

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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

MEDICAL REVIEW

Review and Evaluation of Clinical Data
NDA #20-151

Sponsor: Wyeth-Ayerst Research
Drug: Effexor Tablets
Proposed Indication: Depression
Material Submitted: SE1-017(BL) and SE1-018(BL): Response to Approvable Letter
Correspondence Date: March 19, 2001
Date Received: March 21, 2001
Related Supplements: NDA 20-699(Effexor XR)/
SE1-015(BL) and SE1-016(BL)

The above mentioned supplements were submitted to amend the labeling for both Effexor and Effexor XR to add clinical data regarding the longer-term treatment of depression. A review of these supplements was completed by Erick Turner, M.D., on 2-20-01 and an approvable letter was issued by the Division on 2-28-01. This letter stipulated specific language to be used in labeling to communicate this information to prescribers.

The labeling changes made by the sponsor (as presented under Tabs 4 and 6 of this submission for Effexor and Effexor XR, respectively) were compared to the requested changes conveyed in our approvable letter. The changes are in compliance with our requests with two minor exceptions:

- 1) _____ has been changed to "CGI Severity of Illness item."
- 2) the reference to the clinical trials information has been changed from "see _____" to "see CLINICAL TRIALS."

Also, the addition of certain adverse event terms to the ADVERSE REACTIONS section was verified by comparison to the information in Dr. Turner's review.

All changes are acceptable and it is recommended that the above supplements be approved.

S

Gregory M. Dubitsky, M.D.
March 27, 2001

3-28-01

I agree that these
supplements can now
be approved.

S

cc: NDA #20-151
NDA #20-699
HFD-120 (Division Files)
HFD-120/GDubitsky
/TLaughren
/MShin

REVIEW AND EVALUATION OF CLINICAL DATA

NDA numbers:	20-151 and 20-699
Sponsor:	Wyeth-Ayerst
Submission types:	Labeling supplements
Drug Name	
Generic name:	venlafaxine hydrochloride
Trade name:	Effexor
Reviewer information	
Clinical reviewer:	Erick H. Turner, M.D.

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BACKGROUND AND APPLICATION INFORMATION

The sponsor has submitted these labeling supplements as part of a Phase 4 commitment. There are actually 4 submissions. The sponsor is interested in obtaining 2 related labeling claims for 2 formulations of venlafaxine. The table below summarizes the submissions.

Table 1. Overview of the 2 submissions.

Formulation		IR	XR	
NDA #		20-151	20-699	
IND #		27,323	41,412	
Submission date		18-May-00	19-May-00	
PDUFA due date		18-Mar-01	19-Mar-01	
Study #		0600A1-335-US/EU	0600B1-370-US	
Objective		Recurrence	Relapse	
Duration of initial Rx		6 months open label	8 weeks	
Duration of study in question		12 months	6 months	
N	Randomized	235	318	
	Analyzed for efficacy	213	293	
	Completers	86	121	
Dose (mg)		100-200 mg/d BID	75, 150, or 225 qD	
Primary efficacy variable		time to CGI severity > 4	same + 2 other possible criteria	
Results	Relapse rate	Effexor	22%	28%
		Placebo	55%	52%
	log-rank chi-square		17.6	18.6
	p value		< .001	< .001

As the table shows, the sponsor has submitted data using the immediate release (IR) formulation putatively demonstrating efficacy in the prevention of *recurrence* of depression. The sponsor has also submitted data, under the other NDA, using the extended release (XR) formulation putatively demonstrating efficacy in the prevention of depressive *relapse*. The sponsor wishes to obtain labeling claims not only for these, but also, by cross-reference, that each labeling claim be extended to the other formulation. Thus, the sponsor wishes that the claim for prevention of recurrence be extended to the XR formulation and that the claim for prevention of relapse be extended to the IR formulation.

EFFICACY

Efficacy data from IR Recurrence Study 0600A1-335-US/EU

Title of study

The title of the study is: "Six-month, open-label evaluation of the safety and efficacy of venlafaxine followed by a randomized, double-blind, placebo-controlled, one-year evaluation of venlafaxine in the prophylactic treatment of recurrent major depression."

Investigators and sites

This study was begun November 1992 and ended December 1995. The study was conducted at 30 sites in the US, the UK, and Germany. A list of investigators, scanned in from the sponsor's submission, is included in the appendix in Table 13. Of note, one of the investigators listed was Dr. Bruce Diamond.

Study plan

Objectives

The purpose of this study was to determine whether Effexor tablets were superior to placebo in preventing the recurrence of depression in patients who had completely recovered from the index episode during a 6-month course of open-label Effexor treatment.

Population

Patients were to be 18 years of age or older. They were to meet DSM-III-R criteria for major depression, have a minimum prestudy screen and study day -1 (baseline) score of ≥ 20 on the HAMD-21 and no greater than 20% decrease in HAMD between the prestudy screen and the day -1 rating. Also, they were to have symptoms of depression for at least 1 month before starting the open-label period of the study, and have had at least one previous period major depressive episode in the past 5 years, with an interval of at least 6 months between the end of the previous episode and the beginning of the present one. The sponsor added that this 6-month interval was more stringent (longer) than that required by DSM-III-R for a recurrent major depressive episode (2 months).

Excluded were patients who had significant medical illnesses, including MI within the 6 months before the start of open-label treatment and history of seizure disorder (other than single childhood febrile seizure). Patients with a history of bipolar disorder, mania, or of any psychotic disorder not associated with depression were excluded. Organic mental disorders and history of drug or alcohol dependence within 2 years of the start of open-label treatment were excluded, as well.

The patients who entered this study were patients judged to have shown a positive treatment response during a 6-month open label trial. This was defined as a HAMD score ≤ 12 at the study

day 56 evaluation. In addition, they were to have no HAMD score ≥ 20 , no more than 2 HAMD scores > 10 , and no single CGI severity score ≥ 4 ("moderately ill") between study day 56 and study day 180. These entry criteria for the IR recurrence study differed somewhat from those used for the XR relapse study (see below).

Design

Washout and randomization to treatment groups

At the end of the open-label study, patients were receiving a total daily dose of Effexor of 100, 150, or 200 mg/day. Since the tablets were of the 25-mg strength, the number of tablets was 4, 6, or 8.

