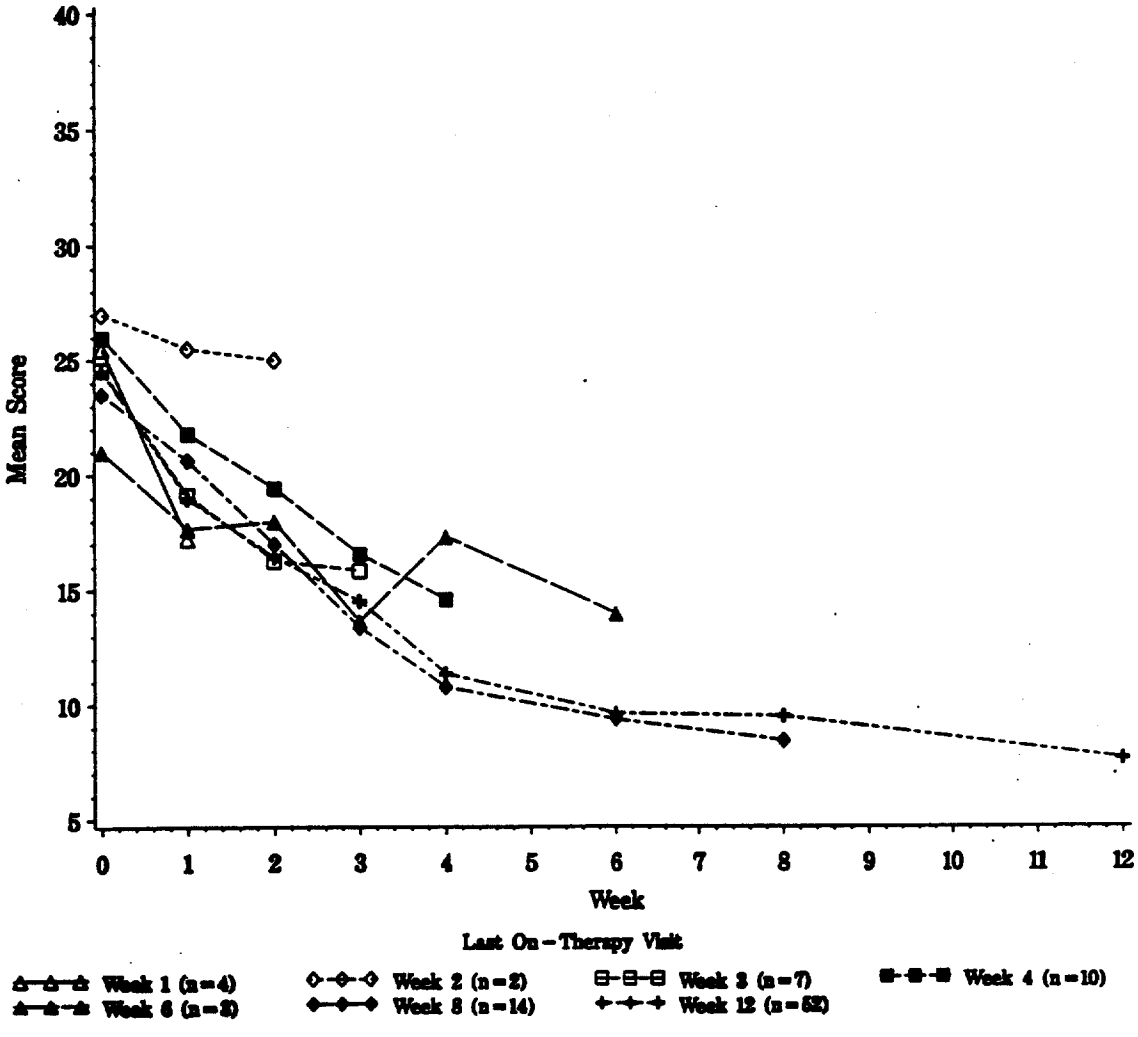


**FIGURE 1.3.7**

**Mean HAM-D Total Score**
**Protocol 208**
**Therapy: Venlafaxine IR**

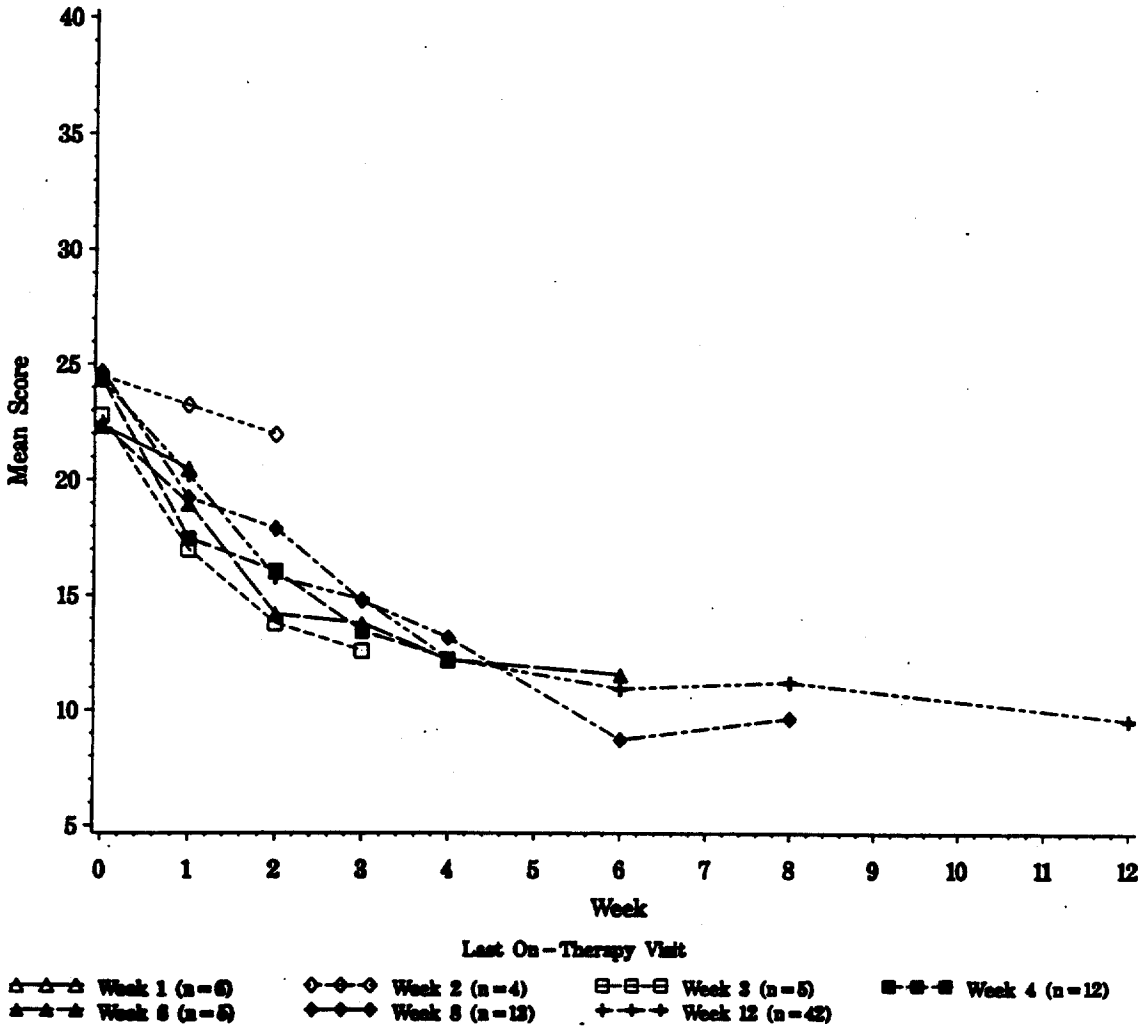


TABLE 1.4.1

208-US

DEPRESSED MOOD ITEM - HAM-D TOTAL/COMPARISON BETWEEN THERAPY GROUPS/LOCF ANALYSIS

| Week On Therapy | Therapy Group | Number of Patients | Adj Change From Baseline | Adj Means (95% CL) | Diff Adj Means (95% CL) Pbo-Therapy | Diff Adj Means (95% CL) Ven ER-Therapy | ----P-VALUES---- F-test | ER[a] | IR[a] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | PBO | 99 | -0.44 | 2.32(2.17 2.48) | | | .07 | .02 | .26 |
| | VEN ER | 92 | -0.70 | 2.06(1.90,2.22) | 0.26(0.04,0.48) | | | | .27 |
| | VEN IR | 87 | -0.57 | 2.19(2.02,2.36) | 0.13(-0.10,0.36) | -0.13(-0.36,0.10) | | | |
| 2 | PBO | 99 | -0.61 | 2.15(1.98,2.33) | | | .01 | .01 | .01 |
| | VEN ER | 92 | -0.94 | 1.82(1.64,2.00) | 0.33(0.08,0.58) | | | | .96 |
| | VEN IR | 87 | -0.94 | 1.82(1.63,2.01) | 0.34(0.08,0.59) | 0.01(-0.25,0.27) | | | |
| 3 | PBO | 99 | -0.92 | 1.84(1.66,2.02) | | | .02 | .005 | .07 |
| | VEN ER | 92 | -1.30 | 1.46(1.26,1.65) | 0.38(0.12,0.65) | | | | .35 |
| | VEN IR | 87 | -1.17 | 1.59(1.39,1.79) | 0.25(-0.02,0.52) | -0.13(-0.41,0.14) | | | |
| 4 | PBO | 99 | -0.95 | 1.81(1.62,1.99) | | | <.001 | <.001 | .003 |
| | VEN ER | 92 | -1.57 | 1.19(0.99,1.38) | 0.62(0.36,0.89) | | | | .14 |
| | VEN IR | 87 | -1.37 | 1.39(1.19,1.59) | 0.41(0.14,0.69) | -0.21(-0.49,0.07) | | | |
| 6 | PBO | 99 | -1.00 | 1.76(1.57,1.95) | | | <.001 | <.001 | <.001 |
| | VEN ER | 92 | -1.74 | 1.02(0.82,1.22) | 0.74(0.47,1.01) | | | | .17 |
| | VEN IR | 87 | -1.54 | 1.22(1.02,1.42) | 0.54(0.26,0.82) | -0.20(-0.48,0.08) | | | |
| 8 | PBO | 99 | -1.01 | 1.75(1.57,1.94) | | | <.001 | <.001 | .002 |
| | VEN ER | 92 | -1.68 | 1.08(0.89,1.28) | 0.67(0.40,0.94) | | | | .11 |
| | VEN IR | 87 | -1.45 | 1.31(1.11,1.52) | 0.44(0.16,0.72) | -0.23(-0.51,-0.05) | | | |
| 12 | PBO | 99 | -0.92 | 1.83(1.64,2.03) | | | <.001 | <.001 | <.001 |
| | VEN ER | 92 | -1.92 | 0.84(0.64,1.04) | 0.99(0.72,1.27) | | | | .04 |
| | VEN IR | 87 | -1.62 | 1.14(0.93,1.35) | 0.69(0.41,0.98) | -0.30(-0.59,-0.01) | | | |

a: pairwise comparison of therapies

SUPPORTIVE TABLE 1.4.2



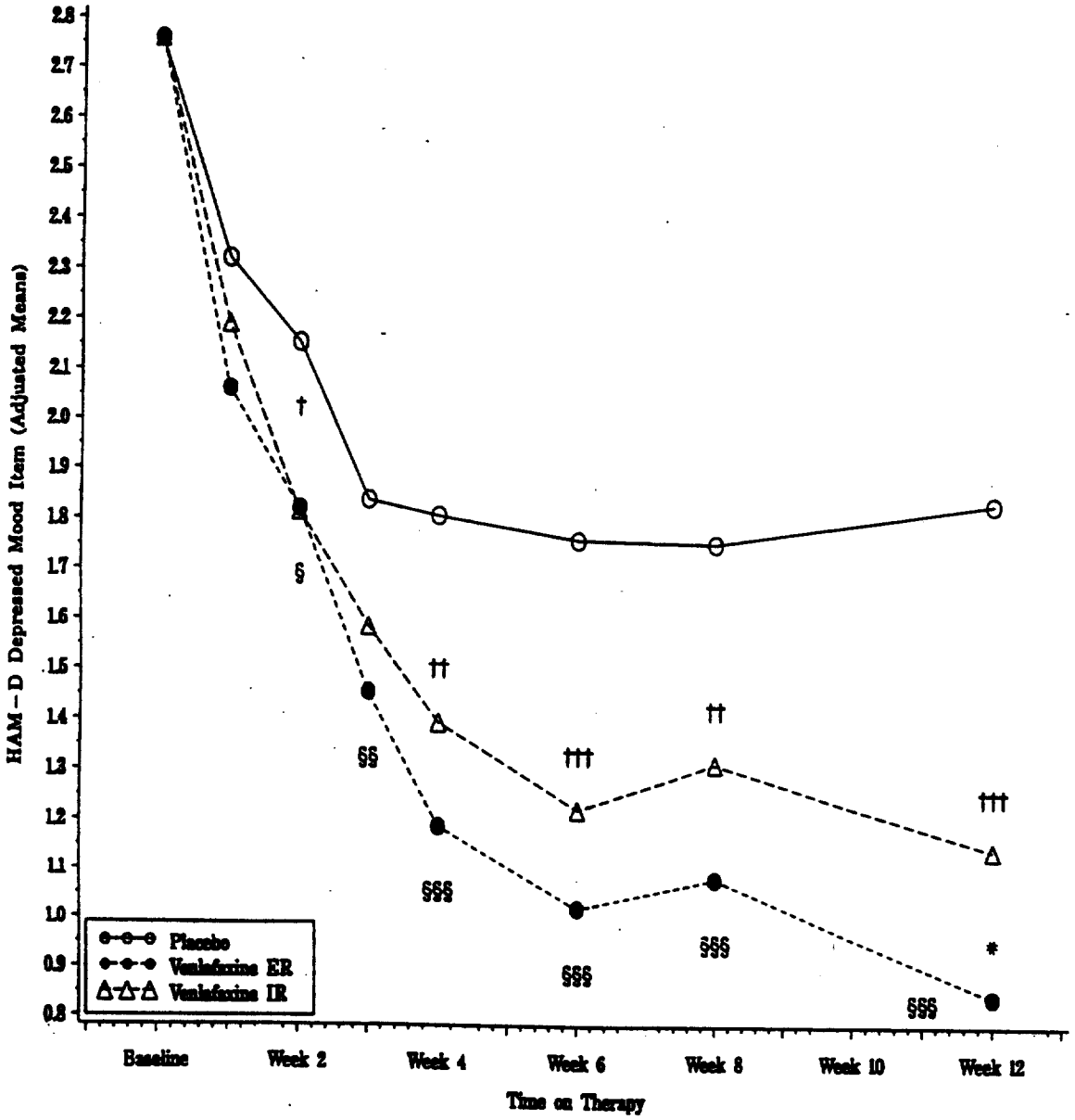
HAM-D DEPRESSED MOOD ITEM: INTENT-TO-TREAT COMPARISON BETWEEN THERAPY GROUPS - OBSERVED CASES ANALYSIS (ADJUSTED MEANS)

