

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

**APPLICATION NUMBER: 20-151/S-017/S-018
20-699/S-015/S-016**

STATISTICAL REVIEW

Statistical Review and Evaluation

JAN 31 2001

NDA: 20-151 (SE1-017) / 20-699 (SE1-015)
Drug Name: EFFEXOR® (venlafaxine HC1) / EFFEXOR XR® (venlafaxine ER)
Indication: On Prevention of Recurrence / Relapse of Major Depression
Sponsor: Wyeth Ayerst Laboratories
Clinical Reviewer: Erick Turner, M.D. (HFD-120)
Date of Document: May 5, 2000

1. Introduction

The original NDA 20-151 for EFFEXOR® (venlafaxine HC1) was submitted in 1991 for the treatment of depression, and was approved for marketing in the USA in 1993. The original NDA 20-699 for EFFEXOR XR® (venlafaxine ER) was submitted in 1996 for the treatment of depression, and was approved for marketing in the USA in 1997. The current submissions are supplemental NDAs for venlafaxine hydrochloride / venlafaxine ER to support a labeling supplement that proposes inclusion of the results from two completed studies to demonstrate the prevention of recurrence / relapse of depression.

Study 0600-A-335-US/EU was a 6-month open label followed by a randomized, double-blind, placebo-controlled, one-year study comparing venlafaxine with placebo in the prophylactic treatment of recurrent major depression conducted in USA, UK and Germany.

Study 0600B1-370-US was a 8-week acute venlafaxine ER treatment period followed by a randomized, double-blind, placebo-controlled, 6-month study comparing venlafaxine with placebo in the prophylactic treatment of relapse major depression conducted in US.

2. Study 0600-A-335-US/EU

2.1. Objective

The primary objective was to evaluate the efficacy and safety of venlafaxine in the prophylactic treatment of patients with recurrent major depression.

2.2. Efficacy Measures

The primary endpoint was the time to recurrence of depression (recurrence is defined by CGI \geq 4).

The efficacy characteristics were measured by Hamilton Psychiatric Rating Scale for Depression (HAM-D), the Montgomery Asberg Depression Rating Scale (MADRS), and the Clinical Global Impression (CGI).

The HAM-D total is the total of 21 items ranging from 0 to 61. The MADRS is the total of 10 items ranging from 0 to 60. The CGI is a single score scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill).

2.3. Study Design

0600-A-335-US/EU was an 18-month study with a 6-month open label venlafaxine treatment period, and a 12-month randomized, double blind, placebo-controlled, parallel study period comparing venlafaxine with placebo. During study days 1 to 13, venlafaxine dose was titrated from 50 or 75 mg/day to 150 mg/day. From study days 14 to 180, all patients took 100, 150, or 200 mg/day of venlafaxine. Responders (The "responder" was defined as a patient whose HAM-D score ≤ 12 at the study day 56 evaluation, and who had no HAM-D score ≥ 20 , no more than 2 HAM-D scores > 10 , no single (CGI) severity score ≥ 4 between study day 56 and study day 180.) were randomized to either venlafaxine (100, 150, or 200 mg/day) group or placebo group (after a 14-day double blind taper period). Efficacy measures HAM-D, MADRS, and CGI were assessed at prestudy screening visit (visit 1), baseline visit (day -1, visit 2), days 7, 14, 28, 56, 90, 120, 150, and 180 (visits 3 - 10) during open label period, and at days 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510, and 540 (visits 12 - 23) during double blind period.

2.4. Statistical Analysis Plan

The primary analysis is log-rank test.

For secondary analysis, a two-way analysis of variance (ANOVA) model with terms for treatment and center was used to compare the two treatment groups for the HAM-D total, the MADRS total, and the depressed mood item on the HAM-D. For CGI, CMH test with modridit score is used.

2.5. Patient Population

2.5.1. Demographic

The study included male/female of 18 years old who met DSM-III-R criteria for major depression, had HAM-D total score ≥ 20 on both prestudy screening visit and baseline visit, without 20% decreasing in HAM-D total score between the pre-study screening visit and baseline visit, had symptoms of depression for at least one month before starting the open label study, and had at least one previous major depressive episode in the last five years with an interval of at least six months between the end of the previous episode and the beginning of the present one.

Table 2.5.1.1 presents the demographic configuration of the open label period.

**Table 2.5.1.1. Demographic and Baseline Configuration for All Patients
(Open Label Period)**

Parameter	Venlafaxine
number of patients	483
age (years, mean±sd)	43.0 ± 11.3
sex	
- Male, n (%)	169 (35%)
- Female, n (%)	314 (65%)
race: n (%)	
- white	313 (65%)
- black	19 (4%)
- other	13 (3%)
- n/a	138 (29%)
weight (lb, mean±sd)	168.5 ± 40.5
duration of current episode (weeks, mean±sd)	41.1 ± 46.2
duration of current episode, n (%)	
- < 5 weeks	26 (5%)
- 5-12 weeks	98 (20%)
- 13-24 weeks	116 (24%)
- 25-48 weeks	110 (23%)
- 49-96 weeks	78 (16%)
- > 96 weeks	54 (11%)
- unknown	1 (<1%)
number of previous episode (within 5 years, mean ± sd)	1.5 ± 1.0
baseline HAM-D total (mean ± sd)	25.2 ± 4.2
baseline MADRS total (mean ± sd)	26.6 ± 5.9
baseline CGI (n (%))	
- missing	1 (<1%)
- 0	1 (<1%)
- 3	7 (1%)
- 4	336 (70%)
- 5	129 (27%)
- 6	8 (2%)
- 7	1 (<1%)

Table 2.5.1.2 presents the demographic configuration of the double blind period.

**Table 2.5.1.2. Demographic and Baseline Configuration for ITT Patients
(Double Blind Period)**

Parameter	Placebo	Venlafaxine
number of patients	107	106
age (years, mean±sd)	44.2 ± 11.2	43.7 ± 11.1
sex		
- Male, n (%)	35 (33%)	31 (29%)
- Female, n (%)	72 (67%)	75 (71%)
race: n (%)		
- white	76 (71%)	76 (72%)
- black	3 (3%)	3 (3%)
- other	2 (2%)	4 (4%)
- n/a	26 (24%)	23 (22%)
weight (lb, mean±sd)	175.4 ± 47.1	171.0 ± 39.9
duration of current episode (weeks, mean±sd)	41.7 ± 47.0	39.9 ± 44.1
duration of current episode, n (%)		
- < 5 weeks	5 (5%)	8 (8%)
- 5-12 weeks	18 (17%)	18 (17%)
- 13-24 weeks	34 (32%)	26 (25%)
- 25-48 weeks	19 (18%)	26 (25%)
- 49-96 weeks	17 (16%)	17 (16%)
- > 96 weeks	14 (13%)	11 (10%)
number of previous episode (within 5 years, mean ± sd)	1.5 ± 0.9	1.4 ± 0.6
baseline (end of 180 study day)		
HAM-D total (mean ± sd)	4.9 ± 3.8	4.3 ± 3.5
MADRS total (mean ± sd)	5.3 ± 4.8	4.3 ± 3.5
CGI (n (%))		
- 1	46 (43%)	51 (49%)
- 2	33 (31%)	38 (36%)
- 3	28 (26%)	15 (14%)
- 4	0 (0%)	1 (1%)

2.5.2. Patient Disposition

Table 2.5.2 presents the patients disposition.