The double-blind recurrence prevention study began with a 15-day period during which patients randomized to continuation on Effexor were maintained at the same dose and patients randomized to placebo underwent a taper. A combination of Effexor tablets and identical placebo tablets was used such that the total number of tablets was held constant. Every 5 days, patients were to take one less tablet BID from bottle "A" and one more tablet BID from bottle "B". Once a patient was no longer taking any tablets from bottle "A", he/she was to continue to take the same number of tablets from bottle "B" through day 195. For all patients, bottle "A" contained 25-mg venlafaxine tablets. The contents of bottle "B" differed according to treatment group: For patients randomized to venlafaxine, it contained 25-mg venlafaxine tablets; for patients randomized to placebo, it contained identical placebo tablets. Thus, patients randomized to placebo underwent a taper at the rate of 50 mg/day (25 mg BID) every 5 days.

Duration

The duration of this double blind study was 6 months.

Dosing plan

For the active treatment group, 2 to 4 tablets of Effexor 25-mg tablets were administered twice daily. Thus the total daily dose was 100, 150, or 200 mg/day. The placebo group received an equal number of identical placebo tablets.

Concomitant medications

Chloral hydrate (up to 1000 mg at bedtime for sleep) was permitted. Outside the US, short-acting benzodiazepines were permitted at bedtime for sleep. Other than these drugs, concomitant use of investigational or psychopharmacologic drugs (including antidepressants, antipsychotics, anxiolytics, and sedative-hypnotics) was prohibited. Also prohibited was ECT or introduction or change in intensity of formal psychotherapy. Nonpsychopharmacologic drugs with psychotropic effects were prohibited unless the patient had been receiving a stable dose for at least 3 months before the start of the open-label period.

Efficacy assessments

Efficacy was determined by using the following scales: HAM-D, MADRS, and CGI. The study visits took place at 30-day time intervals.

Analysis plan

The primary efficacy measure was the number of patients who entered the double-blind segment

of the study and had a recurrence of depression, defined by CGI Severity score ≥ 4 . Time to recurrence was to be analyzed by survival analysis procedure using the log-rank test.

Comparability of treatment groups was to be tested by ANOVA for age, weight, duration of current episode of depression, and baseline scores on the HAM-D total and factor scores and the MADRS total score. The Kruskal-Wallis test was to be used to compare the scores on the HAM-D and the MADRS items. The Kruskal-Wallis test was also to be used to compare the CGI Severity item. [The sponsor used a different test in its submission – see below.] The chi-square test of Fisher's exact was to be used to compare the distribution of nominal attributes, such as race and sex, to test for equivalence with respect to concurrent diagnoses and concomitant medications.

Amendments

Three changes were made after the initiation of the study. In the US, the protocol was amended to provide revised information concerning treatment of overdoses and to change the laboratory used, in the event of overdose, for analyzing study drug plasma concentrations. In Europe, the protocol was amended to exclude collection of data on race because of legal considerations.

Study conduct / outcome

Patient disposition

A total of 495 patients began the open-label study. 12 of these failed to return after the day-1 visit. 286 patients completed the open-label period and 237 of these continued into the double-blind period, 2 of whom were lost to follow-up. Of the remaining 235 patients, 123 were randomized to the placebo arm, while the remaining 112 were randomized to the venlafaxine arm.

213 patients contributed data that were analyzed for efficacy. The number of patients that completed the entire 12 months of the study was 86. The following table summarizes the disposition of patients.

The following table was scanned in from the sponsor's submission. It shows the patient status over time for both the open-label and the double-blind study.

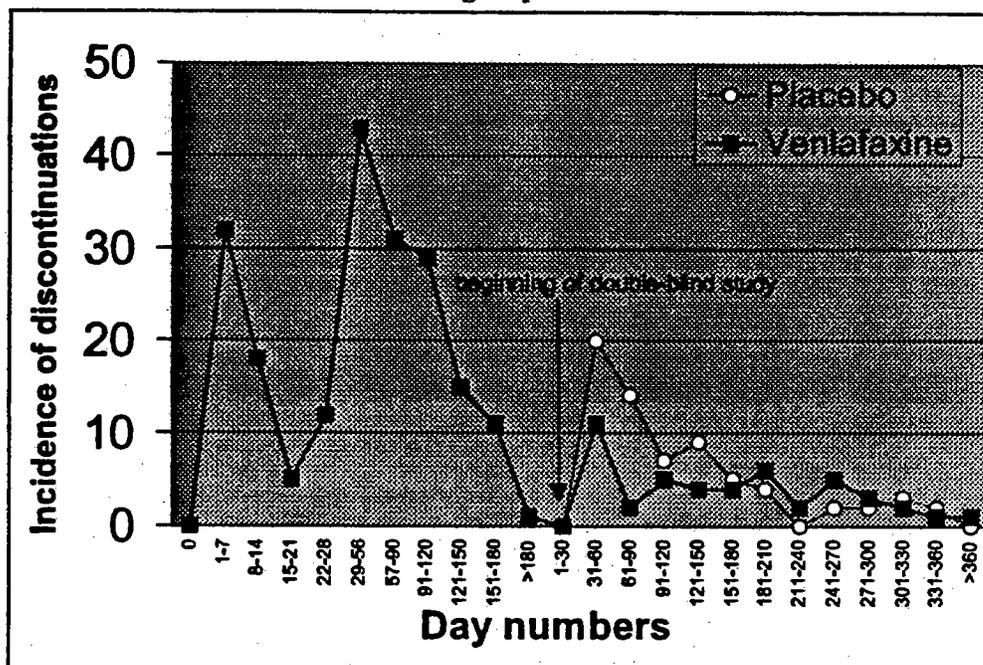
Table 2. Number of patients continuing and discontinuing by drug group for both open-label and double-blind treatment phases.

TABLE 8.1B. PATIENT STATUS OVER TIME: NUMBER OF PATIENTS					
Study Period Time Period (days)	Placebo		Venlafaxine		
	C ^a	D ^a	C ^a	D ^a	
Open-label	NA		(n = 483)		
1-7			451	32	
8-14			433	50	
15-21			428	55	
22-28			416	67	
29-56			373	110	
57-90			342	141	
91-120			313	170	
121-150			298	185	
151-180			287	196	
>180			286	197	
Double-blind	(n = 123)		(n = 112)		
1-30	98	25	102	10	
31-60	78	45	91	21	
61-90	64	59	89	23	
91-120	57	66	84	28	
121-150	48	75	80	32	
151-180	43	80	76	36	
181-210	39	84	70	42	
211-240	39	84	68	44	
241-270	37	86	63	49	
271-300	35	88	60	52	
301-330	32	91	58	54	
331-360	30	93	57	55	
>360	30	93	56	56	

a: C = the number of patients who completed the time period; D = the cumulative number of patients who discontinued by end of the time period.