| Week On Therapy | Therapy Group | Number Of Patients | Adj Change From Baseline | Adj Means (95% CL) | Adj Means (95% CL) Plcb-Therapy | Adj Means (95% CL) Venl ER-Therapy | ----P-VALUES---- F-test | ER* | IR* |
|---|---|---|---|---|---|---|---|---|---|
| WEEK 1 | PLACEBO | 99 | -0.44 | 2.32 (2.17,2.48) | | | .07 | .02 | .22 |
| | VENLAFAXINE ER | 92 | -0.70 | 2.06 (1.90,2.22) | 0.26 (0.04,0.48) | | | | .34 |
| | VENLAFAXINE IR | 86 | -0.58 | 2.18 (2.01,2.35) | 0.15 (-0.09,0.38) | -0.12 (-0.35,0.12) | | | |
| WEEK 2 | PLACEBO | 89 | -0.66 | 2.11 (1.92,2.29) | | | .05 | .06 | .02 |
| | VENLAFAXINE ER | 86 | -0.91 | 1.86 (1.67,2.05) | 0.25 (-0.01,0.51) | | | | .60 |
| | VENLAFAXINE IR | 80 | -0.98 | 1.79 (1.59,1.98) | 0.32 (0.05,0.59) | 0.07 (-0.20,0.34) | | | |
| WEEK 3 | PLACEBO | 86 | -1.00 | 1.76 (1.56,1.95) | | | .07 | .03 | .09 |
| | VENLAFAXINE ER | 81 | -1.32 | 1.44 (1.23,1.65) | 0.32 (0.03,0.60) | | | | .66 |
| | VENLAFAXINE IR | 76 | -1.25 | 1.51 (1.29,1.72) | 0.25 (-0.04,0.54) | -0.07 (-0.37,0.23) | | | |
| WEEK 4 | PLACEBO | 75 | -1.09 | 1.69 (1.47,1.90) | | | <.001 | <.001 | .01 |
| | VENLAFAXINE ER | 78 | -1.67 | 1.11 (0.90,1.32) | 0.58 (0.28,0.87) | | | | .28 |
| | VENLAFAXINE IR | 71 | -1.50 | 1.28 (1.05,1.50) | 0.41 (0.10,0.72) | -0.17 (-0.47,0.14) | | | |
| WEEK 6 | PLACEBO | 63 | -1.13 | 1.63 (1.42,1.83) | | | <.001 | <.001 | <.001 |
| | VENLAFAXINE ER | 61 | -1.96 | 0.80 (0.58,1.02) | 0.82 (0.52,1.13) | | | | .54 |
| | VENLAFAXINE IR | 58 | -1.86 | 0.90 (0.66,1.14) | 0.72 (0.41,1.04) | -0.10 (-0.43,0.22) | | | |
| WEEK 8 | PLACEBO | 57 | -1.11 | 1.65 (1.41,1.89) | | | <.001 | <.001 | <.001 |
| | VENLAFAXINE ER | 62 | -1.80 | 0.96 (0.72,1.19) | 0.70 (0.36,1.04) | | | | .88 |
| | VENLAFAXINE IR | 53 | -1.78 | 0.99 (0.70,1.27) | 0.67 (0.30,1.04) | -0.03 (-0.40,0.34) | | | |
| WEEK 12 | PLACEBO | 44 | -1.27 | 1.52 (1.23,1.81) | | | <.001 | <.001 | <.001 |
| | VENLAFAXINE ER | 52 | -2.17 | 0.62 (0.38,0.86) | 0.90 (0.52,1.28) | | | | .67 |
| | VENLAFAXINE IR | 42 | -2.08 | 0.71 (0.40,1.02) | 0.81 (0.38,1.24) | -0.09 (-0.48,0.31) | | | |

* pairwise comparisons of therapies

FIGURE 1.4.3

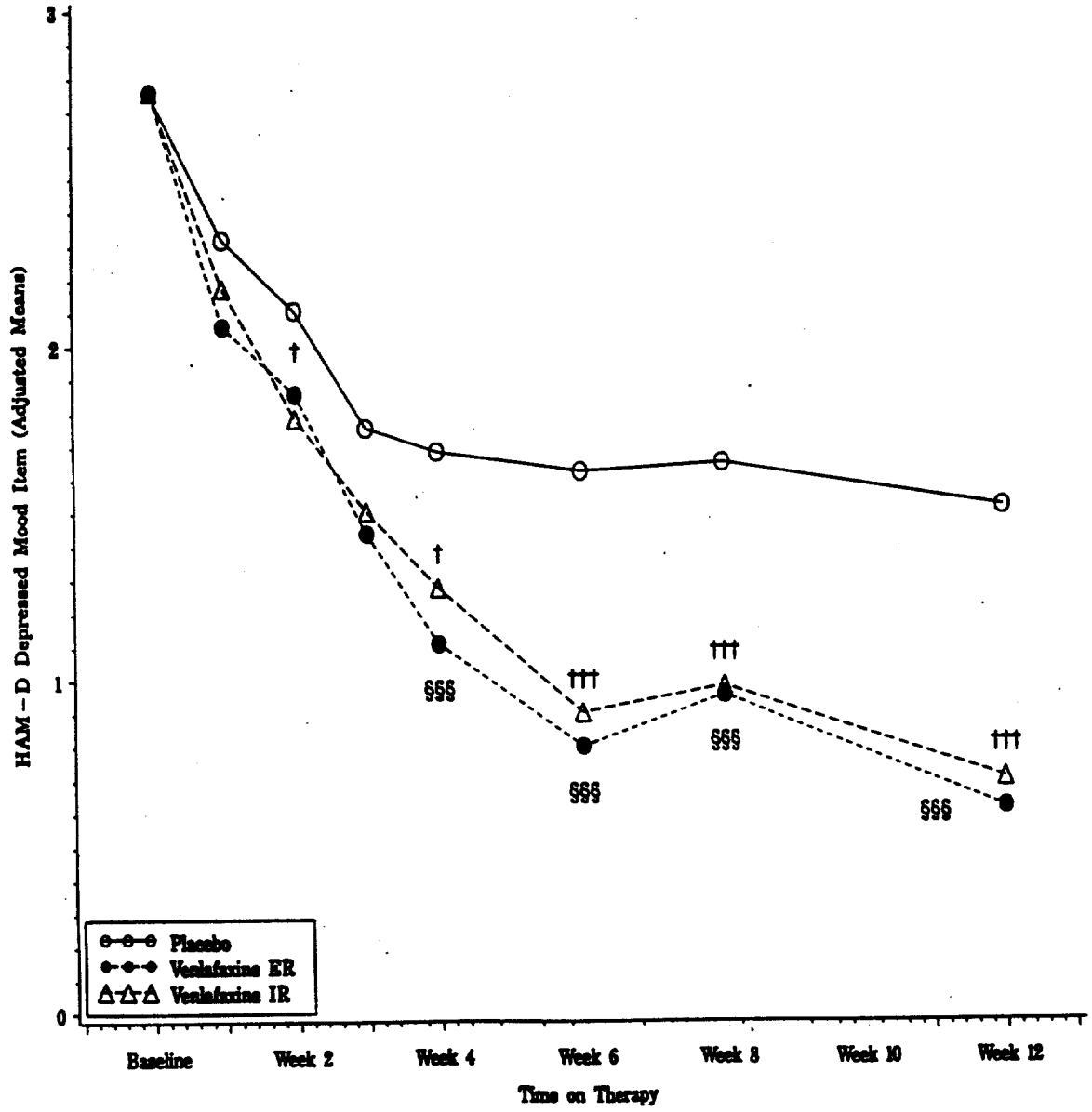
HAM-D DEPRESSED MOOD ITEM VS TIME ON THERAPY
LOCF ANALYSIS
STUDY 208




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

TABLE 1.5.1 208-US

CGI SEVERITY TOTAL/COMPARISON BETWEEN THERAPY GROUPS/LOCF ANALYSIS

| Week On Therapy | Therapy Group | Number of Patients | Adj Change From Baseline | Adj Means (95% CL) | Diff Adj Means (95% CL) Pbo-Therapy | Diff Adj Means (95% CL) Ven ER-Therapy | ----P-VALUES---- F-test | ER[a] | IR[a] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | PBO | 99 | -0.35 | 3.85(3.74 3.96) | | | .67 | .72 | .57 |
| | VEN ER | 92 | -0.38 | 3.82(3.70,3.93) | 0.03(-0.13,0.19) | | | | .37 |
| | VEN IR | 87 | -0.31 | 3.90(3.77,4.02) | -0.05(-0.21,0.12) | -0.08(-0.24,0.09) | | | |
| 2 | PBO | 99 | -0.50 | 3.70(3.54,3.86) | | | .16 | .07 | .15 |
| | VEN ER | 92 | -0.72 | 3.49(3.32,3.65) | 0.21(-0.02,0.45) | | | | .77 |
| | VEN IR | 87 | -0.68 | 3.52(3.35,3.70) | 0.18(-0.06,0.42) | -0.04(-0.28,0.21) | | | |
| 3 | PBO | 99 | -0.76 | 3.44(3.25,3.63) | | | .10 | .03 | .48 |
| | VEN ER | 92 | -1.06 | 3.14(2.95,3.34) | 0.30(0.03,0.57) | | | | .18 |
| | VEN IR | 87 | -0.86 | 3.34(3.13,3.55) | 0.10(-0.18,0.38) | -0.20(-0.48,0.09) | | | |
| 4 | PBO | 99 | -0.95 | 3.25(3.04,3.46) | | | .005 | .001 | .13 |
| | VEN ER | 92 | -1.45 | 2.75(2.53,2.96) | 0.50(0.20,0.80) | | | | .10 |
| | VEN IR | 87 | -1.19 | 3.01(2.79,3.24) | 0.24(-0.07,0.55) | -0.26(-0.57,0.05) | | | |
| 6 | PBO | 99 | -1.07 | 3.13(2.92,3.34) | | | .002 | <.001 | .02 |
| | VEN ER | 92 | -1.62 | 2.58(2.36,2.80) | 0.55(0.25,0.86) | | | | .29 |
| | VEN IR | 87 | -1.45 | 2.75(2.52,2.98) | 0.38(0.07,0.70) | -0.17(-0.49,0.15) | | | |
| 8 | PBO | 99 | -1.09 | 3.11(2.89,3.33) | | | <.001 | <.001 | .02 |
| | VEN ER | 92 | -1.84 | 2.36(2.14,2.58) | 0.75(0.44,1.06) | | | | .03 |
| | VEN IR | 87 | -1.47 | 2.73(2.50,2.97) | 0.38(0.06,0.70) | -0.37(-0.69,-0.05) | | | |
| 12 | PBO | 99 | -1.02 | 3.18(2.96,3.40) | | | <.001 | <.001 | .002 |
| | VEN ER | 92 | -2.12 | 2.08(1.86,2.31) | 1.10(0.78,1.41) | | | | <.001 |
| | VEN IR | 87 | -1.53 | 2.67(2.43,2.91) | 0.51(0.18,0.84) | -0.59(-0.92,-0.26) | | | |

a: pairwise comparison of therapies

SUPPORTIVE TABLE 1.5.2 208-US

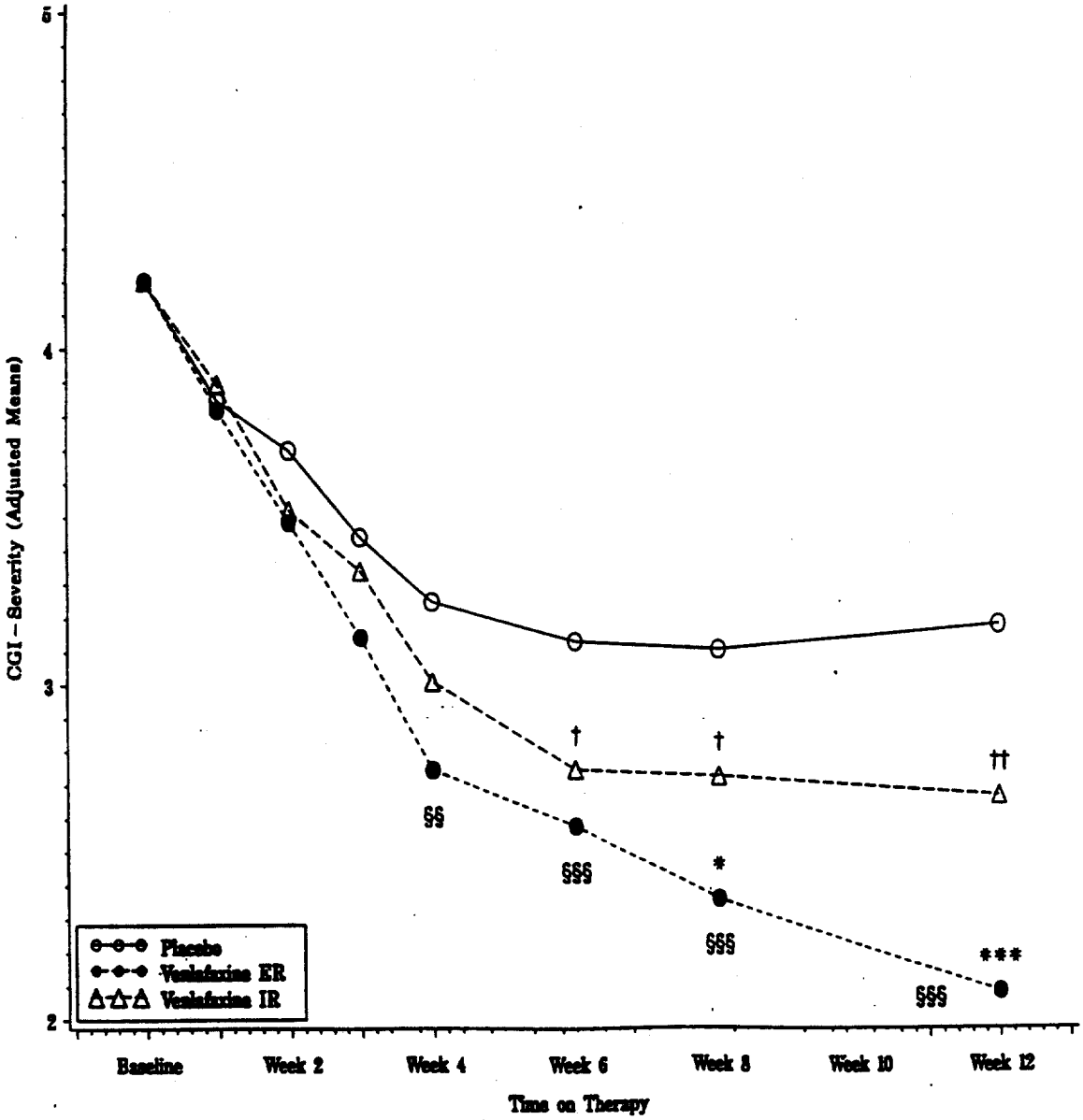
CGI SEVERITY: INTENT-TO-TREAT COMPARISON BETWEEN THERAPY GROUPS - OBSERVED CASES ANALYSIS (ADJUSTED MEANS)