Table 2.5.2. Patients Disposition (All Patients)

Patient group Reason for discontinuation	Placebo	Venlafaxine
Open label period		
Randomized		483
Any		197 (41%)
Adverse reaction		69 (14%)
Failed to return		44 (9%)
Patient request		13 (3%)
Unsatisfactory response – efficacy		45 (9%)
Protocol violation		12 (2%)
Other medical event		12 (2%)
Other non-medical event		2 (<1%)
Double blind period		
Randomized	123	112
Any	93 (76%)	56 (50%)
Adverse reaction	8 (7%)	6 (5%)
Failed to return	11 (9%)	13 (12%)
Patient request	8 (7%)	6 (5%)
Unsatisfactory response – efficacy	59 (48%)	24 (21%)
Protocol violation	3 (2%)	3 (3%)
Other medical event	4 (3%)	3 (3%)
Other non-medical event	0 (0%)	1 (<1%)

2.6. Sponsor's Analyses

There were 495 patients enrolled in the open label period. 12 patients failed to return after the day 1 visit. No documentation was available to substantiate whether these 12 patients took study drug or experienced adverse reactions. Among 483 patients, there were 470 in ITT.

In the double blind period, there were 124, and 113 enrolled in placebo, and venlafaxine groups, respectively. Patients 33501-002, and 33505-027 had no data. There were 107, and 106 in placebo, and venlafaxine groups, who were valid for ITT analysis. The ITT population included all patients who had been randomly assigned to receive double blind medication, completed the initial taper period, took at least one dose of their assigned double blind medication, had at least one baseline evaluation on at least one primary efficacy parameter (not applicable for CGI improvement), and had at least one evaluation on at least one of the primary efficacy parameters, either during the double blind treatment period, or within 3 days of the last day of treatment.

There were 116 and 109 in placebo and venlafaxine groups, respectively in the survival analysis population, which included all patients who had been randomly assigned to receive double blind medication during the double blind period and who had at least one on-therapy CGI severity evaluation.

The sponsor performed the primary analysis for both ITT and the survival analysis population. The results are similar for two populations. In this section, only results for ITT will be presented.

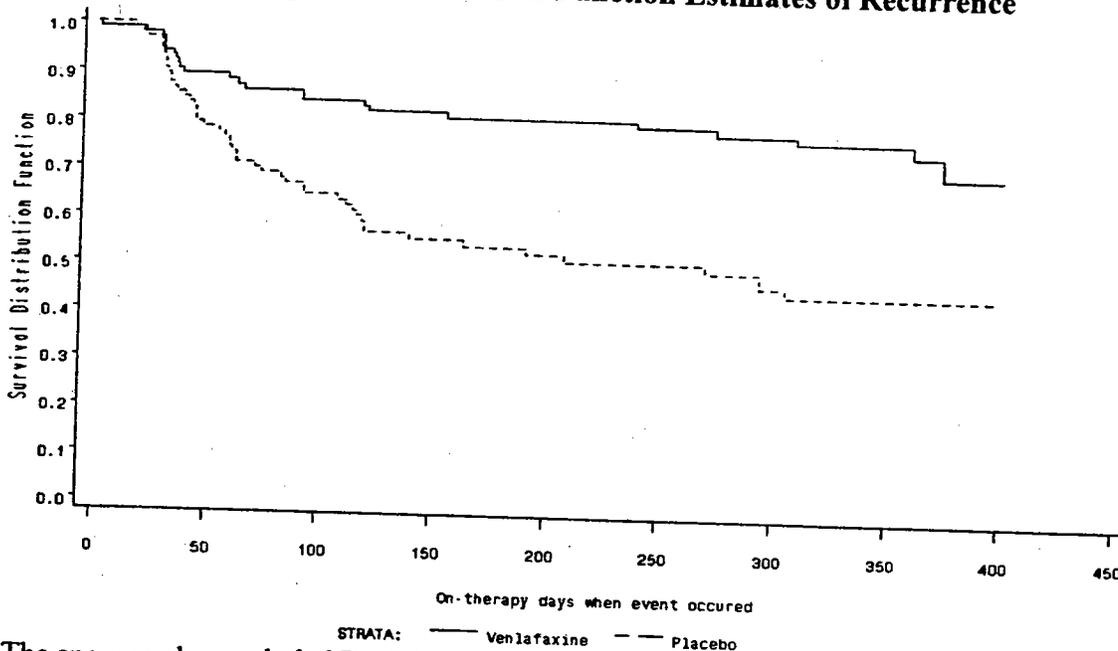
2.6.1. Sponsor's Primary Analysis

The primary analysis is the log-rank test. Table 2.6.1 shows that the probabilities of having the recurrence of a new episode of depression are 23% and 55% for venlafaxine and placebo groups, respectively, after 1 year. Figure 2.6.1 is the survival function estimates of recurrence. The log-rank test gives p-value .0001.

Table 2.6.1. Life-Table Summary for Survival Probability of Recurrence

Month	placebo		Survival	venlafaxine		Survival
	Number Failed	Number Censored		Number Failed	Number Censored	
1	10	4	1.0000	6	1	1.0000
2	17	5	0.9048	6	5	0.9431
3	6	4	0.7348	2	1	0.8845
4	9	2	0.6709	4	0	0.8643
5	1	6	0.5703	0	3	0.8236
6	1	3	0.5581	1	3	0.8236
7	2	3	0.5447	0	6	0.8128
8	0	0	0.5156	1	0	0.8128
9	1	0	0.5156	0	4	0.8009
10	2	1	0.5005	1	2	0.8009
11	1	1	0.4697	1	3	0.7880
12	0	20	0.4538	0	25	0.7745
13	0	8	0.4538	2	29	0.7745

Figure 2.6.1. Survival Function Estimates of Recurrence



The sponsor also excluded Dr. Diamond's site, where there were 6 patients in ITT population with 3 in venlafaxine group, and 3 in placebo group, respectively. The test result is the same.

2.6.2. Sponsor's Analyses on Secondary Endpoints

The Analyses for secondary endpoints are ANOVA with terms for treatment and center, and CMH (for CGI using score) with modridit score. Table 2.6.2 gives p-values for four secondary analyses using LOCF for ITT population. Because there are too many dropouts, none of four analyses using OC are significant.

Table 2.6.2. ANOVA Using LOCF for Secondary Endpoints

		Placebo	Venlafaxine	Diff	P-value
HAM-D:	n	107	106		--
Total	Baseline	4.9	4.5		--
	Change from Baseline	7.7	3.7	-4.0	<.001
HAM-D :	n	107	106		--
Depressed	Baseline	0.5	0.4		--
Mood Item	Change from Baseline	1.0	0.5	-0.5	<.001
MADRS:	n	107	106		--
Total	Baseline	5.3	4.3		--
	Change from Baseline	9.7	5.1	-4.6	<.001
CGI-:	n	107	106		--
Severity	Baseline	1.8	1.7		--
	Change from Baseline	1.1	0.5	-0.6	<.001

2.7. Reviewer’s Analyses

This reviewer verified the sponsor’s analyses according to the statistical plan specified in the protocol, and duplicated the sponsor’s results. In this section, analyses on the censoring pattern and subgroup of gender will be performed.

2.7.1. Analysis on Censoring

Among 106 in venlafaxine group, and 107 in placebo group, there are 24, and 50 had recurrence, respectively.

Since it is difficult to evaluate the potential impact of censoring, one way is to treat censored as failed, i.e., new event is defined as both failed and censored. Log-rank test gives p-value .0001 to compare the new event between venlafaxine and placebo groups. Figure 2.7.1.1 gives the survival function estimates of the new event. The probabilities of having the new event are 71% and 93% for venlafaxine and placebo groups, respectively.