Using the sponsor's data in the table above, I calculated the number of patients discontinuing (for recurrence of depression as well as for dropout) occurring within each time interval. The results are shown in the graph below.

Figure 1. Discontinuations (dropouts + depressive recurrences) by time interval by drug group.



Below is a table showing patient dispositions by treatment group.

Table 3. Patient disposition by treatment group.

Disposition	Treatment group	
	Placebo	Venlafaxine
Enrolled	123	112
Intent-to-treat	107	106
Completed	30	56
Discontinued	93	56
D/C for AEs	12	9
D/C for deterioration	59	24
Lost to follow-up/other	22	23

More detailed information on withdrawals is shown in the Appendix as Table 14.

Demographics and baseline characteristics

The table below summarizes the baseline characteristics of the sample of intent-to-treat patients. "Baseline" was defined as occurring at the end of the open-label study (day 180). P values for the comparisons between the treatment groups were all nonsignificant. (The one that came closest to reaching statistical significance, $p=.08$ for mean baseline MADRS, is shown; the next

lowest p value was .21.) Thus, demographically, the two treatment groups appeared comparable.

Table 4. Demographics and baseline characteristics.

Variable		Treatment group		P value
		Placebo N = 123	Venlafaxine N = 112	
Sex	Male	43 (35%)	34 (30%)	NS
	Female	80 (65%)	78 (70%)	
Mean age (yrs)		43.5	43.7	NS
Race	Caucasian	87 (71%)	81 (72%)	NS
	Black	5 (4%)	3 (3%)	
	Other	2 (2%)	4 (4%)	
	Not available*	29 (24%)	24 (21%)	
Baseline depression rating	HAMD-21	4.9	4.4	NS (.30)
	MADRS	5.2	4.2	NS (.08)
Duration of current episode (wks)		41.6	42.8	NS (.75)
No. previous episodes (past 5 yr)		1.5	1.3	NS (.26)
CGI Severity	0	1 (1%)	0 (0%)	NS (.21)
	1	56 (46%)	54 (49%)	
	2	35 (28%)	41 (37%)	
	3	30 (24%)	15 (14%)	
	4	1 (1%)	1 (1%)	

*Information on ethnicity not collected in Germany or the UK (see section on amendments).

I noticed in the listing of baseline CGI Severity scores that there was a larger number of patients with CGIs = 3 in the placebo group than in the venlafaxine group. Since a CGI score of 4 was the criterion for recurrence of depression, these patients may be thought of as being at the cusp of a recurrence already at baseline. Looking at the other baseline measures of depression, there was a trend toward higher baseline MADRS scores in the placebo group ($p=.08$). Returning to the CGI Severity, the statistical test used by the sponsor was the chi-square test. However, as noted earlier, the protocol-specified method of analysis of the baseline CGI Severity was to be the Kruskal-Wallis test.

Dr. He made the observation that the sponsor's table, recreated above, contained some errors. Although the sponsor presented results on the pool of all patients, the protocol seems to say that the ITT pool of patients was the primary dataset to be analyzed. (I use the word "seems" because the protocol was somewhat vague on this point.) Dr. He used the pool of ITT patients in his analyses. He also noted that the sponsor showed in the table a few patients with CGI scores of 4; these patients should have been excluded, according to the protocol exclusion criteria.

Finally, he noted the sponsor's apparent inclusion the one patient (in the placebo group) with a CGI=0. Since that score means "not assessed", that patient should not have been included in the analysis, either.

Dr. He's Kruskal-Wallis analysis of the CGI, with the above-mentioned adjustments, yielded results similar to that presented in the submission by the sponsor.

Still concerned about the imbalance in the number of patients with CGIs of 3 in the placebo group compared to the drug group, I asked Dr. He if he would perform some additional analyses. I asked if he would redo the survival analysis adjusting for this apparent imbalance in baseline CGI scores. I will report the results of this below in the section on efficacy results.

Efficacy results

Results on primary endpoint for Study 0600A1-335-EUIUS

The sponsor presented the results both including and excluding data collected by Dr. Bruce Diamond (site 33504). Dr. Diamond's site contributed only 6 patients: 3 placebo patients and 3 venlafaxine-treated patients. There were 2 patients in the placebo group who had depressive recurrences and 1 patient in the drug group who had a recurrence. Dr. He analyzed the dataset both including and excluding Dr. Diamond's 6 patients and found no difference in the resulting p value.

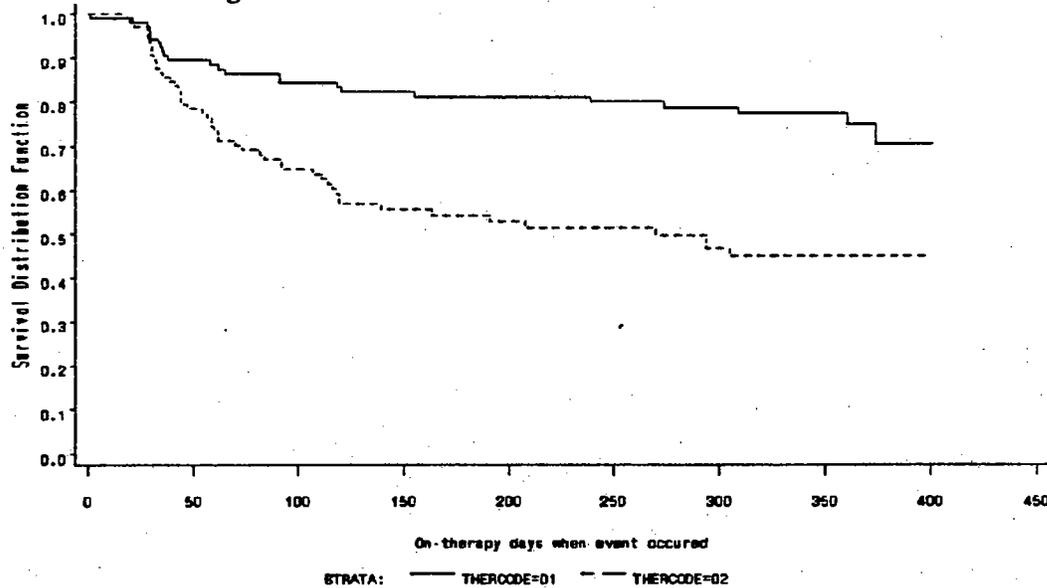
In addition, the sponsor presented the results including and excluding data from the first 28 days of the study. The latter was done to evaluate whether placebo-treated patients who withdrew from the study early (day 1-28) did so because discontinuation symptoms associated with the switch from venlafaxine to placebo, rather than because of a recurrence of depression. As noted above, the dataset including the first 28 days was the pool of all patients. The effect of excluding the first 28 days was similar to that of using the pool of ITT patients, which was the pool analyzed by Dr. He, the statistician.