| Week On Therapy | Therapy Group | Number Of Patients | Adj Change From Baseline | Adj Means (95% CL) | Adj Means (95% CL) Plcb-Therapy | Adj Means (95% CL) Venl ER-Therapy | ----P-VALUES---- F-test | ER* | IR* |
|---|---|---|---|---|---|---|---|---|---|
| WEEK 1 | PLACEBO | 99 | -0.35 | 3.85 (3.74,3.96) | | | .67 | .72 | .57 |
| | VENLAFAXINE ER | 92 | -0.38 | 3.82 (3.70,3.93) | 0.03 (-0.13,0.19) | | | | .37 |
| | VENLAFAXINE IR | 87 | -0.31 | 3.90 (3.77,4.02) | -0.05 (-0.21,0.12) | -0.08 (-0.24,0.09) | | | |
| WEEK 2 | PLACEBO | 99 | -0.50 | 3.70 (3.54,3.86) | | | .16 | .07 | .15 |
| | VENLAFAXINE ER | 92 | -0.72 | 3.49 (3.32,3.65) | 0.21 (-0.02,0.45) | | | | .77 |
| | VENLAFAXINE IR | 87 | -0.68 | 3.52 (3.35,3.70) | 0.18 (-0.06,0.42) | -0.04 (-0.28,0.21) | | | |
| WEEK 3 | PLACEBO | 99 | -0.76 | 3.44 (3.25,3.63) | | | .10 | .03 | .48 |
| | VENLAFAXINE ER | 92 | -1.06 | 3.14 (2.95,3.34) | 0.30 (0.03,0.57) | | | | .18 |
| | VENLAFAXINE IR | 87 | -0.86 | 3.34 (3.13,3.55) | 0.10 (-0.18,0.38) | -0.20 (-0.48,0.09) | | | |
| WEEK 4 | PLACEBO | 99 | -0.95 | 3.25 (3.04,3.46) | | | .005 | .001 | .13 |
| | VENLAFAXINE ER | 92 | -1.45 | 2.75 (2.53,2.96) | 0.50 (0.20,0.80) | | | | .10 |
| | VENLAFAXINE IR | 87 | -1.19 | 3.01 (2.79,3.24) | 0.24 (-0.07,0.55) | -0.26 (-0.57,0.05) | | | |
| WEEK 6 | PLACEBO | 99 | -1.07 | 3.13 (2.92,3.34) | | | .002 | <.001 | .02 |
| | VENLAFAXINE ER | 92 | -1.62 | 2.58 (2.36,2.80) | 0.55 (0.25,0.86) | | | | .29 |
| | VENLAFAXINE IR | 87 | -1.45 | 2.75 (2.52,2.98) | 0.38 (0.07,0.70) | -0.17 (-0.49,0.15) | | | |
| WEEK 8 | PLACEBO | 99 | -1.09 | 3.11 (2.89,3.33) | | | <.001 | <.001 | .02 |
| | VENLAFAXINE ER | 92 | -1.84 | 2.36 (2.14,2.58) | 0.75 (0.44,1.06) | | | | .03 |
| | VENLAFAXINE IR | 87 | -1.47 | 2.73 (2.50,2.97) | 0.38 (0.06,0.70) | -0.37 (-0.69,-0.05) | | | |
| WEEK 12 | PLACEBO | 99 | -1.02 | 3.18 (2.96,3.40) | | | <.001 | <.001 | .002 |
| | VENLAFAXINE ER | 92 | -2.12 | 2.08 (1.86,2.31) | 1.10 (0.78,1.41) | | | | <.001 |
| | VENLAFAXINE IR | 87 | -1.53 | 2.67 (2.43,2.91) | 0.51 (0.18,0.84) | -0.59 (-0.92,-0.26) | | | |

* pairwise comparisons of therapies

FIGURE 1.5.3

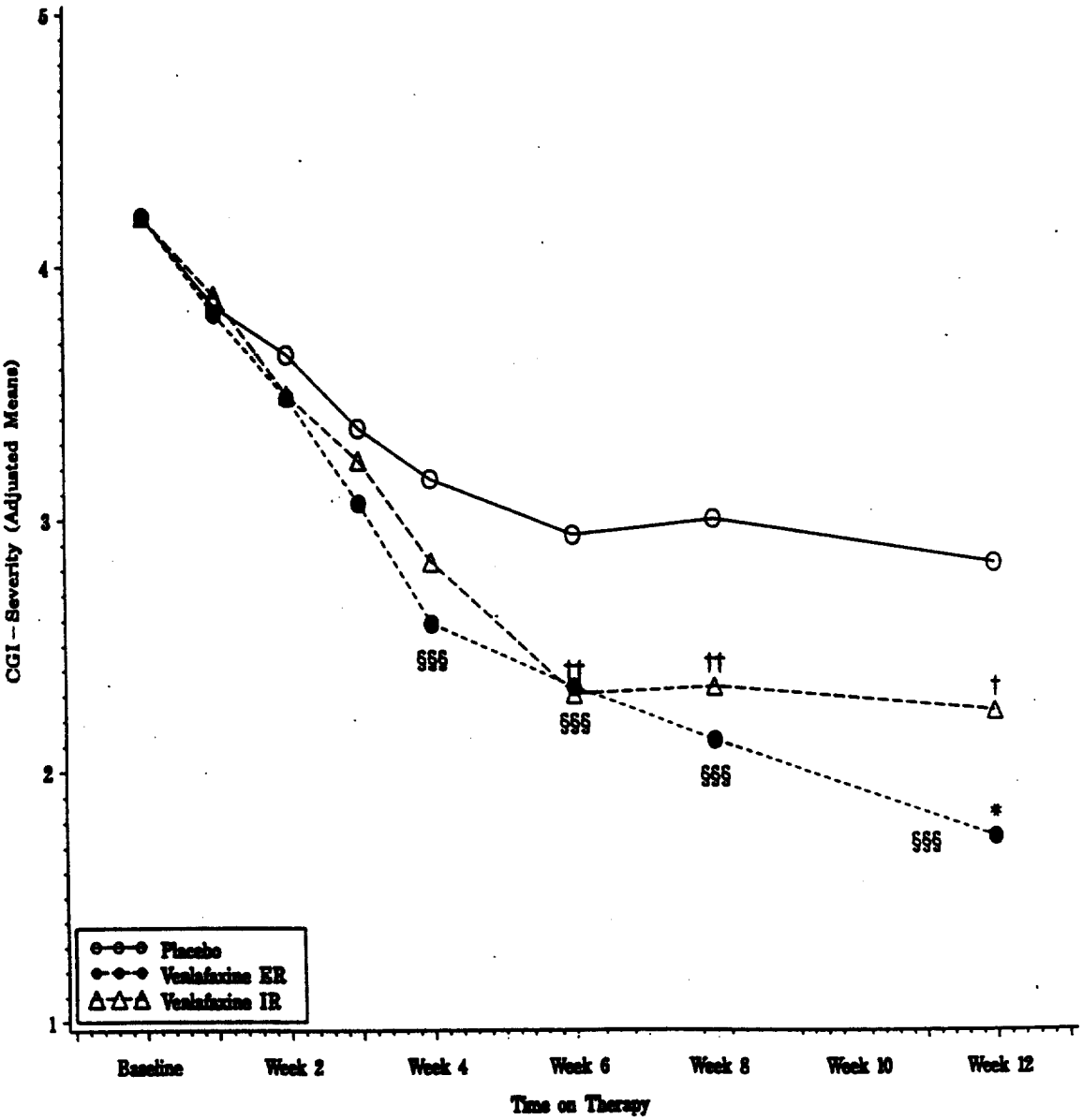
CGI-SEVERITY SCORES VS TIME ON THERAPY
LOCF ANALYSIS
STUDY 208




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 |

TABLE 1.6.1

MADRS TOTAL/COMPARISON BETWEEN THERAPY GROUPS/LOCF ANALYSIS

| Week On Therapy | Therapy Group | Number of Patients | Adj Change From Baseline | Adj Means (95% CL) | Diff Adj Means (95% CL) Pbo-Therapy | Diff Adj Means (95% CL) Ven ER-Therapy | ----P-VALUES---- F-test | ER[a] | IR[a] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | PBO | 99 | -3.79 | 22.78(21.62 23.93) | | | .53 | .59 | .26 |
| | VEN ER | 92 | -4.25 | 22.33(21.13,23.52) | 0.45(-1.21,2.12) | | | | .55 |
| | VEN IR | 87 | -4.77 | 21.80(20.55,23.05) | 0.98(-0.72,2.68) | 0.53(-1.21,2.26) | | | |
| 2 | PBO | 99 | -4.99 | 21.59(20.16,23.01) | | | .12 | .17 | .05 |
| | VEN ER | 92 | -6.43 | 20.14(18.66,21.62) | 1.45(-0.61,3.50) | | | | .53 |
| | VEN IR | 87 | -7.12 | 19.45(17.90,21.00) | 2.14(0.03,4.24) | 0.69(-1.45,2.83) | | | |
| 3 | PBO | 99 | -6.71 | 19.87(18.41,21.32) | | | .03 | .02 | .02 |
| | VEN ER | 92 | -9.16 | 17.41(15.91,18.92) | 2.45(0.36,4.54) | | | | .92 |
| | VEN IR | 87 | -9.27 | 17.30(15.73,18.88) | 2.56(0.42,4.70) | 0.11(-2.07,2.29) | | | |
| 4 | PBO | 99 | -7.89 | 18.68(17.08,20.28) | | | <.001 | <.001 | .01 |
| | VEN ER | 92 | -12.47 | 14.10(12.44,15.76) | 4.58(2.27,6.89) | | | | .24 |
| | VEN IR | 87 | -11.03 | 15.54(13.80,17.28) | 3.14(0.78,5.50) | -1.44(-3.84,0.97) | | | |
| 6 | PBO | 99 | -8.81 | 17.76(16.15,19.37) | | | <.001 | <.001 | <.001 |
| | VEN ER | 92 | -14.22 | 12.35(10.68,14.03) | 5.40(3.08,7.72) | | | | .30 |
| | VEN IR | 87 | -12.95 | 13.62(11.88,15.37) | 4.13(1.76,6.51) | -1.27(-3.69,1.15) | | | |
| 8 | PBO | 99 | -8.65 | 17.93(16.33,19.52) | | | <.001 | <.001 | <.001 |
| | VEN ER | 92 | -14.55 | 12.02(10.36,13.68) | 5.90(3.60,8.21) | | | | .15 |
| | VEN IR | 87 | -12.80 | 13.77(12.04,15.51) | 4.15(1.79,6.51) | -1.75(-4.15,0.65) | | | |
| 12 | PBO | 99 | -8.29 | 18.28(16.55,20.01) | | | <.001 | <.001 | <.001 |
| | VEN ER | 92 | -15.97 | 10.60(8.80,12.40) | 7.68(5.19,10.18) | | | | .04 |
| | VEN IR | 87 | -13.25 | 13.33(11.45,15.20) | 4.96(2.41,7.51) | -2.73(-5.32,-0.13) | | | |

a: pairwise comparison of therapies

SUPPORTIVE TABLE 1.6.2

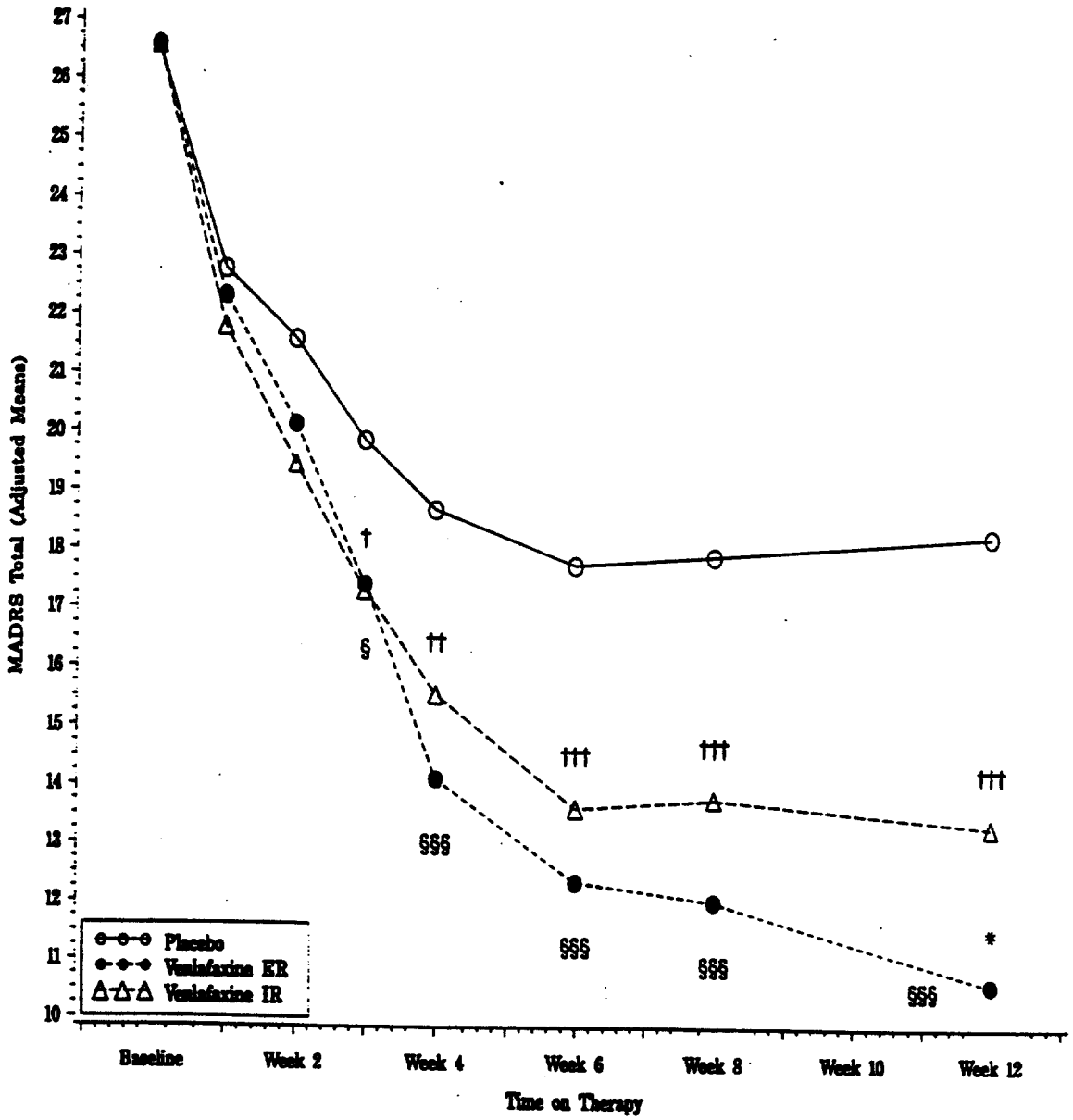
MADRS TOTAL: INTENT-TO-TREAT COMPARISON BETWEEN THERAPY GROUPS - OBSERVED CASES ANALYSIS (ADJUSTED MEANS)