Figure 2.7.1.1. Survival Function Estimates of the New Event

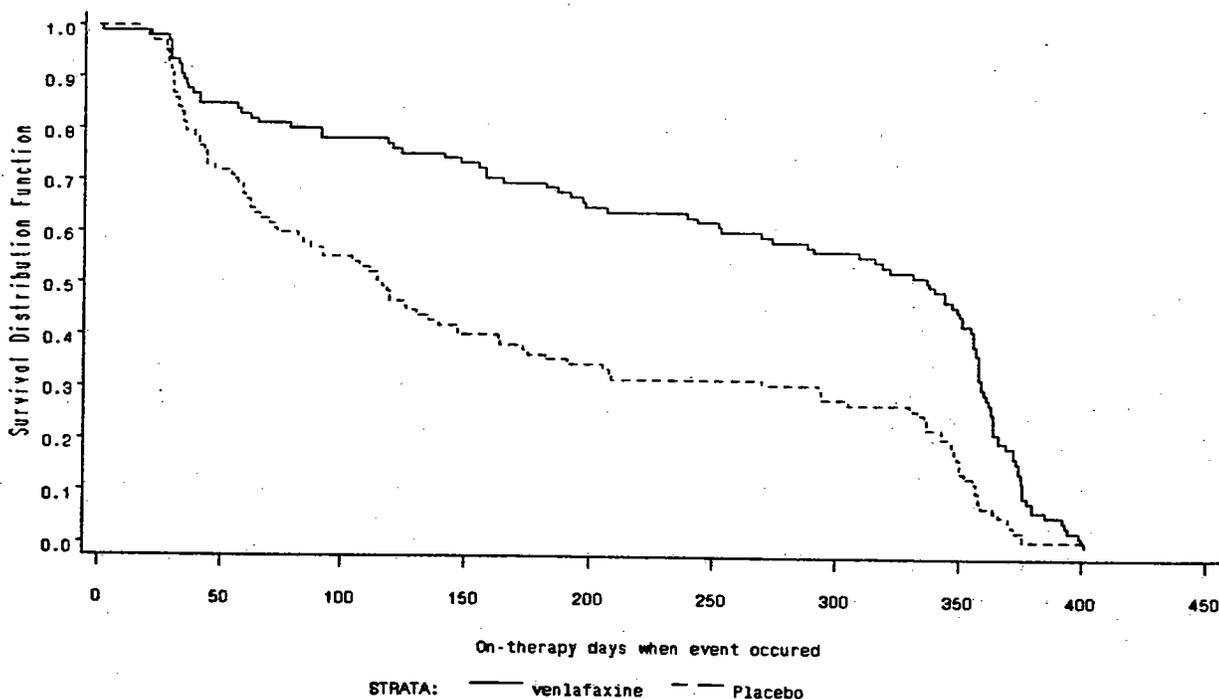


Table 2.7.1.1 presents the censoring rate for placebo and venlafaxine groups. The rate is calculated

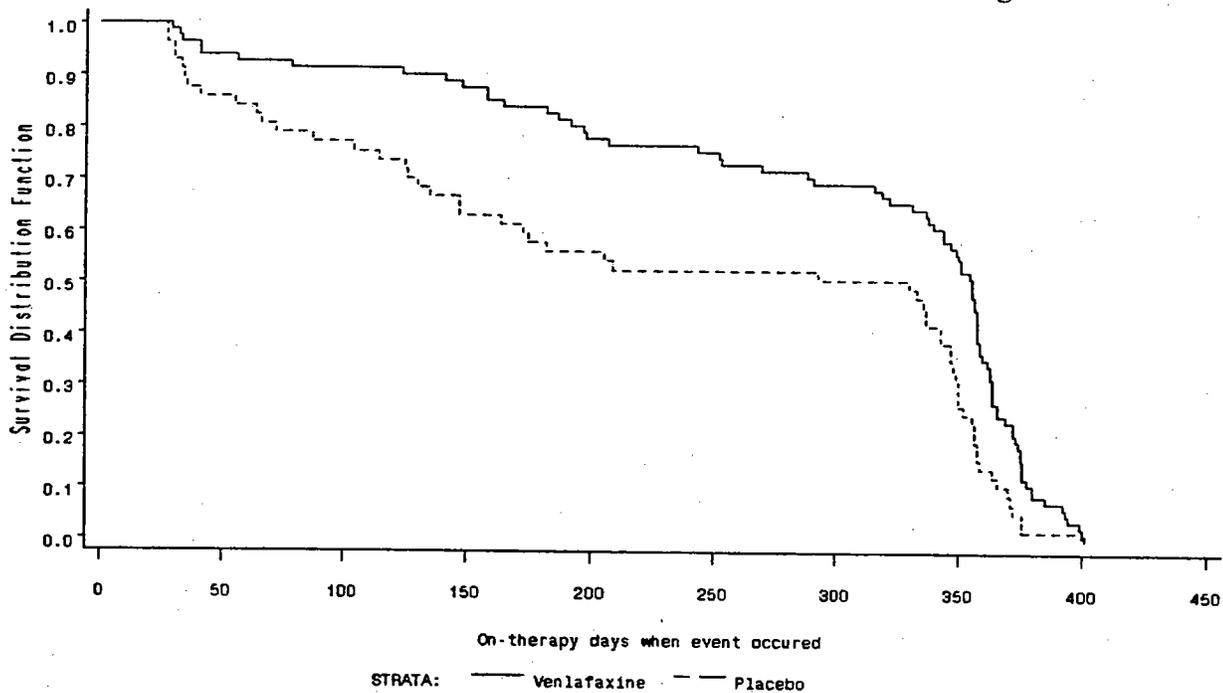
as the number censored divided by the total number left.

Table 2.7.1.1. Censoring Rate for the Remaining Patients

month	Placebo				Venlafaxine			
	number failed	number censored	total left	censoring rate	number failed	number censored	total left	censoring rate
1	10	4	107	4%	6	1	106	1%
2	17	5	93	5%	6	5	99	5%
3	6	4	71	6%	2	1	88	1%
4	9	2	61	3%	4	0	85	0%
5	1	6	50	12%	0	3	81	4%
6	1	3	43	7%	1	3	78	4%
7	2	3	39	8%	0	6	74	8%
8	0	0	34	0%	1	0	68	0%
9	1	0	34	0%	0	4	67	6%
10	2	1	33	3%	1	2	63	3%
11	1	1	30	3%	1	3	60	5%
12	0	20	28	71%	0	25	56	45%

From the above table, it is seen that the censoring rate in placebo group is greater than or equal to that in venlafaxine group up to month 8. A log-rank gives p-value .0009 comparing only censored patients among two groups. Figure 2.7.1.2 gives the survival function estimates of censoring.

Figure 2.7.1.2. Survival Function Estimates of Censoring



From the above figure, it is seen that patients in the venlafaxine group have greater probabilities to stay longer in the trial. To check whether censored patients are comparable, Table 2.7.1.2 presents the change from baseline for CGI, HAM-D total, HAM-D Depressed Mood Item, and MADRS total for the censored patients.