Below I have pasted in the results from Dr. He's statistical review.

Table 5. Life-Table Summary for Survival Probability of Recurrence

Month	placebo			venlafaxine		
	Number Failed	Number Censored	Survival	Number Failed	Number Censored	Survival
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. Survival Function Estimates of Recurrence



As the above table shows, the rate of recurrence was 23% for the Effexor group compared to 55% for the placebo group. The difference between the two treatment groups was statistically significant by the log-rank test (chi-square = 17.6, p=.0001).

As noted earlier, I had questions about whether the imbalance in the number of patients with baseline CGI scores of 3 (substantially more in the placebo than in the drug group presumably

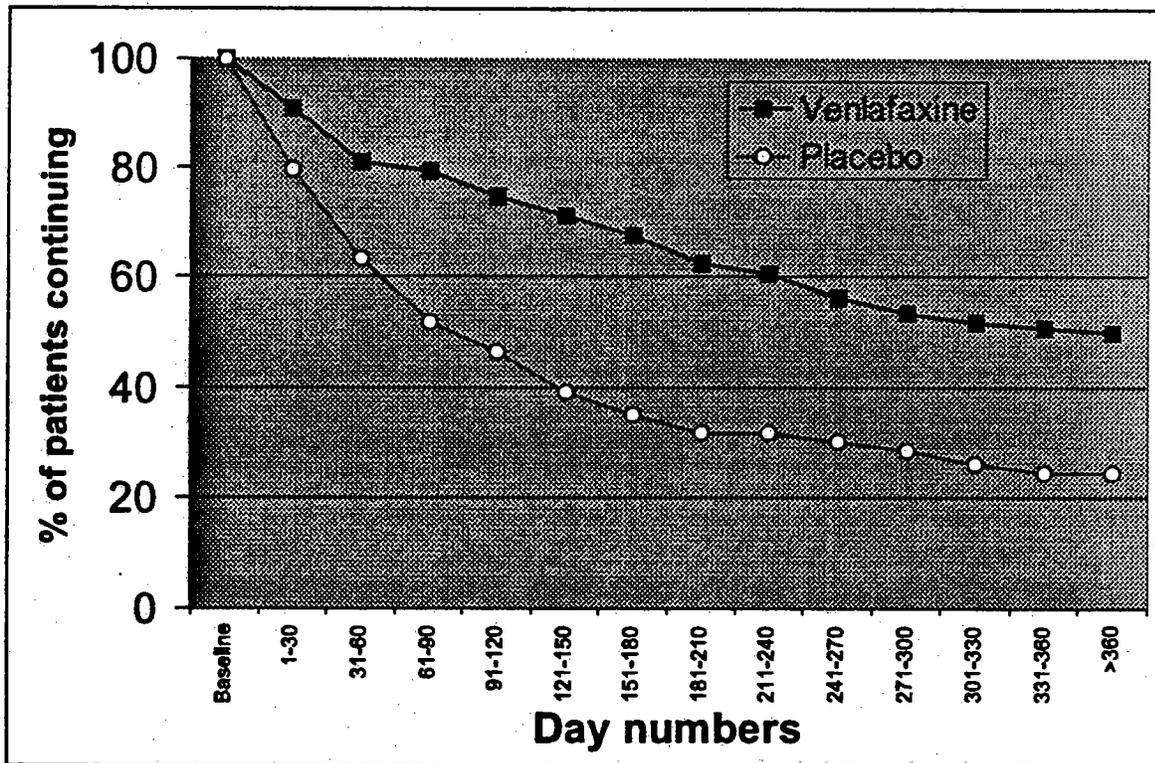
closer to meeting criteria for depressive recurrence). I had asked Dr. He to reanalyze the data making adjustments for this imbalance. First, he removed all patients with CGI scores of 3; this yielded a $p=.0001$, still highly significant.

Second, he balanced the N in the two CGI=3 groups by removing 12 patients who experienced recurrences. (Rather than removing them by choosing 12 at random, he used this method as a "worst case scenario" for venlafaxine, effectively decreasing the recurrence rate within the placebo group and biasing against a finding of superiority for venlafaxine. Even with this bias, venlafaxine remained superior to placebo, with a lower rate of depressive recurrence ($p=.0008$).

Finally, Dr. He performed a survival analysis of just the subset of patients with CGI=3. This yielded a trend level of significance ($p=.14$). However, with such a small sample size (30 placebo patients and 15 venlafaxine patients), we expected that there would not be enough power to detect a difference.

Below I have created a graph of the percentage of patient continuing in the study by treatment group. The purpose of this is to deal with the possibility that the positive study result may have been sensitive to the stated reason for patient discontinuation, ie. whether patients who may have had recurrences, or been at the cusp of recurrences, may have been coded as having dropped out for other reasons, eg. AEs.