| Week On Therapy | Therapy Group | Number Of Patients | Adj Change From Baseline | Adj Means (95% CL) | Adj Means (95% CL) Plcb-Therapy | Adj Means (95% CL) Venl ER-Therapy | ----P-VALUES---- F-test | ER* | IR* |
|---|---|---|---|---|---|---|---|---|---|
| WEEK 1 | PLACEBO | 99 | -3.79 | 22.77 (21.62,23.93) | | | | | |
| | VENLAFAXINE ER | 92 | -4.24 | 22.32 (21.12,23.52) | 0.45 (-1.21,2.12) | | .46 | .59 | .22 |
| | VENLAFAXINE IR | 86 | -4.88 | 21.68 (20.40,22.97) | 1.09 (-0.64,2.82) | 0.64 (-1.12,2.39) | | | .48 |
| WEEK 2 | PLACEBO | 89 | -5.30 | 21.26 (19.73,22.78) | | | | | |
| | VENLAFAXINE ER | 86 | -6.41 | 20.14 (18.58,21.70) | 1.11 (-1.07,3.29) | | .21 | .32 | .08 |
| | VENLAFAXINE IR | 80 | -7.32 | 19.23 (17.61,20.86) | 2.02 (-0.21,4.25) | 0.91 (-1.34,3.16) | | | .43 |
| WEEK 3 | PLACEBO | 86 | -7.15 | 19.37 (17.85,20.90) | | | | | |
| | VENLAFAXINE ER | 81 | -9.65 | 16.88 (15.26,18.50) | 2.50 (0.27,4.72) | | .02 | .03 | .01 |
| | VENLAFAXINE IR | 76 | -10.06 | 16.47 (14.80,18.14) | 2.91 (0.65,5.17) | 0.41 (-1.92,2.74) | | | .73 |
| WEEK 4 | PLACEBO | 75 | -8.75 | 17.80 (15.99,19.61) | | | | | |
| | VENLAFAXINE ER | 78 | -13.59 | 12.96 (11.20,14.73) | 4.84 (2.31,7.37) | | <.001 | <.001 | .02 |
| | VENLAFAXINE IR | 71 | -11.99 | 14.56 (12.66,16.45) | 3.24 (0.62,5.86) | -1.59 (-4.19,1.00) | | | .23 |
| WEEK 6 | PLACEBO | 63 | -9.81 | 16.63 (14.85,18.41) | | | | | |
| | VENLAFAXINE ER | 61 | -16.11 | 10.33 (8.39,12.28) | 6.30 (3.66,8.93) | | <.001 | <.001 | <.001 |
| | VENLAFAXINE IR | 58 | -15.43 | 11.01 (8.89,13.13) | 5.62 (2.85,8.39) | -0.68 (-3.56,2.21) | | | .65 |
| WEEK 8 | PLACEBO | 57 | -9.36 | 17.37 (15.36,19.38) | | | | | |
| | VENLAFAXINE ER | 62 | -16.65 | 10.07 (8.09,12.06) | 7.30 (4.47,10.12) | | <.001 | <.001 | <.001 |
| | VENLAFAXINE IR | 53 | -15.20 | 11.53 (9.14,13.92) | 5.84 (2.72,8.96) | -1.46 (-4.57,1.65) | | | .36 |
| WEEK 12 | PLACEBO | 44 | -11.27 | 15.35 (12.57,18.12) | | | | | |
| | VENLAFAXINE ER | 52 | -18.23 | 8.38 (6.09,10.68) | 6.96 (3.37,10.56) | | .001 | <.001 | .02 |
| | VENLAFAXINE IR | 42 | -16.27 | 10.34 (7.31,13.37) | 5.01 (0.90,9.11) | -1.96 (-5.76,1.84) | | | .31 |

* pairwise comparisons of therapies

FIGURE 1.6.3

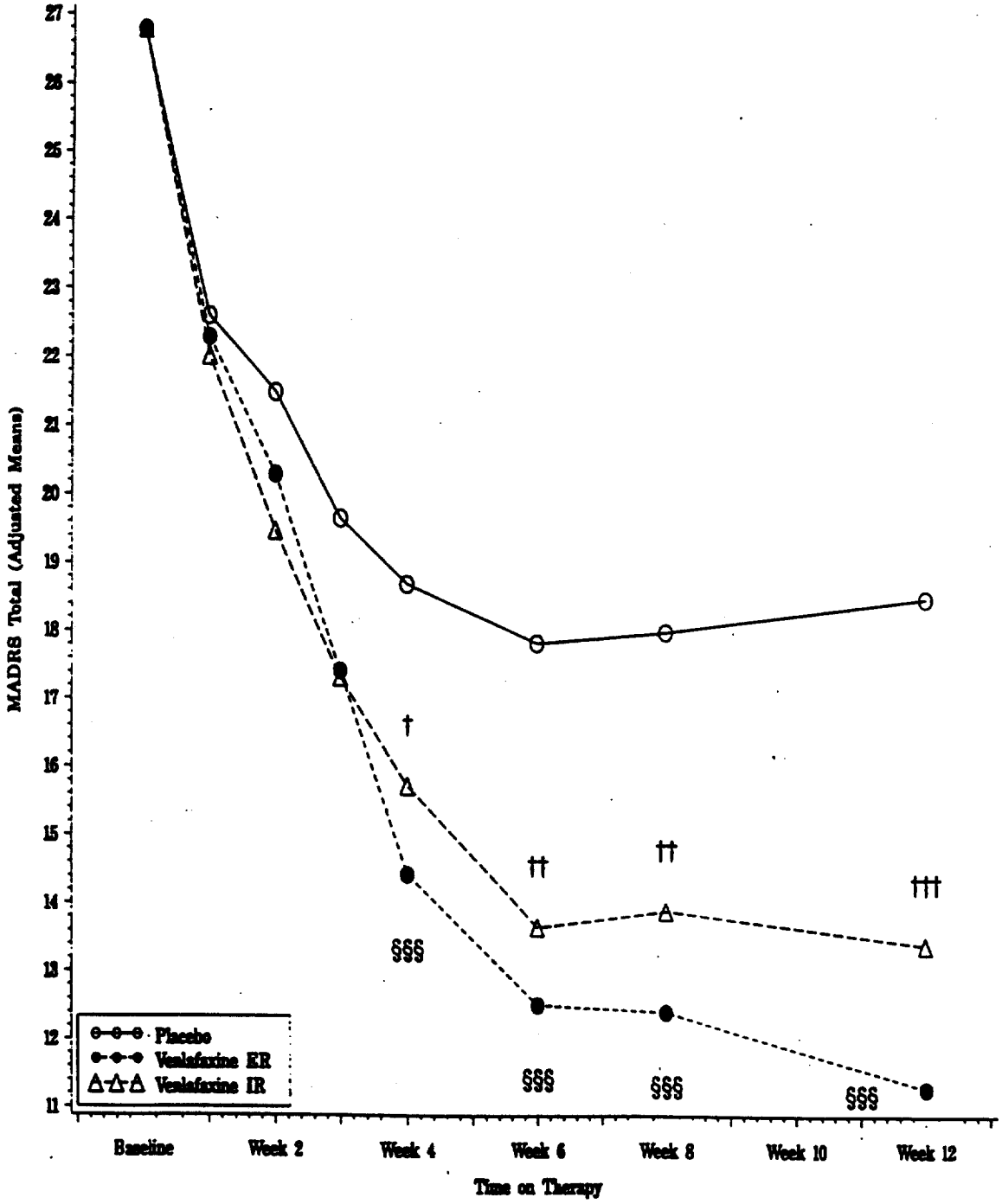
MADRS TOTAL VS TIME ON THERAPY
LOCF ANALYSIS
STUDY 208




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 1.6.4

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

TABLE 2.1.1

PATIENT STATUS OVER TIME FOR ALL RANDOMIZED PATIENTS

WITH DATA: NUMBER OF PATIENTS

| | ----Placebo--- | | | | ---Venlafaxine ER--- | | | |
|---|---|---|---|---|---|---|---|---|
| Time (week) | No. | C[a] | D[b] | CD[c] | No. | C | D | CD |
| 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: $p \leq 0.001$. Fisher's exact test.

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TABLE 2.1.3

NUMBER OF PATIENTS WHO DISCONTINUED PREMATURELY DURING EACH WEEK BY CATEGORY

| | Week 1 | | Week 2 | | Week 3 | | Week 4 | | Week 5 | | Weeks 6 | | Week 7 | | Weeks 8-10 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reason | Pbo | ER | Pbo | ER | Pbo | ER | Pbo | ER | Pbo | ER | Pbo | ER | Pbo | ER | Pbo | ER |
| Adverse event | 1 | 5 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 2 | 2 | 1 | 1 | 0 | 1 | 0 |
| Failed to return | 1 | 0 | 0 | 1 | 1 | 3 | 1 | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 2 | 1 |
| Patient request | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Unsatisfactory efficacy response | 1 | 0 | 2 | 0 | 2 | 0 | 4 | 1 | 3 | 1 | 3 | 0 | 1 | 2 | 6 | 1 |
| Protocol violation | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Other medical event | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other non-medical event | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| Total | 3 | 6 | 5 | 1 | 5 | 5 | 6 | 3 | 3 | 4 | 6 | 2 | 2 | 2 | 11 | 3 |

**FIGURE** 2.1.4

## PERCENTAGE OF PATIENTS OVER TIME

**STUDY 209**

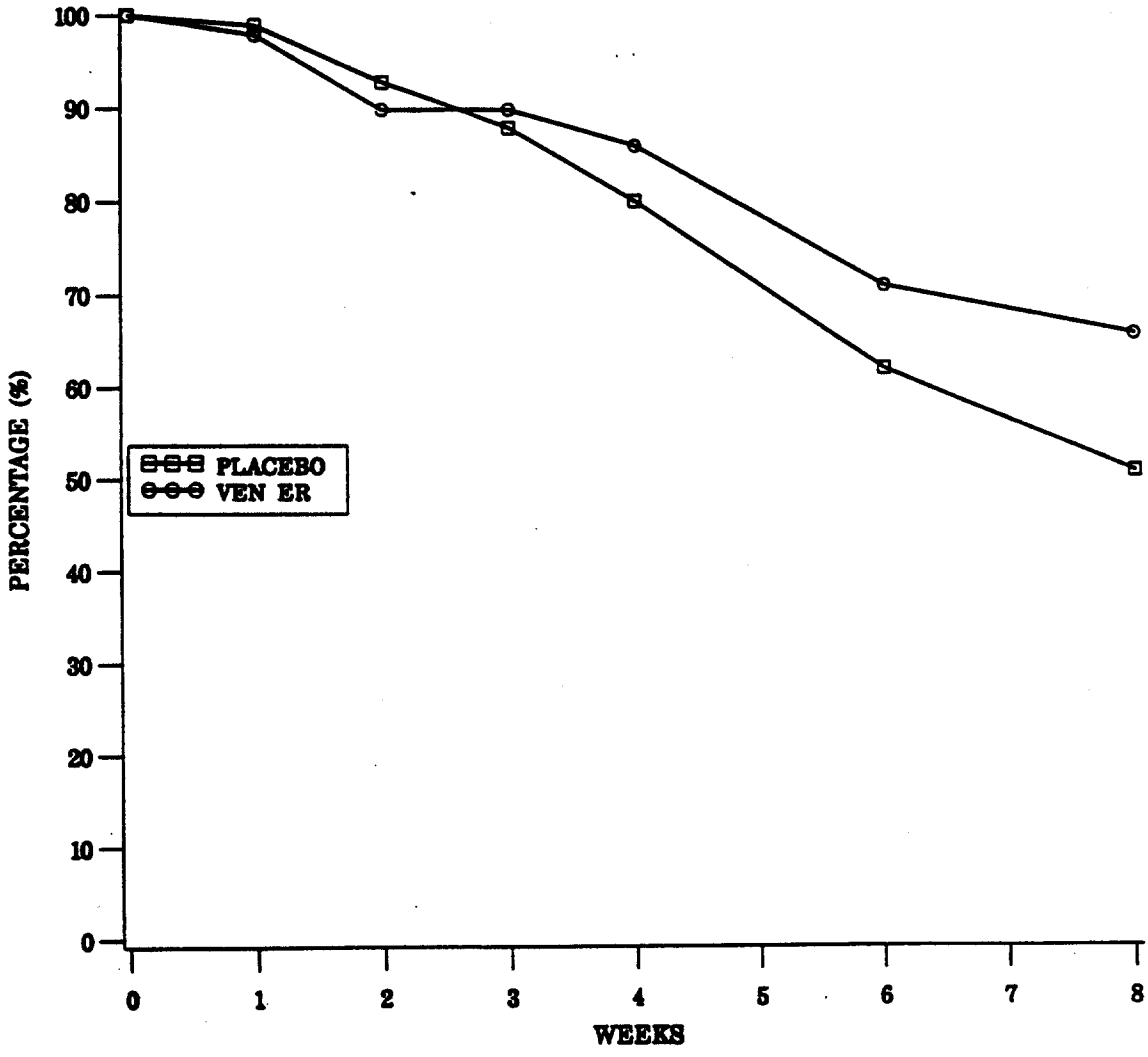

TABLE 2.3.1 HAM-D TOTAL
COMPARISON BETWEEN PBO AND VEN ER - LOCF VALUE ANALYSIS

| 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.

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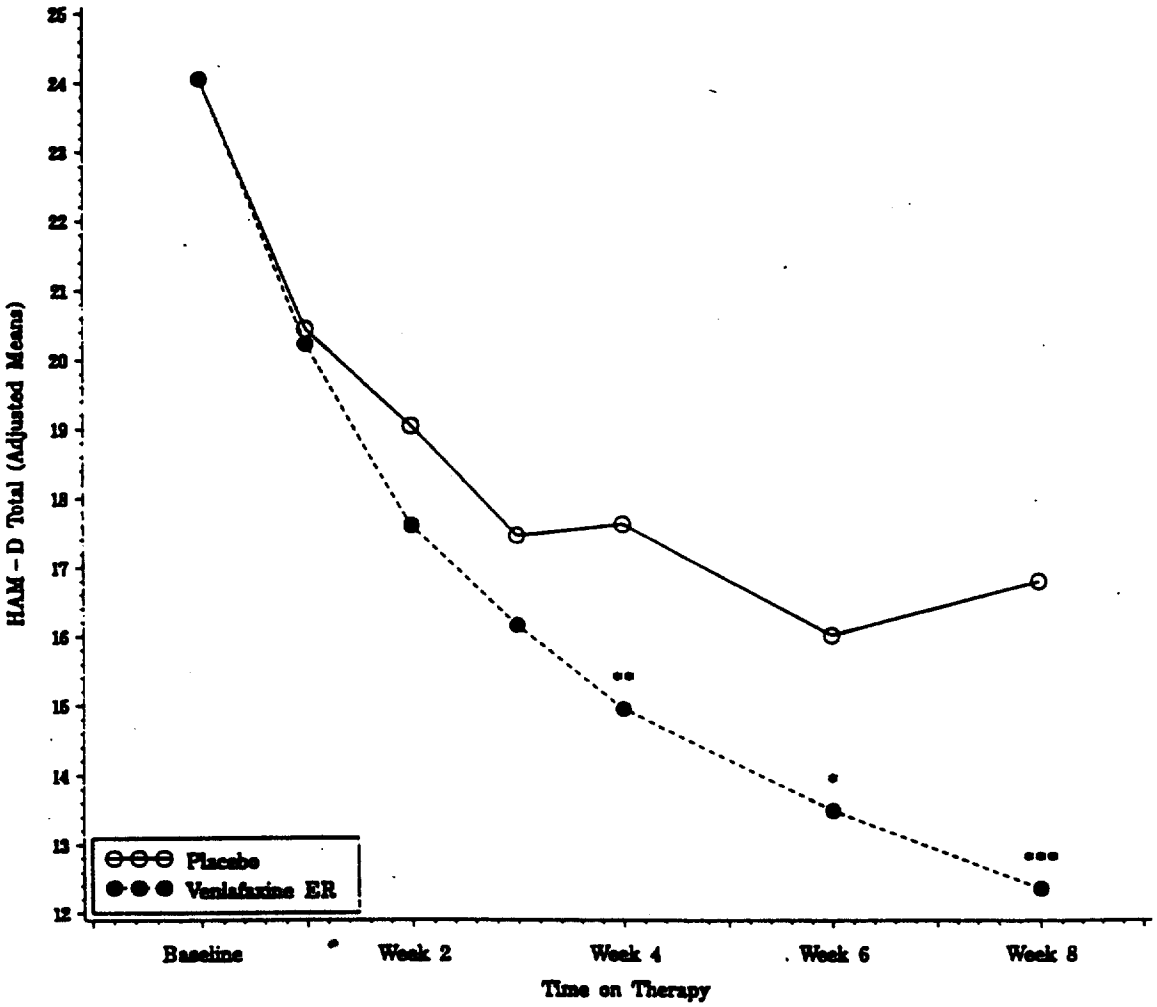
SUPPORTIVE TABLE 2.3.2 209-US