Table 2.7.1.2. Change from Baseline for Censored

month	Censored		CGI		HAM-D:total		HAM-D: Item		MADRS	
	placebo	venlafaxine	placebo	venlafaxine	placebo	venlafaxine	placebo	venlafaxine	placebo	venlafaxine
1	4	1	1.8	1.0	11.5	6.0	1.5	1.0	13.1	10.0
2	5	5	0.6	0.4	5.8	1.8	0.8	0.4	6.8	5.8
3	4	1	1.0	1.0	3.75	3.0	1.5	1.0	8.3	10.0
4	2	0	1.0		3.5		0.5		7.0	
5	6	3	0.2	0.7	1.3	2.3	0.3	0.7	2.5	2.3
6	3	3	0.0	0.3	-0.3	2.0	0.0	0.7	-1.7	2.0
7	3	6	0.0	0.2	5.3	0.8	0.3	0.3	4.3	2.2
8	0	0								
9	0	4		-0.5		-0.8		0.3		0.5
10	1	2	-1.0	0.5	-7.0	2.5	-2.0	0.5	-12.0	1.5
11	1	3	0.0	-0.3	-3.0	1.3	0.0	0.0	-3.0	1.7
12	20	25	0.1	-0.1	0.8	-0.2	0.1	0.0	1.2	0.4

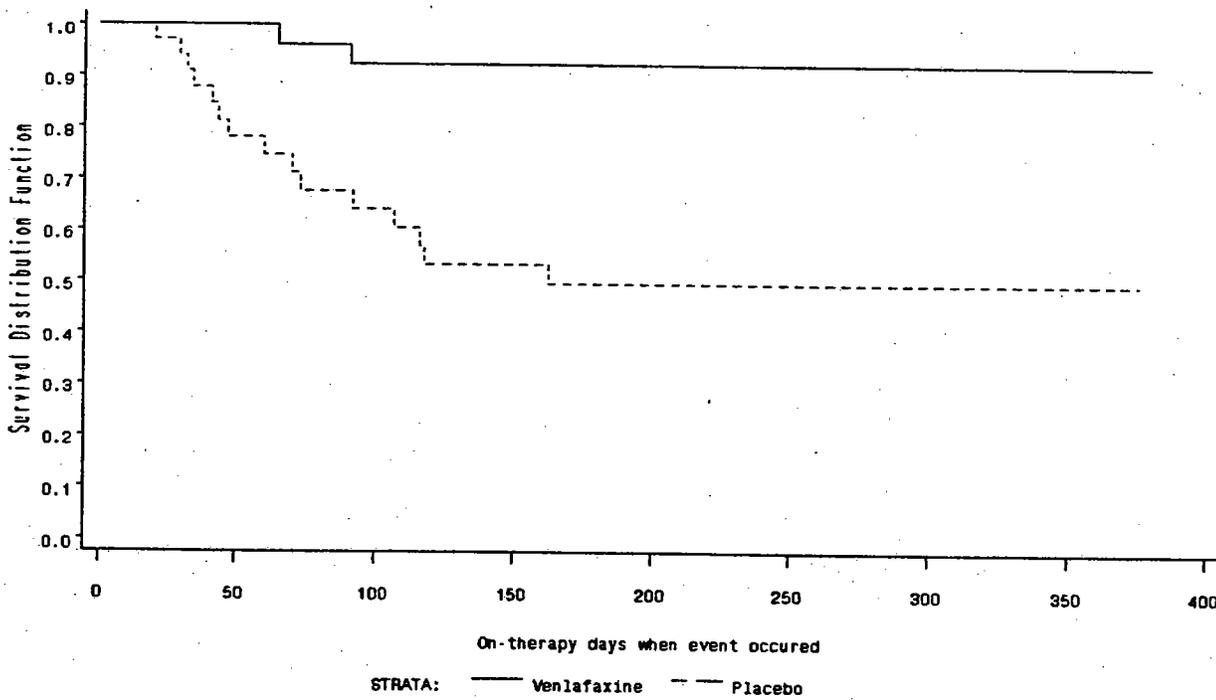
From the above table, no conclusion based on scores can be made among censored patients.

An important question one may ask is whether there are potential impact of censoring. There is no sensible statistical method to handle censoring. However, three facts may support the efficacy of venlafaxine: (i) the log-rank test on the new event gives p-value .0001; (ii) patients in venlafaxine group stayed longer than those in placebo group; and (iii) secondary analyses using LOCF were all favor venlafaxine. This reviewer checked the original submissions to see whether there was any pattern for censoring but the length of the previous trials were much shorter than the current trial, plus responders' data were not available.

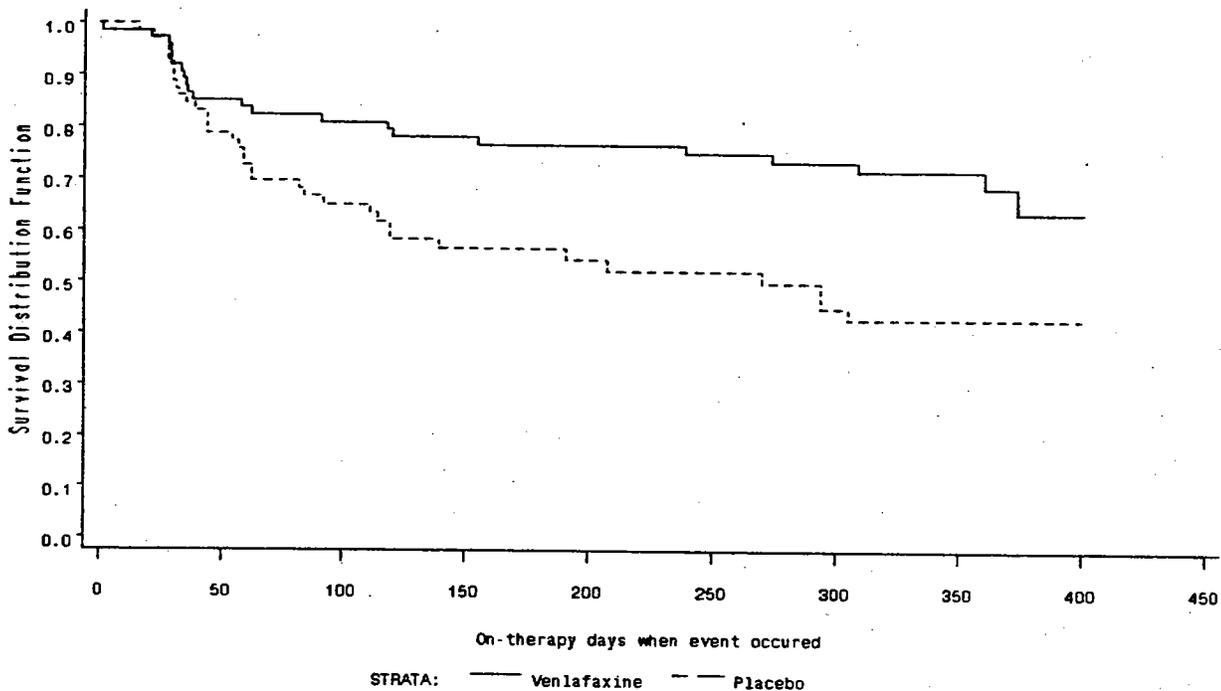
2.7.2. Analysis on Subgroup of Gender

There are 66 males with 31 in venlafaxine group, and 35 in placebo group. Among them, there are 2 in venlafaxine group, and 15 in placebo group who had recurrence. The log-rank test for male gives p-value .0004.

Figure 2.7.2.1. Survival Function Estimates of Recurrence for Male



There are 147 females with 75 in venlafaxine group, and 72 in placebo group. Among them, there are 22 in venlafaxine group, and 35 in placebo group who had recurrence. The log-rank test for female gives p-value .0032.

Figure 2.7.2.2. Survival Function Estimates of Recurrence for Female

3. Study 0600B1-370-US

3.1. Objective

The primary objective was to evaluate the efficacy and safety of venlafaxine ER in the prevention of relapse in outpatients with major depression.

3.2. Efficacy Measures

The efficacy characteristics were measured by Hamilton Psychiatric Rating Scale for Depression (HAM-D), the Montgomery Asberg Depression Rating Scale (MADRS), and the Clinical Global Impression (CGI).