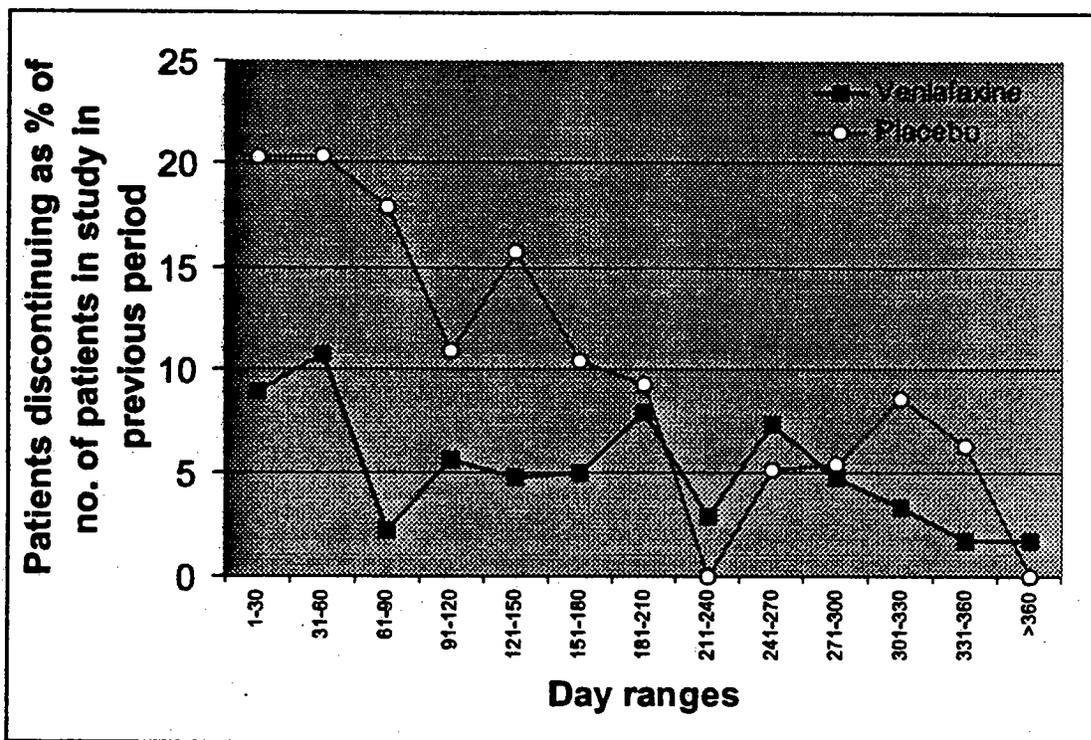
Figure 3. Cumulative continuation rate for patients by drug group in Study 0600A335US/EU.



As this graph shows, the two lines separate during the first 2 to 3 months; after that they appear to parallel one another. At endpoint, the percentages of patients still in the study are 50% for venlafaxine versus 24% for placebo. To look more closely at the how the continuation rate

differs on an “instantaneous”, rather than cumulative, basis, I created the graph below.

Figure 4. “Instantaneous” discontinuation rate for patients by drug group in Study 0600A335US/EU.



This graph more clearly makes the point that most of the difference between the two treatment groups, in terms of number or percentage of patients not continuing for whatever reason, occurs primarily in the first 3 to 5 months. From the 6-month time point onward, the two groups are indistinguishable. It appears that anyone who is going to have a relapse (or recurrence – I will deal with the semantic issue later) has already relapsed by that time point.

Efficacy analyses of secondary endpoints for Study 0600A1-335-EUIUS

Results analyses on secondary endpoints are shown below. These are shown in the table below, which was pasted in from Dr. He’s review.

Table 6: Results of ANOVA on secondary endpoints using LOCF method (from Dr. He' review)

		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

In addition to the LOCF analyses, OC analyses were performed. However, none of these were statistically significant, apparently due to loss of statistical power due to the number of dropouts.

Efficacy conclusions for study 0600A335USIEU

It appears that this study provides evidence of venlafaxine's superiority over placebo in this study design.

Efficacy data from XR Relapse Study 0600B1-370-US

Title of study

The title of the study is: "An evaluation of venlafaxine ER in the prevention of relapse in outpatients with major depression".

Investigators and sites

This study was begun June 1996 and ended April 1998. The study was conducted at 13 sites in the US. A list of investigators, scanned in from the sponsor's submission, is included in the appendix as Table 15. (Dr. Diamond was *not* listed for this study, as was the case for the recurrence study using the IR formulation.)

Study plan

Objectives

The purpose of this study was to determine whether Effexor extended release tablets were superior to placebo in preventing the relapse of in outpatients with major depression.

Population

The sponsor's plan was to recruit 500 outpatients with major depression, 18 years of age or older, in order to allow for the evaluation of approximately 300 patients in the double-blind section of the study. 500 were indeed enrolled, 490 were analyzed for safety, 480 for efficacy, and 401 completed the acute treatment period. Of these, 328 were enrolled in the double-blind treatment period, 318 were randomized. The survival analysis population was 292, 293 were analyzed for efficacy (ITT), and 121 were completed.

In order to enter the double-blind portion of the study, patients were to have a CGI Severity score of ≤ 3 and a HAMD-21 score ≤ 10 at the study day 56 evaluation. These entry criteria for the XR relapse study differed somewhat from those used for the IR recurrence study (see above).

Design

The relapse prevention portion of the study followed (a) a 4 to 10 day single-blind placebo lead-in, (b) an initial acute treatment section consisting of a 2-week double-blind to dose safety and efficacy evaluation, and (c) a 6-week open-label safety and efficacy evaluation. Thus the relapse prevention period was preceded by 6 to 8 weeks of active treatment. The duration of the relapse prevention study was 6 months.

Washout and randomization to treatment groups

During the open-label portion study, ie. prior to the relapse prevention study, patients took one, two, or three 75-mg venlafaxine-ER capsules daily in the AM (total daily dose 75, 150, or 225 mg), according to the discretion of the investigator and the tolerance of the patient. Upon entering the relapse prevention of the study, patients were randomized to either continuation of the same dose of venlafaxine-ER or to be tapered to placebo. This was accomplished with a 2-bottle system in which, each week, patients took one less capsule less daily from bottle A and one more capsule daily from bottle B. Bottle A contained 75-mg capsules for all patients. Bottle B contained 75-mg capsules for the active-treatment group but placebo for patients randomized to placebo. Thus, patients randomized to the placebo group were tapered at the rate of 75 mg per week.

Duration

The double-blind "maintenance" or relapse prevention phase lasted 6 months, beginning at day 71 (day 1 being the start of the initial acute treatment phase) and ending with day 240.

Dosing plan

As noted above, patients were randomized to placebo or to active treatment with 75, 150, or 225 mg venlafaxine-ER. All capsules were taken in the morning.

Concomitant medications

Concomitant medications were essentially as described for the recurrence study using the immediate-release formulation (see above). One difference was that, in the ER study, Ambien, up to 10 mg, was allowed (but not more frequently than twice per week).

Efficacy assessments

As described for the study of the IR formulation, the HAMD-21, MADRS, and CGI scales were performed at 30-day intervals. In addition, the Quality of Life Questionnaire and the Investigator and Patients Subjective Rating were conducted at study days 56 and 240 (beginning and end of

relapse prevention portion of study, respectively).

Analysis plan

The primary efficacy variable was to be the number of patients who entered the double-blind portion of the study and had a relapse of depression. (In the protocol, no distinction was made between an "all patients" population and a "survival analysis" population; the study report presented results from the latter.)

The definition of relapse was somewhat more elaborate than the definition of recurrence described for the IR study (see above). Relapse was defined by (a) a reappearance of major depressive disorder as defined by DSM-IV criteria *and* a CGI-Severity score ≥ 4 ("moderately ill"), *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. The key efficacy parameter was to be time to relapse which was to be analyzed by survival analysis procedure using the log-rank test (as was the case for the IR recurrence study).