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

| Week On Therapy | Therapy Group | Number Of Patients | Adj Change From Baseline | Adj Means (95% CL) | Diff Adj Means (95% CL) Plcb-Therapy | ----P-VALUES---- Overall F-test |
|---|---|---|---|---|---|---|
| BASELINE | PLACEBO | 100 | | 24.06 (24.06,24.06) | | |
| | VENLAFAXINE ER | 91 | | 24.06 (24.06,24.06) | 0.00 (0.00,0.00) | |
| WEEK 1 | PLACEBO | 99 | -3.64 | 20.43 (19.46,21.41) | | .72 |
| | VENLAFAXINE ER | 89 | -3.89 | 20.18 (19.15,21.21) | 0.25 (-1.15,1.65) | |
| WEEK 2 | PLACEBO | 93 | -5.11 | 18.98 (17.88,20.07) | | .04 |
| | VENLAFAXINE ER | 82 | -6.78 | 17.31 (16.15,18.47) | 1.67 (0.10,3.23) | |
| WEEK 3 | PLACEBO | 88 | -7.28 | 16.71 (15.36,18.07) | | .30 |
| | VENLAFAXINE ER | 82 | -8.29 | 15.70 (14.31,17.09) | 1.02 (-0.89,2.92) | |
| WEEK 4 | PLACEBO | 80 | -7.18 | 16.94 (15.39,18.49) | | .03 |
| | VENLAFAXINE ER | 78 | -9.52 | 14.60 (13.02,16.17) | 2.34 (0.19,4.49) | |
| WEEK 6 | PLACEBO | 62 | -10.33 | 13.85 (12.09,15.61) | | .19 |
| | VENLAFAXINE ER | 65 | -11.93 | 12.26 (10.52,13.99) | 1.59 (-0.80,3.98) | |
| WEEK 8 | PLACEBO | 51 | -9.55 | 14.75 (12.38,17.13) | | <.001 |
| | VENLAFAXINE ER | 60 | -14.48 | 9.83 (7.72,11.93) | 4.93 (2.12,7.73) | |

FIGURE 2.3.3

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




* = p≤ .05 ** = p≤ .01 *** = p≤ .001

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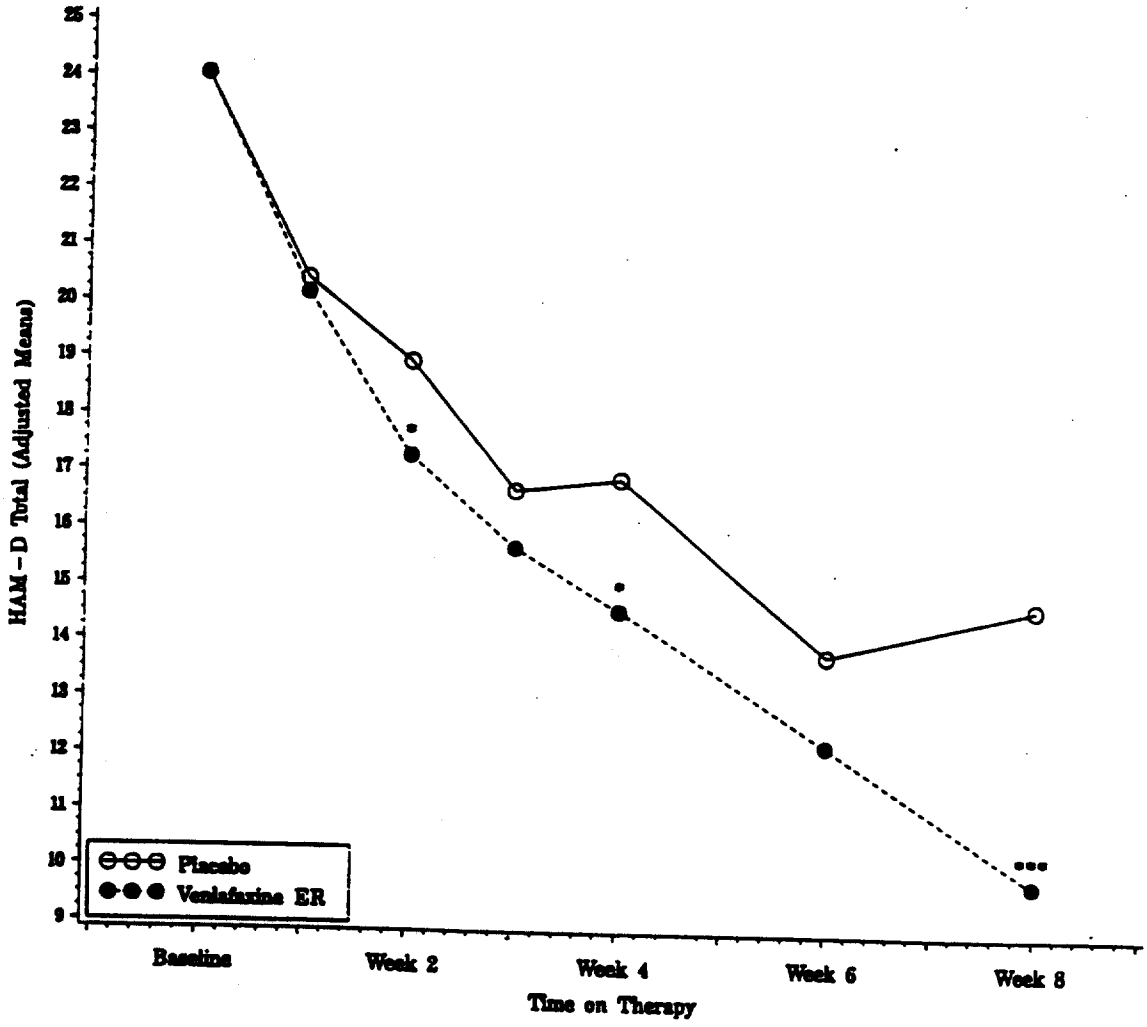
FIGURE 2.3.4

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




* = p≤ .05 ** = p≤ .01 *** = p≤ .001

**FIGURE 2.3.5**

Mean HAM-D Total Score
Protocol 209
Therapy: Placebo

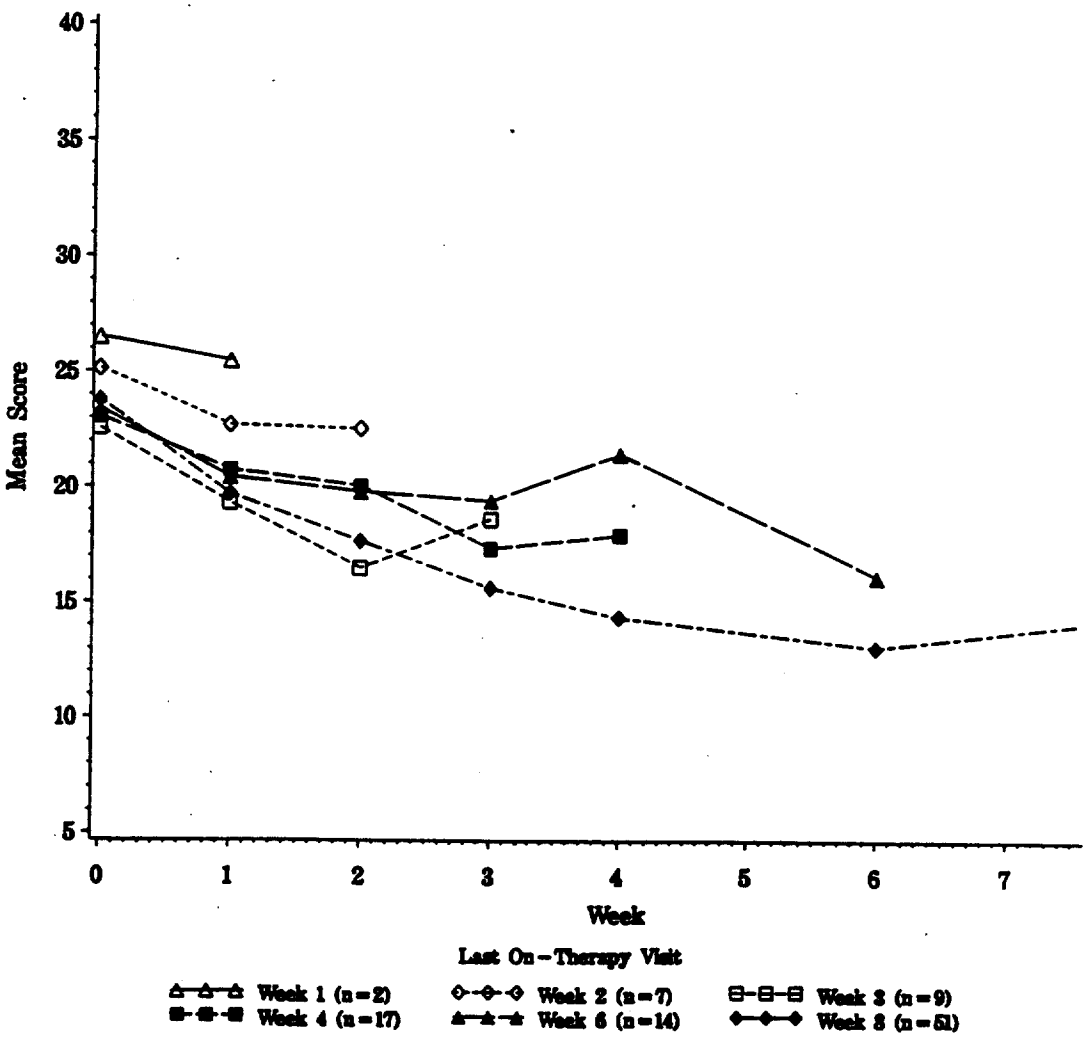


**FIGURE 2.3.6**

**Mean HAM-D Total Score**
**Protocol 209**
**Therapy: Venlafaxine ER**

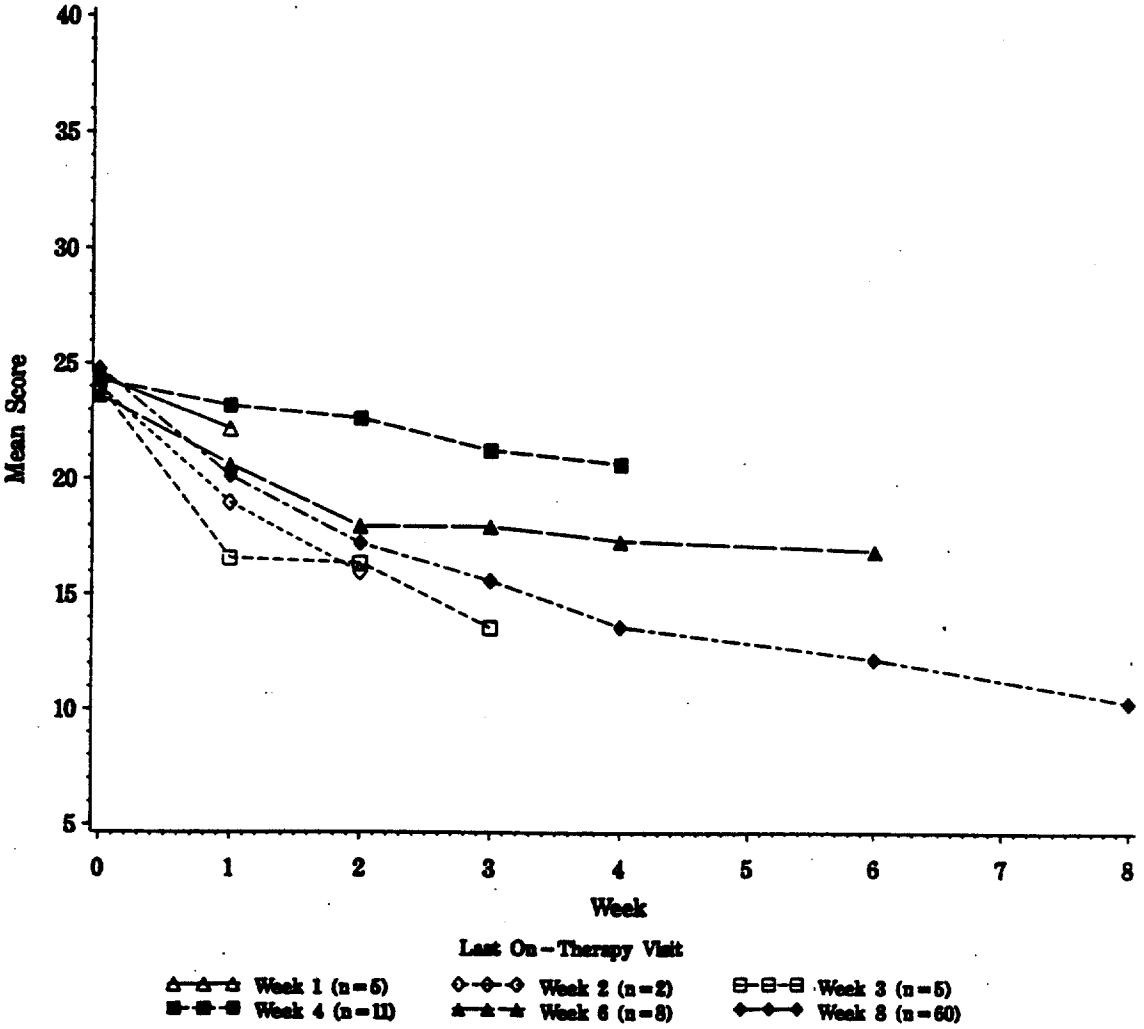


TABLE 2.4.1 209-US

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] |
|---|---|---|---|---|---|---|
| 1 | Pbo | 100 | -0.42 | 2.38 (2.22,2.53) | | |
| | Ven ER | 91 | -0.60 | 2.19 (2.03,2.35) | 0.19 (-0.03,0.41) | .09 |
| 2 | Pbo | 100 | -0.57 | 2.22 (2.03,2.40) | | |
| | Ven ER | 91 | -0.81 | 1.98 (1.79,2.18) | 0.24 (-0.03,0.50) | .08 |
| 3 | Pbo | 100 | -0.71 | 2.08 (1.89,2.27) | | |
| | Ven ER | 91 | -1.03 | 1.76 (1.56,1.96) | 0.32 (0.05,0.59) | .02 |
| 4 | Pbo | 100 | -0.72 | 2.07 (1.87,2.28) | | |
| | Ven ER | 91 | -1.15 | 1.65 (1.43,1.86) | 0.43 (0.14,0.72) | .005 |
| 6 | Pbo | 100 | -0.83 | 1.96 (1.75,2.18) | | |
| | Ven ER | 91 | -1.32 | 1.47 (1.25,1.70) | 0.49 (0.18,0.79) | .002 |
| 8 | Pbo | 100 | -0.74 | 2.05 (1.83,2.28) | | |
| | 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.