The primary endpoint was the time to relapse of depression. Relapse is defined as one of the following: a) the reappearance of major depressive disorder as defined by DSM-IV criteria and CGI severity score of ≥ 4 , or b) two consecutive CGI severity scores of ≥ 4 , or c) a final CGI severity score of ≥ 4 for any patient who withdrew from the study for any reason. Determination of relapse

according to criterion a) was made by the investigator and recorded on the case report form, to b) and c) was made programmatically.

3.3. Study Design

0600B1-370-US was an 8-month study with an 8-week acute venlafaxine treatment period, and a 6-month randomized, double blind, placebo-controlled, parallel study period comparing venlafaxine with placebo. After a 7-day single-blind placebo lead-in period, all eligible patients were randomly assigned to receive either 37.5 mg or 75 mg venlafaxine for 1 week (study days 1 through 7). During second week (study days 8 to 14), all patients received 75 mg of venlafaxine. From study days 15 to 28, at the discretion of the investigator and according to the tolerance of the patient, each patient took 75 or 150 mg/day of venlafaxine. Based on the same guideline, from study days 29 to 56, each patient took 75, 150, or 225 mg/day of venlafaxine. Patients unable to tolerate a dose within this dose range were withdrawn. On study day 56, patients not meeting the criteria for continuation in the 6-month double-blind treatment period were withdrawn from the study. Responders (The "responder" was defined as a patient whose CGI severity score ≤ 3 and HAM-D score ≤ 10 at the study day 56 evaluation.) who were randomly assigned to placebo group were tapered for up to 2 weeks (study days 57 to 70), and then randomized to either venlafaxine (75, 150, or 225 mg/day) or placebo groups. Efficacy measures HAM-D, MADRS, and CGI were assessed at prestudy screening visit (visit 1), baseline visit (day -1, visit 2), days 7, 14, 28, and 56, (visits 3 - 6) during acute-treatment period, and at days 90, 120, 150, 180, 210, and 240 (visits 8-13) during double blind period.

3.4. Statistical Analysis Plan

The primary analysis is log-rank test.

For secondary analysis, a two-way analysis of variance (ANOVA) model with terms for treatment and center was used to compare the two treatment groups for the HAM-D total, the MADRS total, and the depressed mood item on the HAM-D. For CGI, Kruskal-Wallis test is used.

3.5. Patient Population

3.5.1. Demographic

The study included male/female of 18 years old who met DSM-IV criteria for major depression, had HAM-D total score ≥ 20 on both prestudy screening visit and baseline visit, without 20% decreasing in HAM-D total score between the pre-study screening visit and baseline visit, and had symptoms of depression for at least one month before starting the acute treatment period.

Table 3.5.1.1 presents the demographic configuration of the acute-treatment period.

**Table 3.5.1.1. Demographic and Baseline Configuration for All Patients
(Acute-treatment period)**

Parameter	Venlafaxine
number of patients	490
age (years, mean±sd)	42.0 ± 10.8
sex	
- Female, n (%)	308 (63%)
- Male, n (%)	182 (37%)
race: n (%)	
- white	455 (93%)
- black	15 (3%)
- hispanic	14 (3%)
- asian	3 (1%)
- other	3 (1%)
weight (kg, mean±sd)	79.4 ± 22.2
duration of current episode (days, mean±sd)	167 ± 296
duration of current episode, n (%)	
- < 5 weeks	12 (2%)
- 5-12 weeks	44 (9%)
- 13-24 weeks	63 (13%)
- 25-48 weeks	70 (14%)
- 49-96 weeks	86 (18%)
- > 96 weeks	215 (44%)
number of previous episode (within 5 years, mean ± sd)	1.0 ± 1.2
baseline HAM-D total (mean ± sd)	24.5 ± 3.5
baseline MADRS total (mean ± sd)	28.0 ± 5.6
baseline CGI (n (%))	(n=489)
- 3	7 (1%)
- 4	386 (79%)
- 5	93 (19%)
- 6	3 (1%)

Table 3.5.1.2 presents the demographic configuration of the double blind period.

**Table 3.5.1.2. Demographic and Baseline Configuration for ITT Patients
(Double Blind Period)**

Parameter	Placebo	Venlafaxine
number of patients	157	161
age (years, mean±sd)	41.0 ± 10.6	42.6 ± 9.8
sex		
- Female, n (%)	99 (63%)	105 (65%)
- Male, n (%)	58 (37%)	56 (35%)
race: n (%)		
- white	148 (94%)	155 (96%)
- black	2 (1%)	4 (2%)
- hispanic	3 (2%)	2 (1%)
- asian	3 (2%)	0 (0%)
- other	1 (1%)	0 (0%)
weight (kg, mean±sd)	79.5 ± 21.6	80.4 ± 23.4
duration of current episode (days, mean±sd)	167 ± 306	154 ± 274
duration of current episode, n (%)		
- < 5 weeks	3 (2%)	3 (2%)
- 5-12 weeks	15 (10%)	13 (8%)
- 13-24 weeks	21 (13%)	24 (15%)
- 25-48 weeks	21 (13%)	23 (14%)
- 49-96 weeks	29 (18%)	29 (18%)
- > 96 weeks	68 (43%)	69 (43%)
number of previous episode (within 5 years, mean ± sd)	1.1 ± 1.3	1.0 ± 1.0
baseline (study day 56)		
HAM-D total (mean ± sd)	6.4 ± 3.0	6.5 ± 2.9
MADRS total (mean ± sd)	7.2 ± 4.7	7.4 ± 4.6
CGI (n (%))		
- 1	67 (43%)	58 (36%)
- 2	51 (32%)	61 (38%)
- 3	38 (24%)	42 (26%)
- 4	1 (1%)	0 (0%)

3.5.2. Patient Disposition

Table 3.5.2 presents the patients disposition.

Table 3.5.2. Patients Disposition (All Patients)

Patient group Reason for discontinuation	Placebo	Venlafaxine
Acute-treatment period		
Randomized		490
Any		89 (18%)
Adverse reaction		40 (8%)
Failed to return		23 (5%)
Patient request		9 (2%)
Unsatisfactory response – efficacy		13 (3%)
Protocol violation		1 (<1%)
Other non-medical event		3 (1%)
Double blind period		
Randomized	157	161
Any	115 (73%)	82 (51%)
Adverse reaction	16 (10%)	12 (7%)
Failed to return	22 (14%)	14 (9%)
Patient request	7 (4%)	7 (4%)
Unsatisfactory response – efficacy	66 (42%)	39 (24%)
Protocol violation	1 (1%)	2 (1%)
Other medical event	-	3 (2%)
Other non-medical event	3 (2%)	5 (3%)

3.6. Sponsor's Analyses

There were 500 patients enrolled in the acute-treatment period. Among 500 patients, there were 480 in ITT.

In the double blind period, there were 163 and 165 enrolled in placebo and venlafaxine groups, respectively. There were 138 and 154 in placebo and venlafaxine groups, respectively, in the survival analysis population, which included all patients who had been randomly assigned to receive double blind medication during the double blind treatment period and who had at least one on-therapy CGI severity evaluation.

There were 139 and 154 in placebo and venlafaxine groups, respectively, in the ITT population, which included all patients who completed the acute-treatment period, had been randomly assigned to receive double blind medication, completed the initial taper period, took at least one dose of their assigned double blind medication, had at least one baseline evaluation on at least one primary efficacy parameter (not applicable for CGI improvement), and had at least one evaluation on at least

one of the primary efficacy parameters, either during the double blind treatment period, or within 3 days of the last day of treatment.

The sponsor performed the primary analysis for the survival analysis population, and secondary analyses for ITT population.