Amendments

Amendment 3 is the protocol submitted along with the NDA. (The location of the protocol was not listed in the submission table of contents. I obtained the location (in volume 12) after calling the sponsor.) This amendment was submitted April 11, 1997. In this amendment, the sponsor stated its intent to recruit 500, rather than 400, patients to allow for the evaluation of 300 in the double blind portion of the study. The amendment also allowed for the use of Ambien as a sedative-hypnotic.

Study conduct / outcome

Patient disposition

Table 7. Number of patients over time in acute treatment period

Time Period (Days)	Venlafaxine ER ^a (n = 490)	
	C ^b	D ^b
1-7	474	16
8-14	455	28
15-21	447	43
22-28	437	53
29-35	428	62
36-42	419	71
43-49	413	77
50-56	410	80
> 56	401	89

a: Patients received 37.5 or 75 mg of venlafaxine ER (double-blind administration) for the first week of the 8-week acute-treatment period. All patients received 75 mg (double-blind administration) during week 2. Thereafter, an open-label dose was given with single-step increases, up to a maximum dose of 225 mg.

b: C = the number of patients who completed the time period; D = the cumulative number of patients who discontinued by end of the time period.

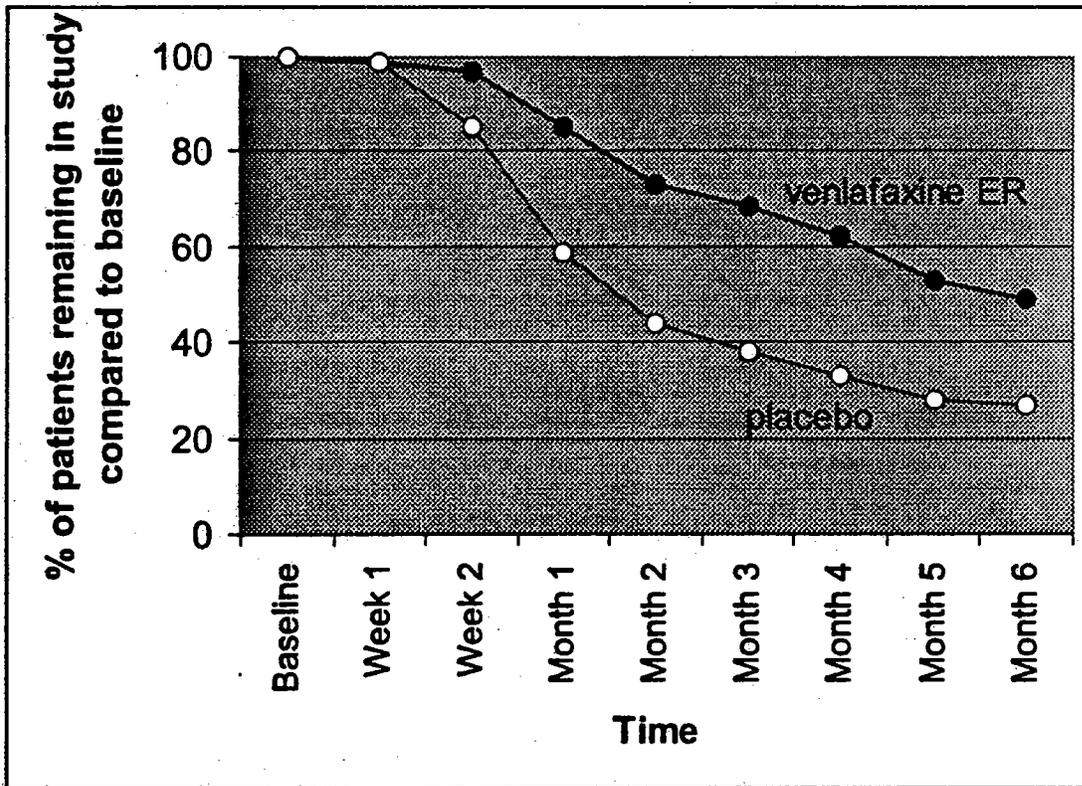
Table 8. Number of patients over time in double-blind relapse prevention period.

Time Period Long Term (LT)	Placebo (n = 157)		Venlafaxine ER (n = 161)	
	C ^a	D ^a	C	D
Week 1	155	2	159	2
Week 2	134	23	156	5
Month 1	92	65	137	24
Month 2	69	88	118	43
Month 3	60	97	110	51
Month 4	52	105	100	61
Month 5	44	113	85	76
Month 6	42	115	79	82

a: C = the number of patients who completed the long-term time period; D = the cumulative number of patients who discontinued by end of the long-term time period.

Using the data above, I constructed the graph below. It shows the percentage of the original number of patients in each drug group that remained in the study over time.

Figure 5. Percentage of patients (compared to baseline) remaining in relapse prevention study by drug group.



As this graph shows, the percentage of patients remaining in the Effexor XR group was higher than in the placebo group. At the end of the study, the percentages were 49% and 27%, respectively. Looked at another way, the percentage of completers was 81% higher for the drug

group than for the placebo group. I performed a chi-square test on the number of patients at the end of the study who had continued versus discontinued using the program Epi-Info. Chi-squared (Yates corrected) = 15.9, p = .00007.

The reasons for withdrawal are shown in the table below.

Table 9. Number (%) of patients who withdrew by primary reason.

Study Period Primary Reason	Placebo	Venlafaxine ER	P-value ^a
Acute-treatment		(n = 490)	
Any reason	NA ^b	89 (18)	-
Adverse reaction	NA	40 (8)	-
Failed to return	NA	23 (5)	-
Patient request	NA	9 (2)	-
Unsatisfactory response - efficacy	NA	13 (3)	-
Protocol violation	NA	1 (<1)	-
Other non-medical event	NA	3 (1)	-
Double-blind treatment	(n = 157)	(n = 161)	
Any reason	115 (73)	82 (51)	< 0.001
Adverse reaction	16 (10)	12 (7)	0.433
Failed to return	22 (14)	14 (9)	0.158
Patient request	7 (4)	7 (4)	1.000
Unsatisfactory response - efficacy	66 (42)	39 (24)	< 0.001
Protocol violation	1 (1)	2 (1)	1.000
Other medical event	-	3 (2)	-
Other non-medical	3 (2)	5 (3)	0.723
a: Significance based on Fisher's exact test.			
b: Not applicable (NA) for the acute-treatment period because patients were randomly assigned to the placebo group only for the double-blind treatment period.			