TABLE 2.4.2

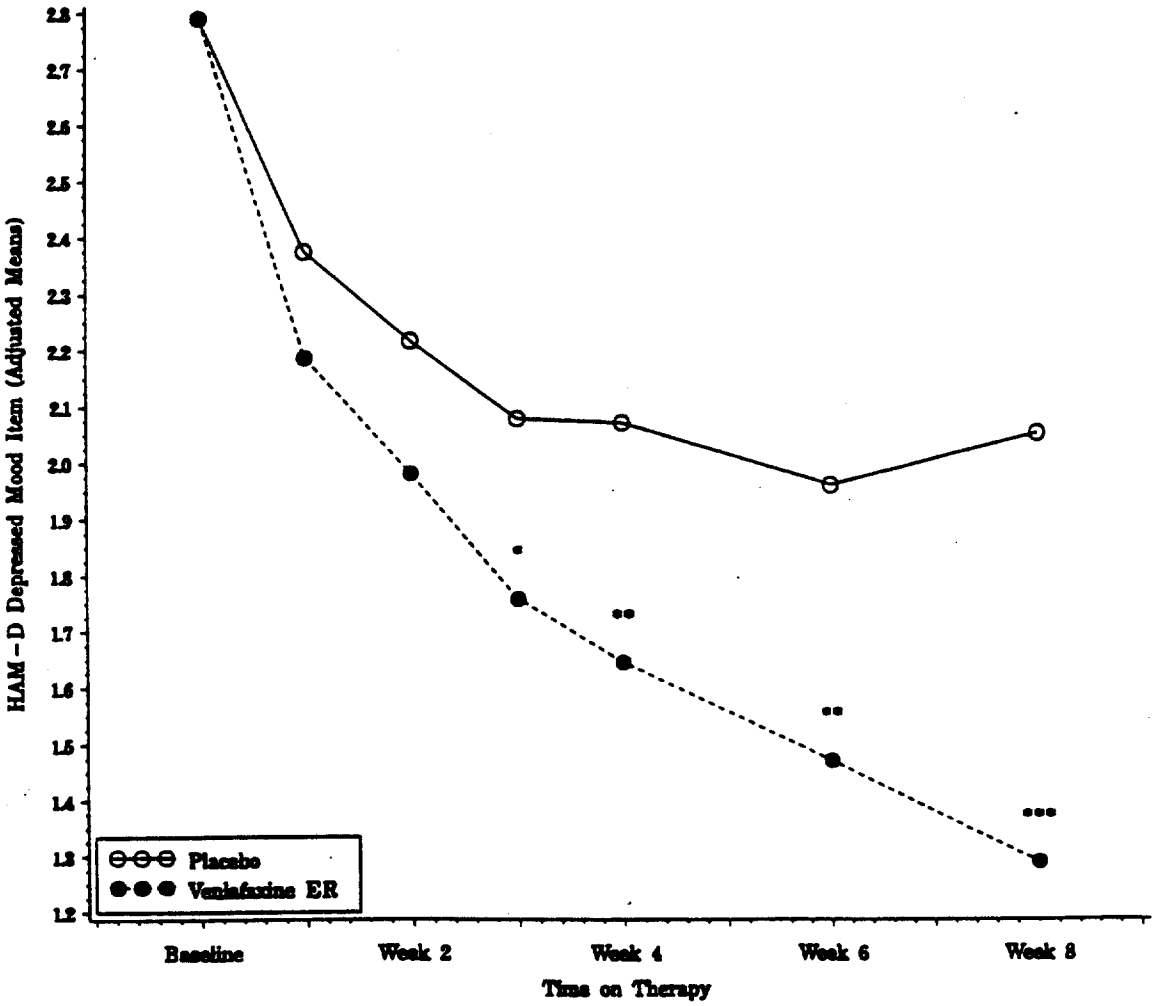
209-US

HAM-D DEPRESSED MOOD ITEM: INTENT-TO-TREAT COMPARISON BETWEEN THERAPY GROUPS - OBSERVED CASES ANALYSIS (ADJUSTED MEANS)

| Week On Therapy | Therapy Group | Number Of Patients | Adj Change From Baseline | Adj Means (95% CL) | Diff Adj Means (95% CL) Plcb-Therapy | ----P-VALUES---- Overall F-test |
|---|---|---|---|---|---|---|
| BASELINE | PLACEBO | 100 | | 2.79 (2.79,2.79) | | |
| | VENLAFAXINE ER | 91 | | 2.79 (2.79,2.79) | 0.00 (0.00,0.00) | |
| WEEK 1 | PLACEBO | 99 | -0.42 | 2.38 (2.23,2.54) | | .08 |
| | VENLAFAXINE ER | 89 | -0.62 | 2.18 (2.02,2.35) | 0.20 (-0.02,0.42) | |
| WEEK 2 | PLACEBO | 93 | -0.56 | 2.23 (2.04,2.42) | | .11 |
| | VENLAFAXINE ER | 82 | -0.79 | 2.00 (1.80,2.21) | 0.23 (-0.05,0.50) | |
| WEEK 3 | PLACEBO | 88 | -0.84 | 1.93 (1.73,2.14) | | .09 |
| | VENLAFAXINE ER | 82 | -1.09 | 1.69 (1.48,1.89) | 0.25 (-0.04,0.53) | |
| WEEK 4 | PLACEBO | 80 | -0.86 | 1.90 (1.66,2.14) | | .05 |
| | VENLAFAXINE ER | 78 | -1.18 | 1.58 (1.34,1.82) | 0.32 (-0.00,0.65) | |
| WEEK 6 | PLACEBO | 62 | -1.10 | 1.67 (1.40,1.94) | | .10 |
| | VENLAFAXINE ER | 65 | -1.41 | 1.36 (1.10,1.63) | 0.31 (-0.05,0.68) | |
| WEEK 8 | PLACEBO | 51 | -1.27 | 1.55 (1.19,1.92) | | .005 |
| | VENLAFAXINE ER | 60 | -1.90 | 0.92 (0.60,1.25) | 0.63 (0.20,1.06) | |

FIGURE 2.4.3

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




* = ps .05 ** = ps .01 *** = ps .001

FIGURE 2.4.4

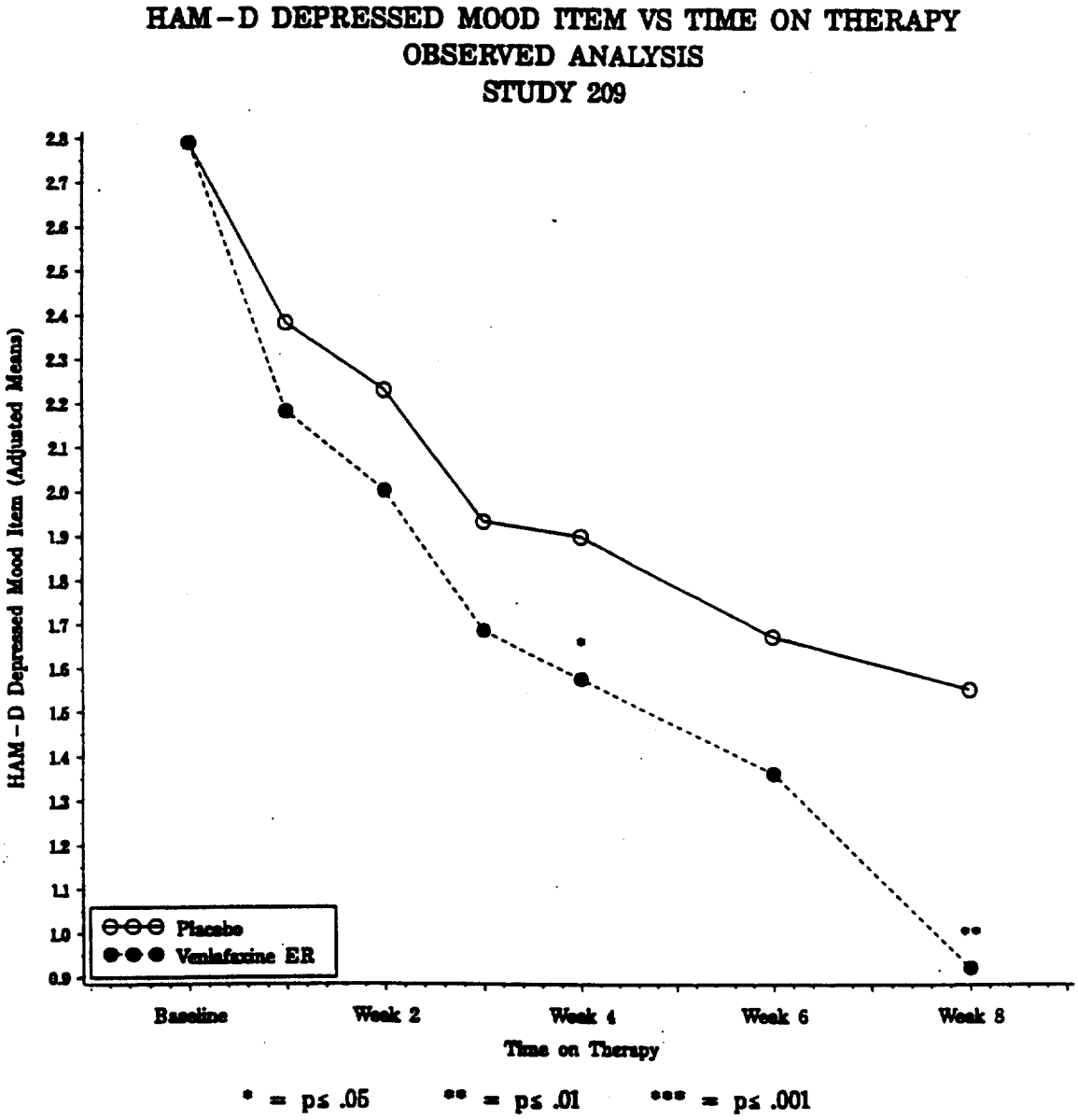

HAM-D DEPRESSED MOOD ITEM VS TIME ON THERAPY
OBSERVED ANALYSIS
STUDY 209
HAM-D Depressed Mood Item (Adjusted Means)
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
Placebo
Venlafaxine ER
Baseline
Week 2
Week 4
Week 6
Week 8
Time on Therapy
* = p≤ .05
** = p≤ .01
*** = 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.

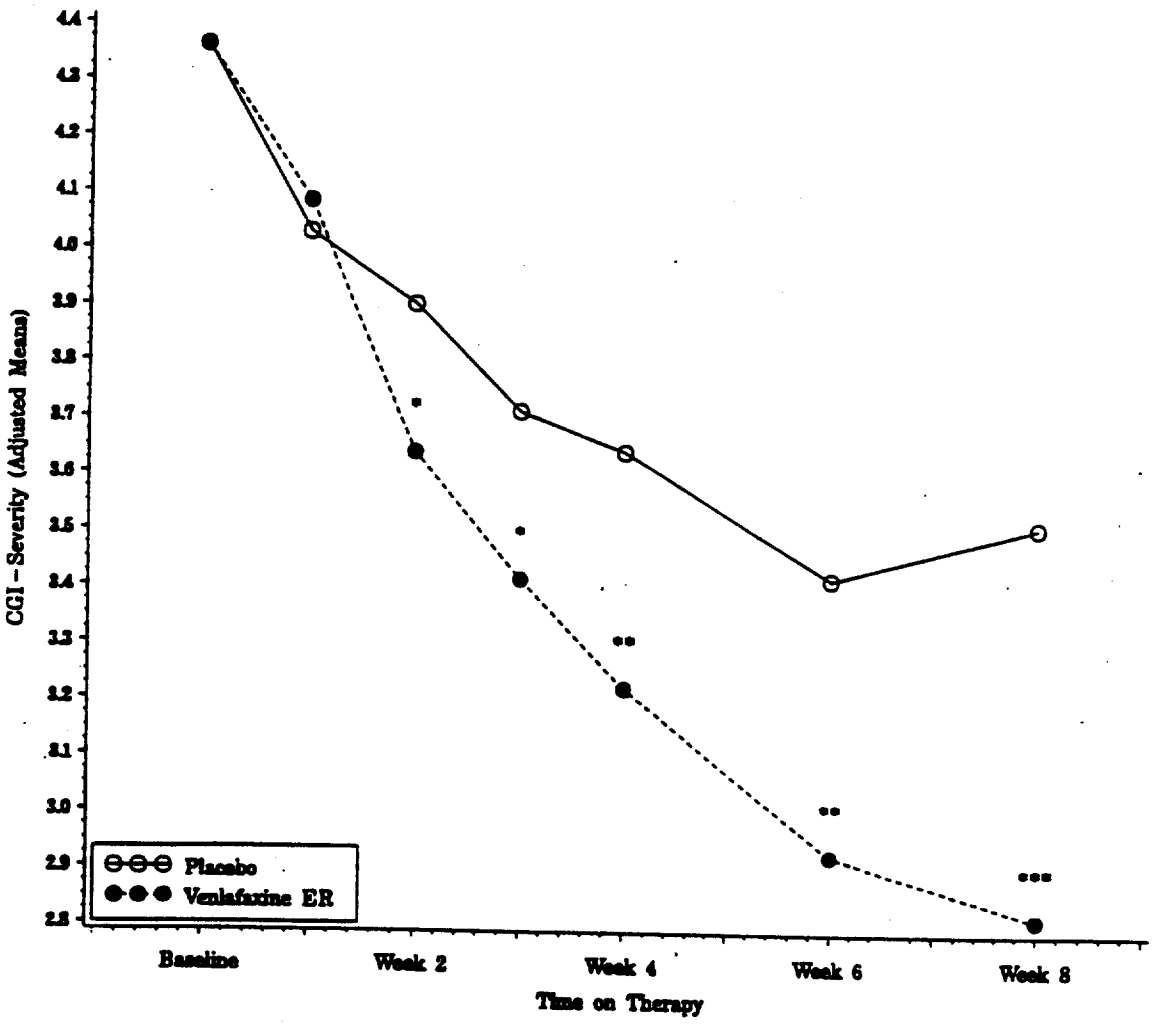
TABLE 2.5.2 209-US

CGI SEVERITY: INTENT-TO-TREAT COMPARISON BETWEEN THERAPY GROUPS - OBSERVED CASES ANALYSIS (ADJUSTED MEANS)

| Week On Therapy | Therapy Group | Number Of Patients | Adj Change From Baseline | Adj Means (95% CL) | Diff Adj Means (95% CL) Plcb-Therapy | ----P-VALUES---- Overall F-test |
|---|---|---|---|---|---|---|
| BASELINE | PLACEBO | 100 | | 4.36 (4.36,4.36) | | |
| | VENLAFAXINE ER | 91 | | 4.36 (4.36,4.36) | -0.00 (-0.00,-0.00) | |
| WEEK 1 | PLACEBO | 99 | -0.34 | 4.03 (3.89,4.16) | | .58 |
| | VENLAFAXINE ER | 89 | -0.28 | 4.08 (3.94,4.22) | -0.05 (-0.24,0.13) | |
| WEEK 2 | PLACEBO | 93 | -0.48 | 3.89 (3.72,4.06) | | .03 |
| | VENLAFAXINE ER | 82 | -0.75 | 3.62 (3.45,3.80) | 0.27 (0.03,0.51) | |
| WEEK 3 | PLACEBO | 88 | -0.73 | 3.63 (3.42,3.85) | | .10 |
| | VENLAFAXINE ER | 81 | -0.98 | 3.38 (3.17,3.60) | 0.25 (-0.04,0.55) | |
| WEEK 4 | PLACEBO | 80 | -0.83 | 3.54 (3.30,3.77) | | .02 |
| | VENLAFAXINE ER | 77 | -1.21 | 3.16 (2.92,3.40) | 0.38 (0.05,0.70) | |
| WEEK 6 | PLACEBO | 62 | -1.28 | 3.10 (2.79,3.41) | | .17 |
| | VENLAFAXINE ER | 65 | -1.57 | 2.80 (2.50,3.10) | 0.30 (-0.12,0.72) | |
| WEEK 8 | PLACEBO | 51 | -1.30 | 3.10 (2.68,3.52) | | .01 |
| | VENLAFAXINE ER | 60 | -1.92 | 2.49 (2.13,2.85) | 0.61 (0.13,1.10) | |