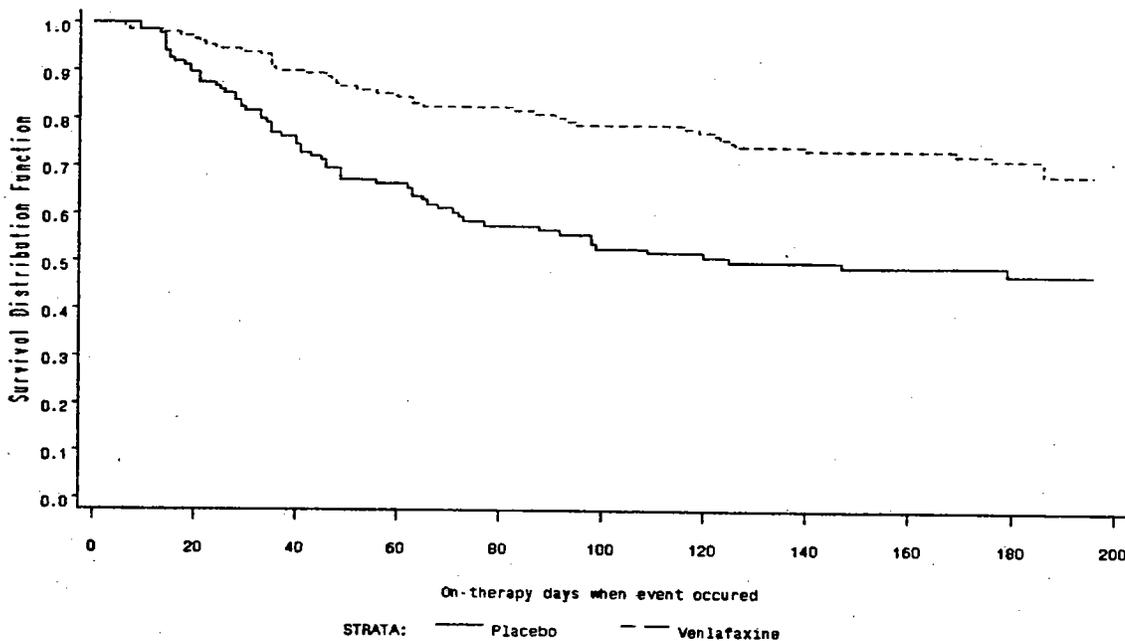
[Reviewer's Remark: The sponsor used 139 and 154 in placebo and venlafaxine groups, respectively, for ITT population. The correct number should be 117 and 144 in placebo and venlafaxine groups, respectively. The sponsor stated to include the log-rank test for ITT population in appendix but forgot to do so. Consequently, the sponsor's secondary analyses, which used 139 and 154 in baseline, were invalid. The sponsor's secondary analyses will not be reported here.]

3.6.1. The Primary Analysis for the Survival Analysis Population

The primary analysis is log-rank test. The result in Table 3.6.1 shows that the probabilities of having the relapse of depression were 28% and 52% after 6 months for venlafaxine and placebo groups, respectively. Figure 3.6.1 is the survival function estimates of relapse. The log-rank test gives p-value .0001.

Table 3.6.1. Life-Table Summary for Survival Probability of Relapse

Month	placebo			venlafaxine		
	Number Failed	Number Censored	Survival	Number Failed	Number Censored	Survival
1	25	4	1.0000	9	3	1.0000
2	19	11	0.8162	14	5	0.9410
3	11	5	0.6663	5	4	0.8465
4	6	4	0.5705	5	5	0.8116
5	2	3	0.5144	5	10	0.7752
6	1	24	0.4944	2	33	0.7360
7	0	23	0.4807	1	53	0.7157

Figure 3.6.1. Survival Function Estimates of Relapse

3.7. Reviewer's Analyses

The sponsor used 139 and 154 in placebo and venlafaxine groups, respectively, for the ITT population, while the correct number should be 117 and 144. There were 22 and 10 in placebo and venlafaxine groups, respectively, who were in the survival analysis population but not in ITT population. This reviewer performed analysis according to the statistical plan specified in the protocol for ITT population. There were 117 and 144 in the ITT population for placebo and venlafaxine groups, respectively.

3.7.1. The Primary Analysis for ITT Population

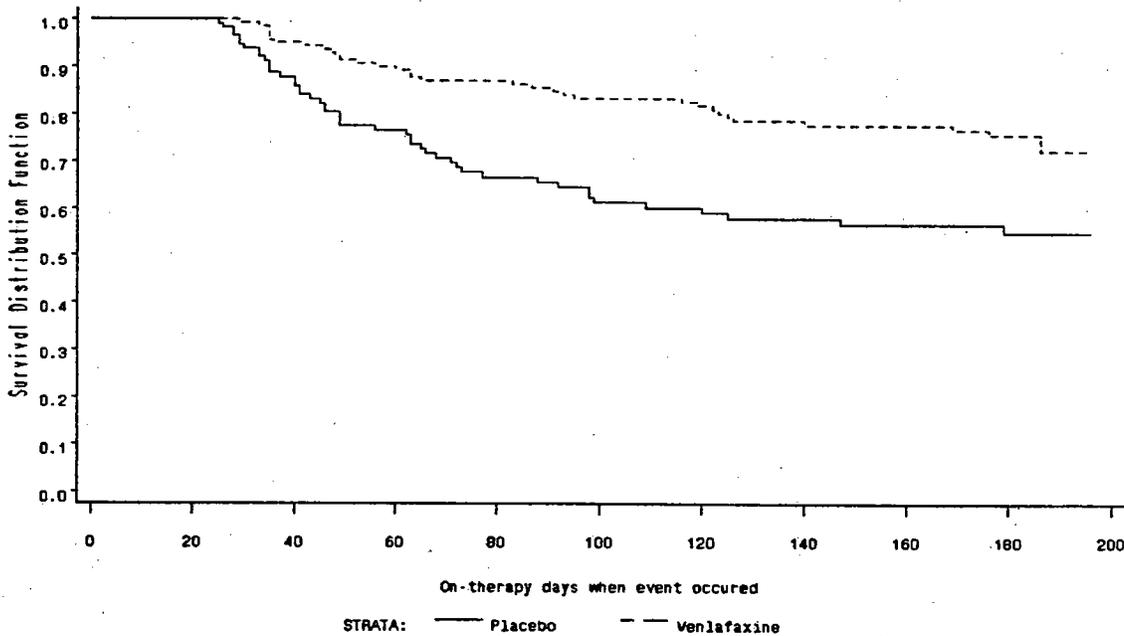
The primary analysis is log-rank test. The result in Table 3.7.1 shows that the probabilities of having the relapse of depression are 24% and 44% after 6 months for venlafaxine and placebo groups, respectively, for ITT population. Figure 3.7.1 is the survival function estimates of relapse. The log-rank test gives p-value .0003.

Analyses on the survival analysis population and ITT population give the similar results.

Table 3.7.1. Life-Table Summary for Survival Probability of Relapse

Month	placebo			venlafaxine		
	Number Failed	Number Censored	Survival	Number Failed	Number Censored	Survival
1	7	1	1.0000	1	1	1.0000
2	19	11	0.9399	14	5	0.9930
3	11	5	0.7674	5	4	0.8934
4	6	4	0.6570	5	5	0.8565
5	2	3	0.5924	5	10	0.8180
6	1	24	0.5694	2	33	0.7767
7	0	23	0.5536	1	53	0.7553

Figure 3.7.1. Survival Function Estimates of Relapse



3.7.2. Analyses on Secondary Endpoints

The Analyses for secondary endpoints are ANOVA with terms for treatment and center, and Kruskal-Wallis test (for CGI using score). Table 3.7.2 gives p-values for four secondary analyses using LOCF. Because there are too many dropouts, none of four analyses using OC are significant.