As the above table shows, the difference between the drug and placebo groups was statistically significant for "any reason" and for "unsatisfactory response – efficacy".

Below is a table from the study report showing the number of patents in each population subset for each treatment group. The footnotes define what the sponsor means by survival analysis population and ITT population.

Table 10. Summary of patient evaluability in Effexor XR relapse study.

Population Subset	Placebo	Venlafaxine ER
Acute-treatment period		
Enrolled	NA	500
Valid for safety analysis	NA	490
Intent-to-treat analysis	NA	480
Double-blind treatment period		
Enrolled	163	165
Valid for safety analysis ^a	157	161
Valid for efficacy analyses		
Survival analysis ^b	138	154
Intent-to-treat (ITT) ^c	139	154
<p>a: All patients who entered the double-blind period, ie, all randomized patients, except the 10 no-data patients listed in Table 8.1B, footnote b.</p> <p>b: The survival-analysis population 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.</p> <p>c: The intent-to-treat population 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.</p>		

Demographics and baseline characteristics

The two treatment groups were very comparable in terms of demographic differences. There were no significant differences between the two groups. The sponsor's table appears in this review in the appendix as Table 16.

Efficacy results

Results on primary endpoint for Study 0600B1-370-US

Below I have pasted in the life table summary from the study report, which is based on the survival analysis population.

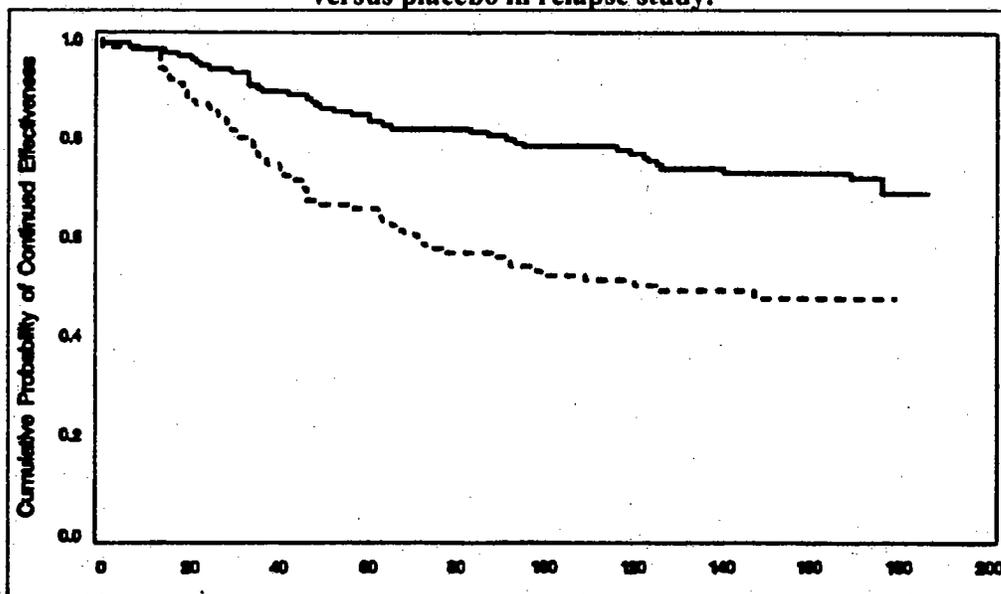
Table 11. Life table summary for cumulative probability of continued effectiveness for survival analysis population in Effexor XR relapse study.

Time Period Double-blind Treatment	Placebo (n = 138)			Venlafaxine ER (n = 154)		
	SR ^a	W/D ^b	Cumulative Probability	SR	W/D	Cumulative Probability
Month 1	25	4	0.82	9	3	0.94
2	19	11	0.67	14	5	0.85
3	11	5	0.57	5	4	0.81
4	6	4	0.51	5	5	0.78
5	2	3	0.49	5	10	0.74
6	1	24	0.48	2	33	0.72

a: SR = Number of patients with relapses.
b: W/D = number of withdrawals without relapses.

The survival analysis showed that, during the 6-month double-blind period, significantly more placebo-treated patients than venlafaxine ER-treated patients had a relapse of depression (log-rank chi square 18.6, df 1, $p \leq .001$). After 6 months of treatment, the cumulative probability of relapse of depression was 52% for placebo-treated patients and 28% for venlafaxine-ER-treated patients. The figure below shows the Kaplan-Meier curves.

Figure 6. Survival function estimates (survival analysis population) for venlafaxine ER versus placebo in relapse study.



I consulted with the statistician, Kun He, Ph.D., who stated that the results are essentially the same whether one analyzes the ITT population or the survival analysis population.

Efficacy analyses of secondary endpoints for Study 0600B1-370-US

The survival analysis showed that significantly more placebo-treated patients (18%) than venlafaxine ER patients (6%) had relapse of depression after one month of treatment ($p=.002$).

The sponsor also examined the data after excluding the first 28 days of treatment. (The sponsor performed a similar analysis for the IR recurrence study. This analysis seems to be appropriate,

since more placebo-treated than venlafaxine ER-treated patients dropped out early.) The results showed that significantly more placebo-treated (43%) than drug-treated (24%) patients had a relapse of depression during the 6-month double-blind period (log-rank chi square 10.1, df 1, $p \leq .002$). According to the sponsor, these results suggest that the results were not affected by any potential discontinuation symptoms that may have occurred during the first month of long-term treatment.