FIGURE 2.5.3

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




* = p≤ .05 ** = p≤ .01 *** = p≤ .001

FIGURE 2.5.4

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

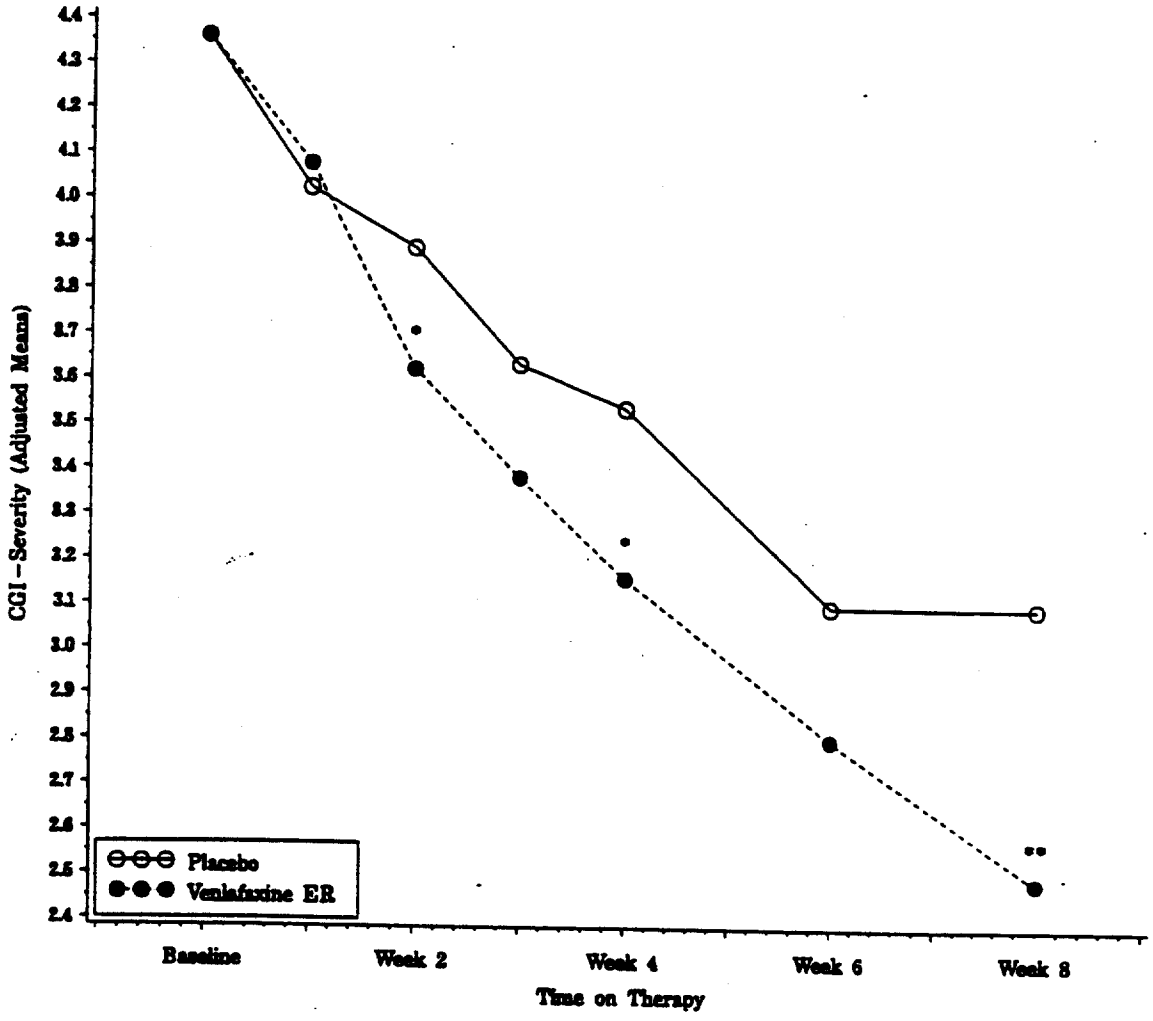


TABLE 2.6.1 MADRS TOTAL 209–US
COMPARISON BETWEEN PBO AND VEN ER - LOCF VALUE ANALYSIS

| 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.

TABLE 2.6.2 209-US

HADRS TOTAL: INTENT-TO-TREAT COMPARISON BETWEEN THERAPY GROUPS - OBSERVED CASES ANALYSIS (ADJUSTED MEANS)

| Week On Therapy | Therapy Group | Number Of Patients | Adj Change From Baseline | Adj Means (95% CL) | Diff Adj Means (95% CL) Plcb-Therapy | ----P-VALUES---- Overall F-test |
|---|---|---|---|---|---|---|
| BASELINE | PLACEBO | 100 | | 27.86 (27.86,27.86) | | |
| | VENLAFAXINE ER | 91 | | 27.86 (27.86,27.86) | 0.00 (0.00,0.00) | |
| WEEK 1 | PLACEBO | 98 | -4.77 | 23.15 (21.90,24.39) | | .62 |
| | VENLAFAXINE ER | 89 | -4.32 | 23.60 (22.30,24.90) | -0.45 (-2.22,1.31) | |
| WEEK 2 | PLACEBO | 93 | -5.60 | 22.27 (20.75,23.80) | | .18 |
| | VENLAFAXINE ER | 82 | -7.06 | 20.81 (19.20,22.42) | 1.46 (-0.69,3.62) | |
| WEEK 3 | PLACEBO | 88 | -7.02 | 20.61 (18.81,22.42) | | .21 |
| | VENLAFAXINE ER | 82 | -8.61 | 19.02 (17.20,20.84) | 1.59 (-0.90,4.08) | |
| WEEK 4 | PLACEBO | 79 | -7.50 | 20.13 (18.09,22.17) | | .08 |
| | VENLAFAXINE ER | 78 | -10.05 | 17.59 (15.55,19.62) | 2.55 (-0.24,5.33) | |
| WEEK 6 | PLACEBO | 63 | -11.47 | 16.46 (14.10,18.83) | | .21 |
| | VENLAFAXINE ER | 65 | -13.52 | 14.42 (12.11,16.73) | 2.04 (-1.14,5.23) | |
| WEEK 8 | PLACEBO | 51 | -10.47 | 17.55 (14.24,20.87) | | .005 |
| | VENLAFAXINE ER | 60 | -16.11 | 11.92 (9.02,14.81) | 5.63 (1.79,9.48) | |

FIGURE 2.6.3

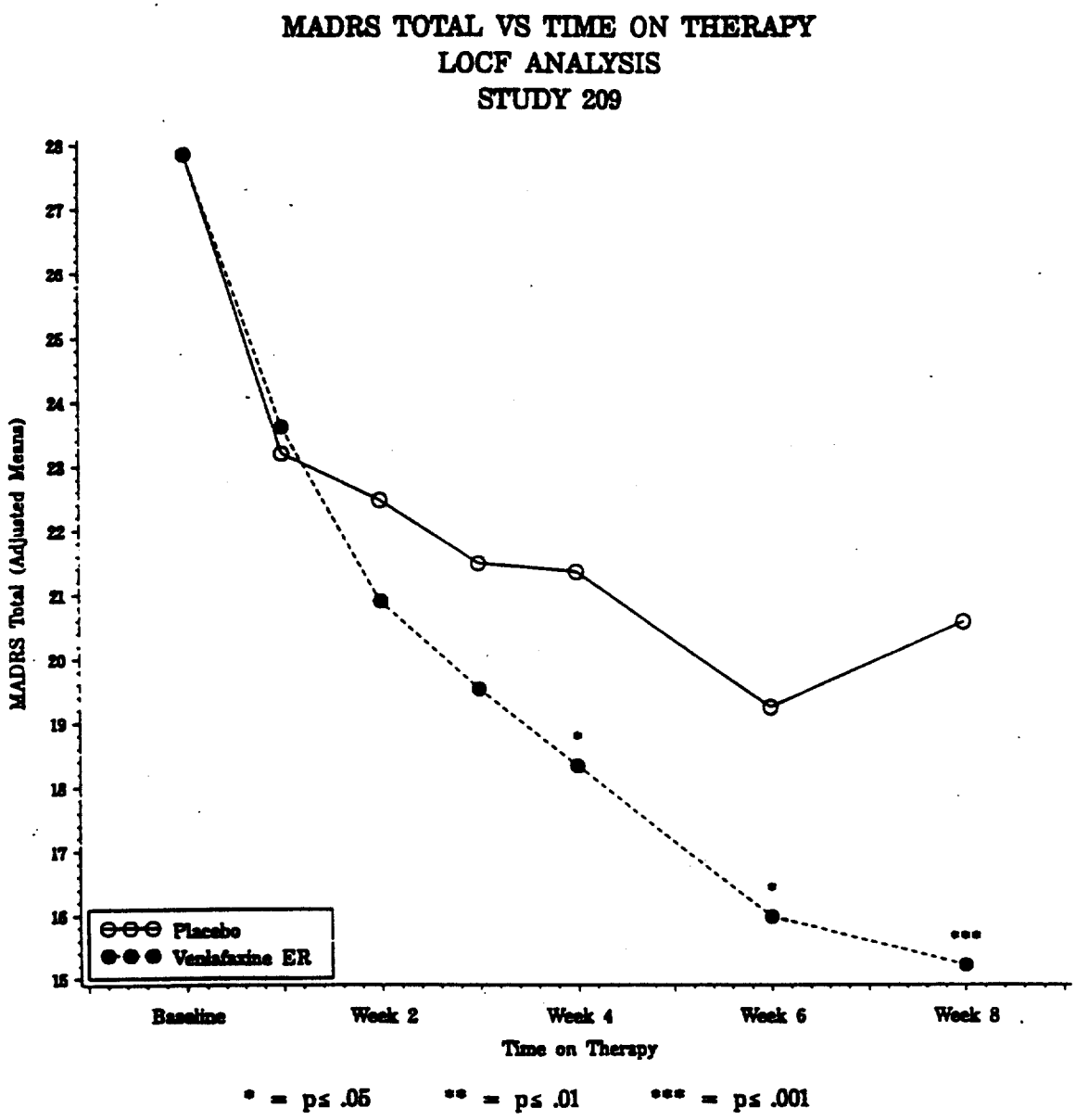

MADRS TOTAL VS TIME ON THERAPY
LOCF ANALYSIS
STUDY 209
MADRS Total (Adjusted Means)
28
27
26
25
24
23
22
21
20
19
18
17
16
15
Placebo
Venlafaxine ER
Baseline
Week 2
Week 4
Week 6
Week 8
Time on Therapy
* = p≤ .05
** = p≤ .01
*** = p≤ .001

FIGURE 2.6.4

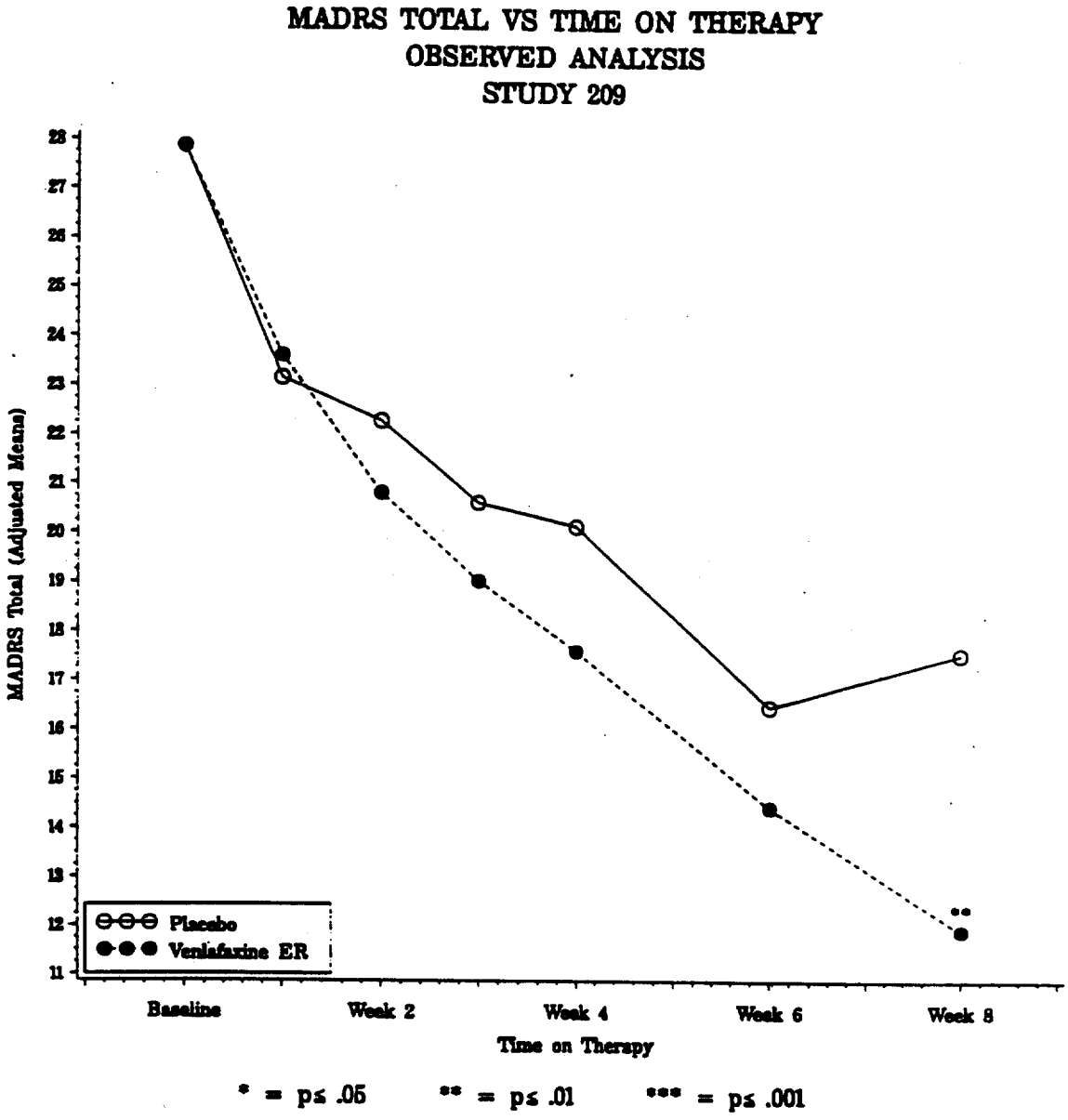

MADRS TOTAL VS TIME ON THERAPY
OBSERVED ANALYSIS
STUDY 209
MADRS Total (Adjusted Means)
28
27
26
25
24
23
22
21
20
19
18
17
16
15
14
13
12
11
Placebo
Venlafaxine ER
Baseline
Week 2
Week 4
Week 6
Week 8
Time on Therapy
* = p≤ .05
** = p≤ .01
*** = p≤ .001