Table 3.7.2. ANOVA Using LOCF for Secondary Endpoints

		Placebo	Venlafaxine	Diff	P-value
HAM-D:	n	117	144		--
Total	Baseline	6.2	6.5		--
	Change from Baseline	6.9	2.7	-4.2	<.001
HAM-D:	n	117	144		--
Depressed	Baseline	0.5	0.5		--
Mood Item	Change from Baseline	1.1	0.4	-0.7	<.001
MADRS:	n	117	144		--
Total	Baseline	7.1	7.4		--
	Change from Baseline	9.0	3.3	-5.7	<.001
CGI-:	n	116	144		--
Severity	Baseline	1.8	1.9		--
	Change from Baseline	1.0	0.2	-0.8	<.001

3.7.3. Analysis on Censoring

Among 144 in venlafaxine group, and 117 in placebo group, there are 33, and 46 had recurrence, respectively.

Using the same method in Section 2.7.1., i.e., new event is defined as both failed and censored. Log-rank test gives p-value .0007 to compare the new event between venlafaxine and placebo groups. Figure 3.7.3.1 gives the survival function estimates of the new event. The probabilities of having the new event are 63% and 80% for venlafaxine and placebo groups, respectively.

Figure 3.7.3.1. Survival Function Estimates of the New Event

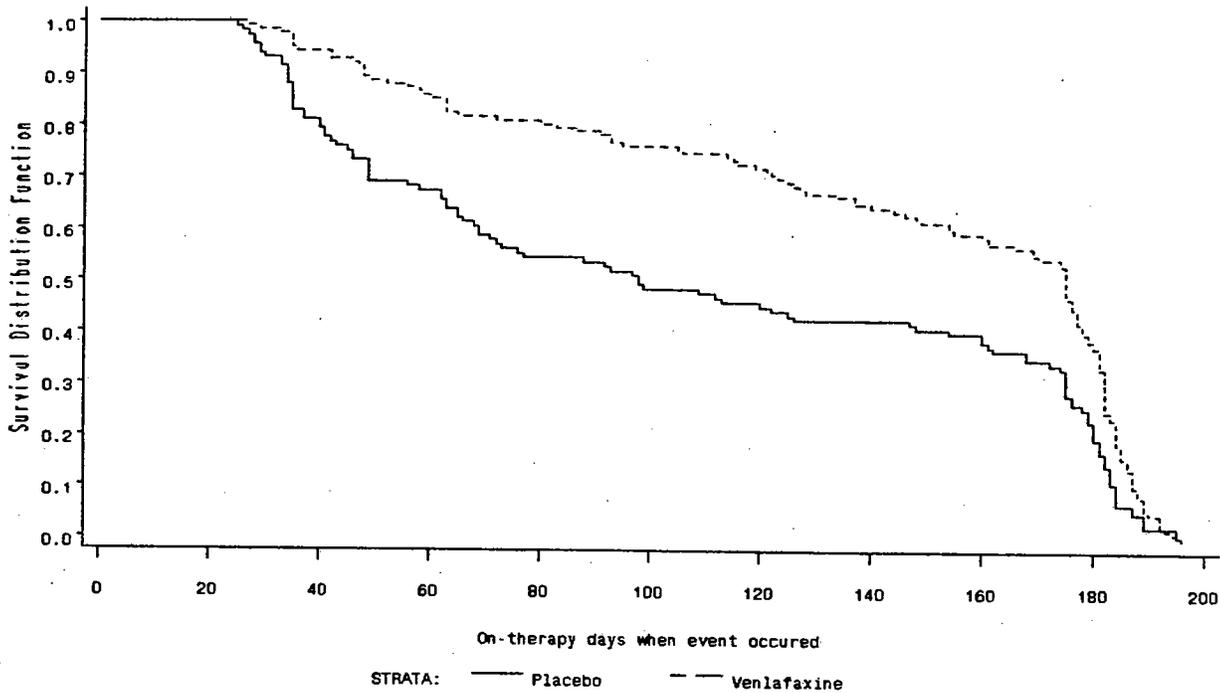


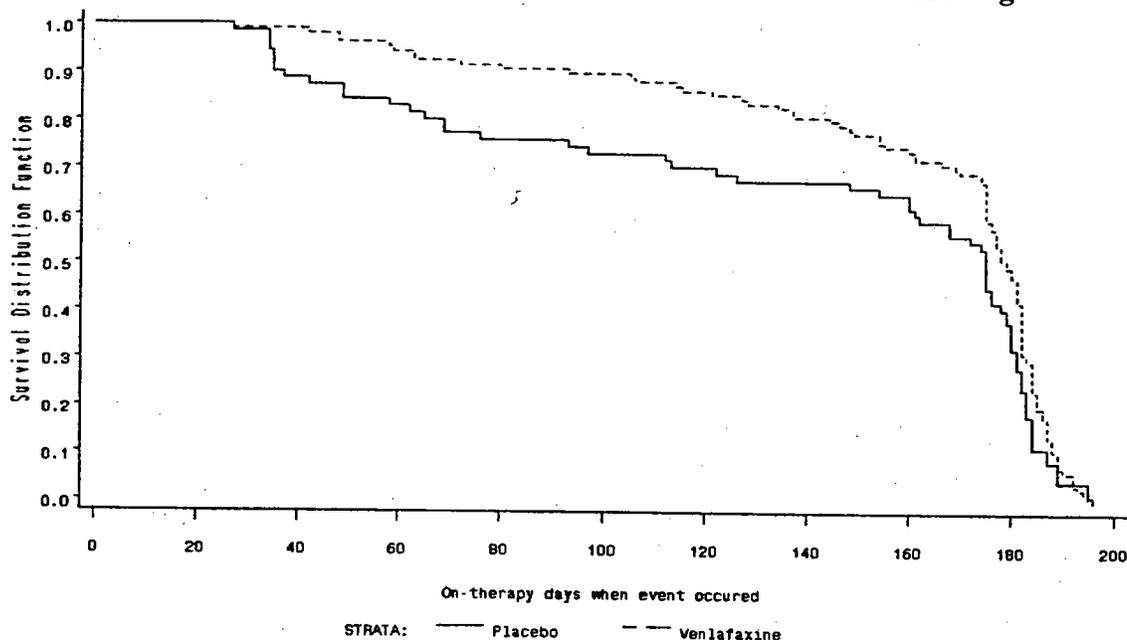
Table 3.7.3.1 presents the censoring rate for placebo group and venlafaxine group. The rate is calculated as the number censored divided by the total number left.

Table 3.7.3.1. Censoring Rate for the Remaining Patients

month	Placebo				Venlafaxine			
	number failed	number censored	total left	censoring rate	number failed	number censored	total left	censoring rate
1	7	1	117	1%	1	1	144	1%
2	19	11	109	10%	14	5	142	4%
3	11	5	79	6%	5	4	123	3%
4	6	4	63	6%	5	5	114	4%
5	2	3	53	6%	5	10	104	10%
6	1	24	48	50%	2	33	89	37%
7	0	23	23	100%	1	53	54	98%

From the above table, it is seen that the censoring rate in placebo group is greater than or equal to that in venlafaxine group up to month 4. A log-rank test gives p-value .0888 when comparing only censored patients among two groups. Figure 3.7.3.2 gives the survival function estimates of censoring. Although the log-rank test is not significant, the two survival curves are separated.

Figure 3.7.3.2. Survival Function Estimates of Censoring



From the above figure, it is seen that patients in the venlafaxine group have greater probabilities to stay longer in the trial. Table 3.7.3.2 gives the change from baseline for censored patients.