TABLE 3.1.1 PATIENT DISPOSITION 367-EU

| | Screening R | Screening C | Screening D | 1-7 C | 1-7 D | 8-14 C | 8-14 D | 15-28 C | 15-28 D | 29-42 C | 29-42 D | 43-56 C | 43-56 D | >56 C | >56 D | Taper C | Taper 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

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

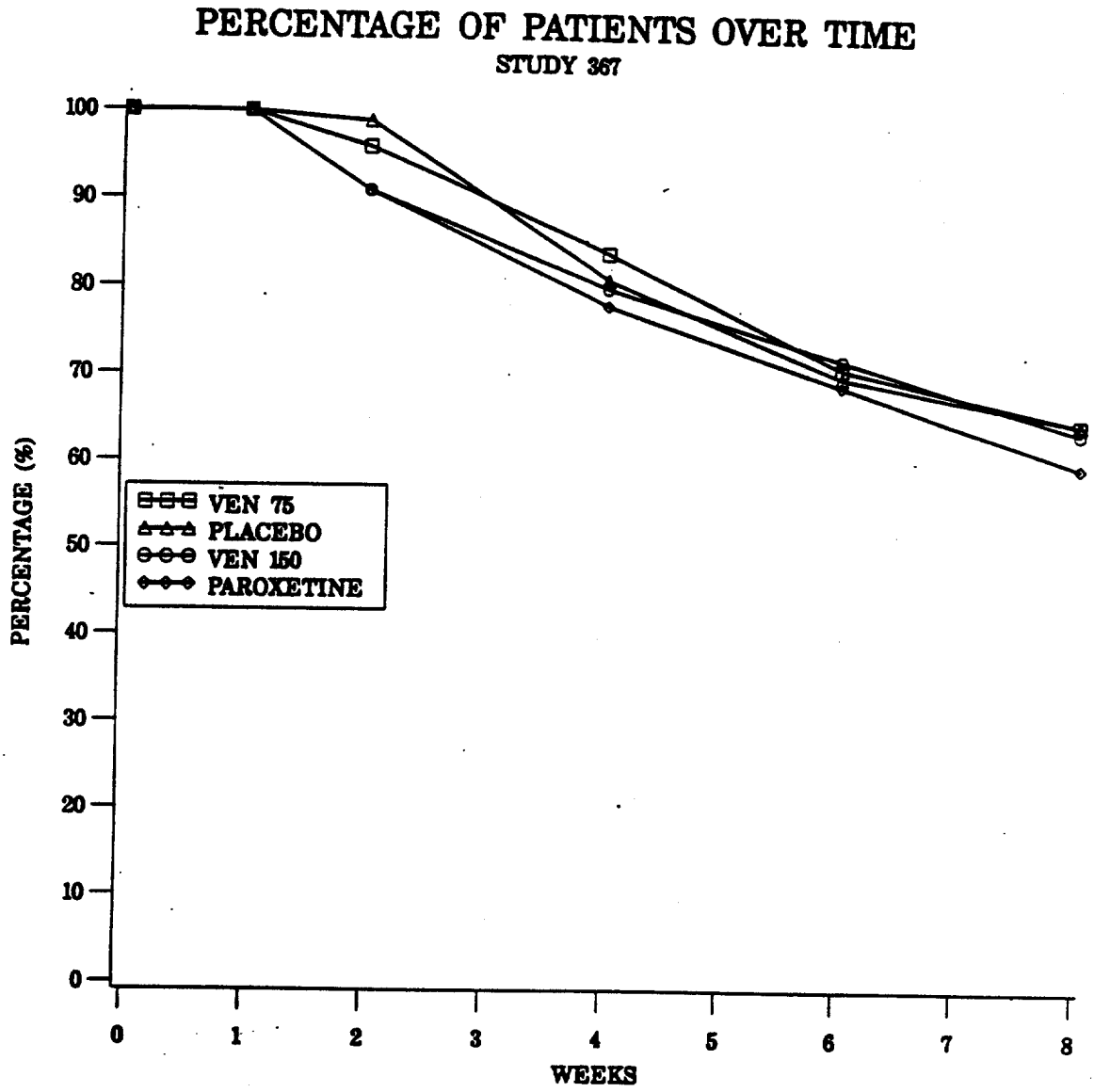
TABLE 3.1.3

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
PERCENTAGE (%)
100
90
80
70
60
50
40
30
20
10
0
VEN 75
PLACEBO
VEN 150
PAROXETINE
0
1
2
3
4
5
6
7
8
WEEKS

# 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 | -3.47 | | | | .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 | | | | |

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 | | | | |

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# TABLE 3.4.2

VENLAFAXINE ER STUDY 600B-367

HAM-D DEPRESSED MOOD ITEM: 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 | 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 | 80 | 2.88 | -0.99 | .26 | .07 | .55 | .87 |
| | V 75 MG | 79 | 2.94 | -1.28 | | | .26 | .11 |
| | V 150 MG | 68 | 2.82 | -1.09 | | | | .66 |
| | PAROXETINE | 73 | 2.82 | -1.01 | | | | |
| WEEK 4 | PLACEBO | 66 | 2.85 | -1.52 | .88 | .66 | .53 | .93 |
| | V 75 MG | 69 | 2.91 | -1.59 | | | .83 | .61 |
| | V 150 MG | 60 | 2.77 | -1.63 | | | | .48 |
| | PAROXETINE | 62 | 2.79 | -1.50 | | | | |
| WEEK 6 | PLACEBO | 57 | 2.86 | -1.88 | .19 | .25 | .81 | .31 |
| | V 75 MG | 58 | 2.88 | -2.09 | | | .17 | .03 |
| | V 150 MG | 54 | 2.76 | -1.83 | | | | .45 |
| | PAROXETINE | 55 | 2.78 | -1.69 | | | | |
| WEEK 8 | PLACEBO | 53 | 2.83 | -1.94 | .31 | .14 | .12 | .67 |
| | V 75 MG | 53 | 2.85 | -2.21 | | | .91 | .31 |
| | V 150 MG | 48 | 2.81 | -2.23 | | | | .26 |
| | PAROXETINE | 48 | 2.79 | -2.02 | | | | |

# TABLE 3.5.1

VENLAFAXINE ER STUDY 600B-367

CGI SEVERITY: 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 | 4.78 | -0.31 | .40 | .34 | .99 | .44 |
| | V 75 MG | 82 | 4.70 | -0.44 | | | .35 | .09 |
| | V 150 MG | 75 | 4.85 | -0.31 | | | | .46 |
| | PAROXETINE | 79 | 4.65 | -0.20 | | | | |
| WEEK 2 | PLACEBO | 81 | 4.78 | -0.96 | .07 | .23 | .42 | .20 |
| | V 75 MG | 82 | 4.70 | -1.21 | | | .72 | .01 |
| | V 150 MG | 75 | 4.85 | -1.13 | | | | .04 |
| | PAROXETINE | 79 | 4.65 | -0.70 | | | | |
| WEEK 4 | PLACEBO | 81 | 4.78 | -1.47 | .03 | .66 | .14 | .14 |
| | V 75 MG | 82 | 4.70 | -1.57 | | | .30 | .06 |
| | V 150 MG | 75 | 4.85 | -1.83 | | | | .004 |
| | PAROXETINE | 79 | 4.65 | -1.11 | | | | |
| WEEK 6 | PLACEBO | 81 | 4.78 | -1.73 | .12 | .47 | .41 | .18 |
| | V 75 MG | 82 | 4.70 | -1.91 | | | .90 | .04 |
| | V 150 MG | 75 | 4.85 | -1.95 | | | | .03 |
| | PAROXETINE | 79 | 4.65 | -1.38 | | | | |
| WEEK 8 | PLACEBO | 81 | 4.78 | -1.91 | .19 | .47 | .62 | .20 |
| | V 75 MG | 82 | 4.70 | -2.11 | | | .84 | .05 |
| | V 150 MG | 75 | 4.85 | -2.05 | | | | .08 |
| | PAROXETINE | 79 | 4.65 | -1.56 | | | | |

# TABLE 3.5.2

VENLAFAXINE ER STUDY 600B-367

CGI SEVERITY: 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 | P-VALUES V75 MG | P-VALUES PARO |
|---|---|---|---|---|---|---|---|---|
| WEEK 1 | PLACEBO | 81 | 4.78 | -0.31 | .40 | .34 | .99 | .44 |
| | V 75 MG | 82 | 4.70 | -0.44 | | | .35 | .09 |
| | V 150 MG | 75 | 4.85 | -0.31 | | | | .46 |
| | PAROXETINE | 79 | 4.65 | -0.20 | | | | |
| WEEK 2 | PLACEBO | 80 | 4.76 | -0.98 | .10 | .18 | .23 | .39 |
| | V 75 MG | 79 | 4.71 | -1.25 | | | .93 | .03 |
| | V 150 MG | 68 | 4.85 | -1.24 | | | | .05 |
| | PAROXETINE | 72 | 4.58 | -0.79 | | | | |
| WEEK 4 | PLACEBO | 66 | 4.71 | -1.74 | .03 | .99 | .09 | .19 |
| | V 75 MG | 69 | 4.71 | -1.74 | | | .08 | .19 |
| | V 150 MG | 60 | 4.85 | -2.18 | | | | .003 |
| | PAROXETINE | 62 | 4.53 | -1.40 | | | | |
| WEEK 6 | PLACEBO | 57 | 4.72 | -2.21 | .15 | .63 | .40 | .18 |
| | V 75 MG | 58 | 4.71 | -2.34 | | | .72 | .07 |
| | V 150 MG | 54 | 4.83 | -2.44 | | | | .03 |
| | PAROXETINE | 55 | 4.56 | -1.84 | | | | |
| WEEK 8 | PLACEBO | 53 | 4.70 | -2.43 | .53 | .79 | .25 | .78 |
| | V 75 MG | 53 | 4.64 | -2.51 | | | .37 | .59 |
| | V 150 MG | 48 | 4.77 | -2.77 | | | | .16 |
| | PAROXETINE | 48 | 4.58 | -2.35 | | | | |

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.

TABLE 3.5.4 PRIMARY EFFICACY VARIABLES (CONTINUED) 367-EU
PAIRWISE COMPARISONS OF ADJUSTED MEANS OBSERVED CASES 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 | 0.3 | 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.

VENLAFAXINE ER STUDY 600B-367

# TABLE 3.6.1

## MADRS 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 | P-TEST | P-VALUES V150 MG | P-VALUES V75 MG | P-VALUES PARO |
|---|---|---|---|---|---|---|---|---|
| WEEK 1 | PLACEBO | 81 | 29.88 | -4.37 | .05 | .18 | .28 | .29 |
| | V 75 MG | 82 | 29.66 | -5.66 | | | .02 | .02 |
| | V 150 MG | 75 | 30.61 | -3.31 | | | | .96 |
| | PAROXETINE | 79 | 29.38 | -3.35 | | | | |
| WEEK 2 | PLACEBO | 81 | 29.88 | -9.40 | .13 | .20 | .77 | .27 |
| | V 75 MG | 82 | 29.66 | -11.12 | | | .34 | .02 |
| | V 150 MG | 75 | 30.61 | -9.80 | | | | .17 |
| | PAROXETINE | 79 | 29.38 | -7.90 | | | | |
| WEEK 4 | PLACEBO | 81 | 29.88 | -12.96 | .10 | .42 | .15 | .35 |
| | V 75 MG | 82 | 29.66 | -14.35 | | | .51 | .08 |
| | V 150 MG | 75 | 30.61 | -15.49 | | | | .02 |
| | PAROXETINE | 79 | 29.38 | -11.37 | | | | |
| WEEK 6 | PLACEBO | 81 | 29.88 | -14.32 | .09 | .25 | .26 | .30 |
| | V 75 MG | 82 | 29.66 | -16.52 | | | .99 | .03 |
| | V 150 MG | 75 | 30.61 | -16.52 | | | | .03 |
| | PAROXETINE | 79 | 29.38 | -12.33 | | | | |
| WEEK 8 | PLACEBO | 81 | 29.88 | -14.95 | .12 | .17 | .36 | .40 |
| | V 75 MG | 82 | 29.66 | -17.70 | | | .66 | .03 |
| | V 150 MG | 75 | 30.61 | -16.81 | | | | .08 |
| | PAROXETINE | 79 | 29.38 | -13.27 | | | | |

VENLAFAXINE ER STUDY 600B-367

## TABLE 3.6.2

MADRS 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 | P-VALUES V75 MG | P-VALUES PARO |
|---|---|---|---|---|---|---|---|---|
| WEEK 1 | PLACEBO | 81 | 29.88 | -4.37 | .05 | .18 | .28 | .29 |
| | V 75 MG | 82 | 29.66 | -5.66 | | | .02 | .02 |
| | V 150 MG | 75 | 30.61 | -3.31 | | | | .96 |
| | PAROXETINE | 79 | 29.38 | -3.35 | | | | |
| WEEK 2 | PLACEBO | 80 | 29.71 | -9.46 | .24 | .13 | .39 | .70 |
| | V 75 MG | 79 | 29.82 | -11.49 | | | .55 | .06 |
| | V 150 MG | 68 | 30.47 | -10.66 | | | | .23 |
| | PAROXETINE | 72 | 29.04 | -8.93 | | | | |
| WEEK 4 | PLACEBO | 66 | 28.89 | -15.45 | .28 | .77 | .21 | .46 |
| | V 75 MG | 69 | 29.84 | -15.94 | | | .33 | .31 |
| | V 150 MG | 60 | 30.38 | -17.62 | | | | .05 |
| | PAROXETINE | 62 | 28.85 | -14.19 | | | | |
| WEEK 6 | PLACEBO | 57 | 28.96 | -18.19 | .10 | .32 | .23 | .30 |
| | V 75 MG | 58 | 29.81 | -20.09 | | | .81 | .04 |
| | V 150 MG | 54 | 30.56 | -20.54 | | | | .03 |
| | PAROXETINE | 55 | 28.40 | -16.20 | | | | |
| WEEK 8 | PLACEBO | 53 | 28.26 | -18.87 | .12 | .22 | .03 | .78 |
| | V 75 MG | 53 | 29.21 | -21.04 | | | .31 | .36 |
| | V 150 MG | 48 | 30.48 | -22.88 | | | | .06 |
| | PAROXETINE | 48 | 28.46 | -19.38 | | | | |

TABLE 3.6.3 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] |
|---|---|---|---|---|---|---|
| **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.

TABLE 3.6.4 PRIMARY EFFICACY VARIABLES (CONTINUED) 367-EU
PAIRWISE COMPARISONS OF ADJUSTED MEANS OBSERVED CASES ANALYSIS

| 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.