Table 3.7.3.2. Change from Baseline for Censored

month	Censored		HAM-D:total		HAM-D: Item		MADRS		CGI	
	placebo	venlafaxine	placebo	venlafaxine	placebo	venlafaxine	placebo	venlafaxine	placebo	venlafaxine
1	1	1	11	4.0	3	1.0	13	5.0	2	0.0
2	11	5	6.9	-1.4	1.1	-0.6	9.1	-4.0	1	-0.2
3	5	4	2.8	-3.5	0.2	-0.3	2.2	-3.8	0.2	-1.0
4	4	5	3.8	-0.6	0.8	-0.2	4.5	-0.8	0.5	-0.4
5	3	10	-0.7	-0.4	-0.3	-0.1	1.3	-0.8	-0.3	-0.4
6	24	33	1	-1.3	0.5	-0.1	-0.3	-2.1	0.1	-0.5
7	23	53	0.9	-1.0	0.1	-0.1	0	-1.8	0	-0.2

From the above table, no conclusion based on scores can be made among censored patients.

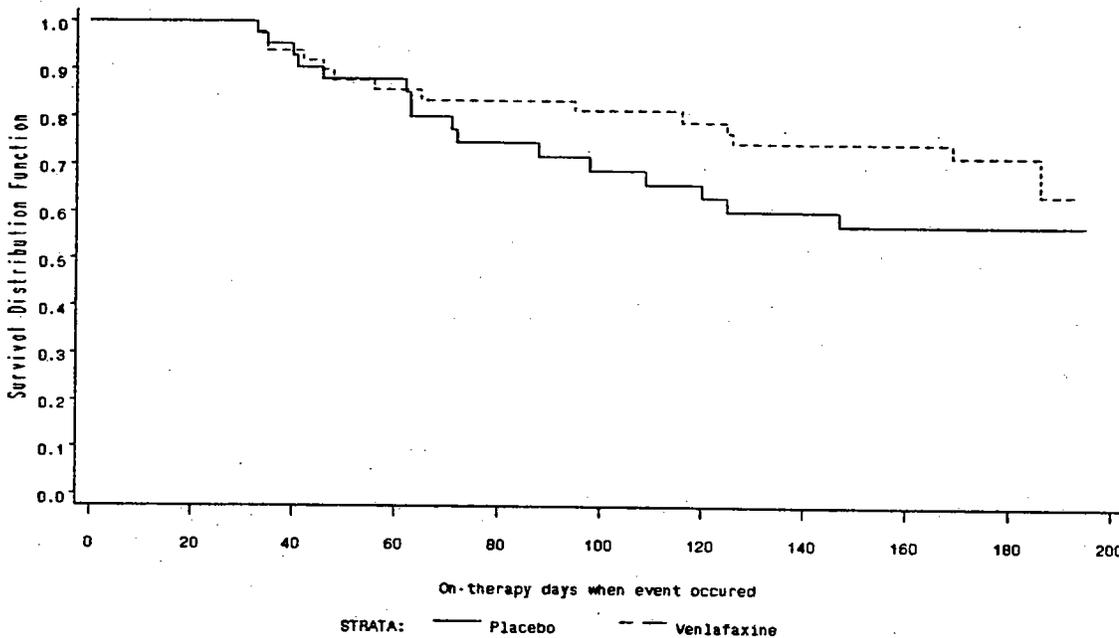
As pointed out in Section 2.7.1, three facts may support the efficacy of venlafaxine: (i) the log-rank test on the new event gives p-value .0007; (ii) patients in venlafaxine group stayed longer than those in placebo group; and (iii) secondary analyses using LOCF were all favor venlafaxine. This reviewer checked the original submissions to see whether there was any pattern for censoring but the length

of the previous trials were much shorter than the current trial, plus responders' data were not available.

3.7.4. Analysis on Subgroup of Gender

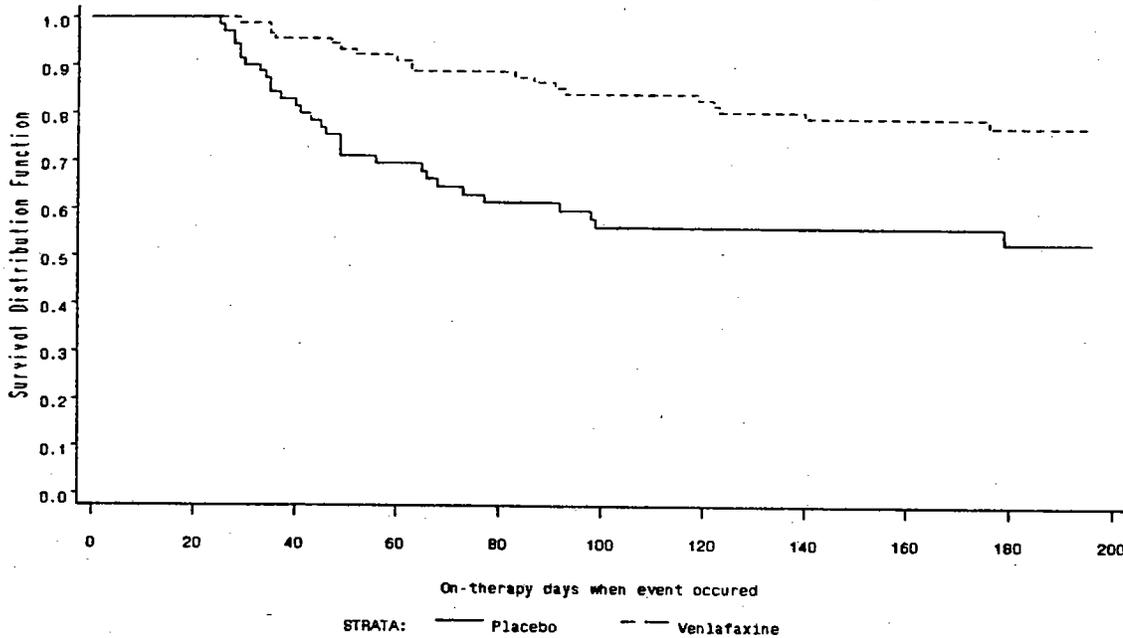
There are 96 males with 50 in venlafaxine group, and 46 in placebo group. Among them, there are 14 in venlafaxine group, and 16 in placebo group who had recurrence. The log-rank test for male gives p-value .2079.

Figure 3.7.4.1. Survival Function Estimates of Relapse for Male



There are 165 females with 94 in venlafaxine group, and 71 in placebo group. Among them, there are 19 in venlafaxine group, and 30 in placebo group who had recurrence. The log-rank test for female gives p-value .0003.

Figure 3.7.4.2. Survival Function Estimates of Relapse for Female



4. Conclusion

The primary analysis based on the submission of NDA 20-151/20-699 provides statistically significant evidence that venlafaxine-treated patients had longer time to the recurrence/relapse of depression than those placebo-treated patients had.

Although there is no sensible statistical method to evaluate possible impact of censoring, analyses on the new event (defined as both failed and censored), on the censoring, and on secondary endpoints are all supportive.

One issue in the design is that potential bias might be introduced when patients were switched from drug (open-label) to placebo (double blind). It is not clear whether the patients would be still blinded once there were certain changes (taste of drug, side effect, etc) caused by such switching.

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Kun He, Statistical Reviewer

Concurrence:

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Dr. Kun Jin, Team Leader

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Dr. George Chi, Director

- CC: HFD-120/Shin
- HFD-120/Turner
- HFD-120/Laughren
- HFD-120/Katz
- HFD-710/Jin
- HFD-710/Chi
- HFD-700/Anello