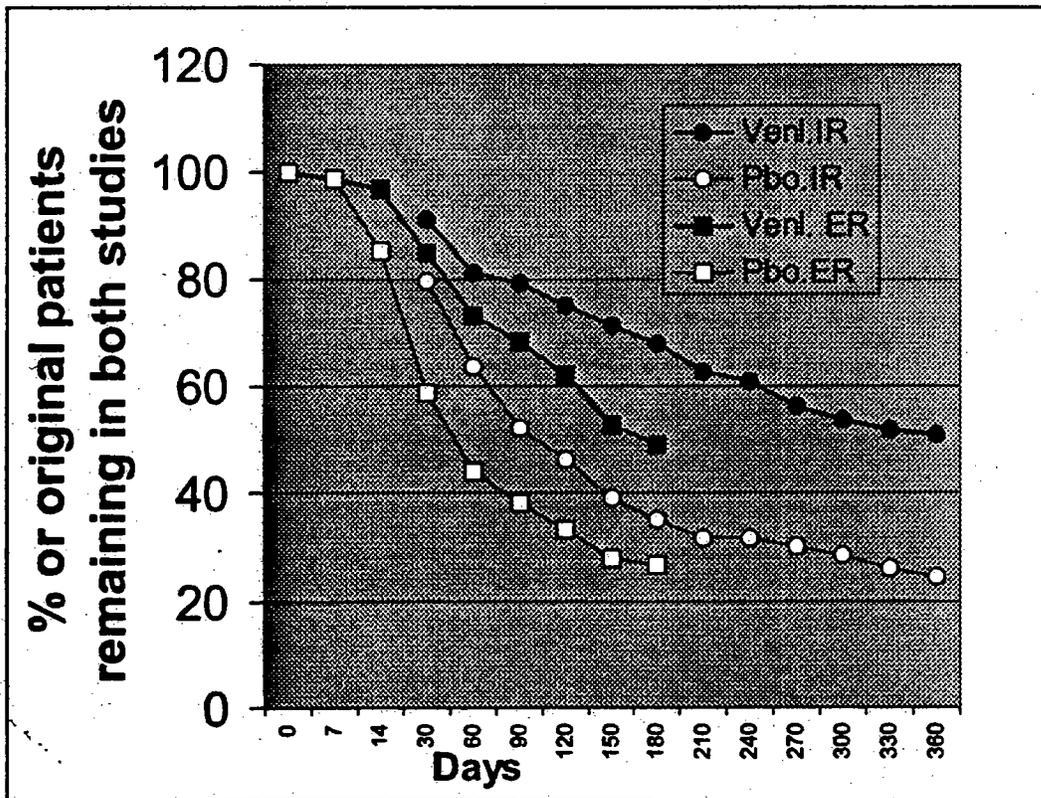
LOCF analyses for the HAM-D total, the HAM-D depressed mood item, MADRS total, and CGI severity scores were significantly lower for the venlafaxine ER-treated patients than for the placebo-treated patients, from long-term month 1 through 6. For the HAM-D, the p value was .003 at month 1 and $<.001$ thereafter. For HAM-D item 1, the p value was $<.001$ for all monthly time points. For the MADRS total, it was .002 at month 1 and $<.001$ thereafter. For CGI Severity, the p value was .005 at month 1 and $<.001$ thereafter.

Efficacy conclusions for Study 0600B1-370-US

Synthesis of efficacy results for IR recurrence and XR relapse studies

In the graph below, I have combined data from the two studies. If recurrence and relapse are two different phenomena, one would expect that their graphs over time would differ from one another.

Figure 7. Combined results for IR recurrence and XR relapse studies: Percentage of patients remaining in study, compared to baseline, by drug group.

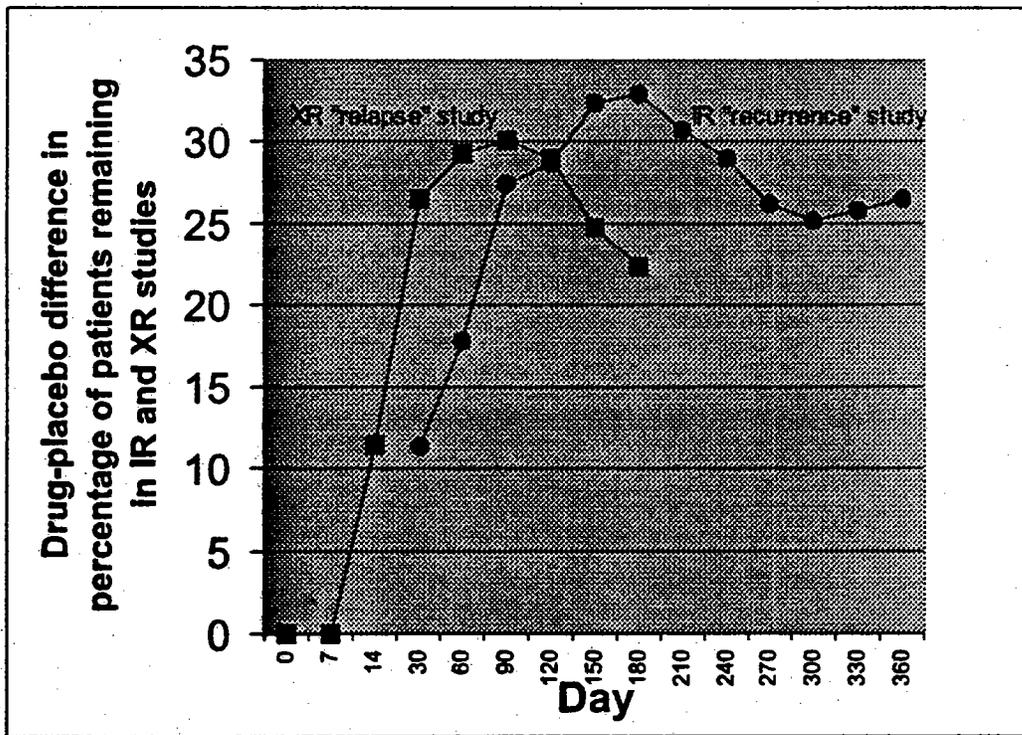


Rather than looking immediately at the drug group, I will begin by looking at the placebo lines in the graph below. The placebo line for the XR study drops more steeply than does the placebo line for the IR study. It might be argued that this is due to the fact that the XR-treated patients received the benefit of less treatment than the IR-treated patients. This might seem to support the sponsor's desire for separate labeling for recurrence and relapse. On the other hand, looking at the two active treatment lines, we see that fewer patients remained on XR than on IR. I see only two good reasons for why these two lines differ from so markedly from one another: Either Effexor XR is inferior to Effexor IR, or the differences between the two studies are due to differences in assay sensitivity between the two studies. The latter seems more likely, especially in view of the fact that the two studies used different definitions for responders and for relapse/recurrence.

As a result, the apparent difference in assay sensitivity would seem a likely explanation for why the two placebo lines differ.

Next, in attempt to make a more meaningful comparison between the two studies, I calculated the difference in the continuation rates, between the drug and placebo groups, for each study. I have graphed the results below.

Figure 8. Net difference in rate of continuation rate between drug and placebo groups for both IR recurrence and XR relapse prevention studies.



As this graph shows, the "net" (drug minus placebo) continuation rate curves differ somewhat. The relapse curve rises earlier, and peaks earlier, than does the recurrence curve. However, note that, in the XR relapse study, there were two time points, days 7 and 14 (weeks 1 and 2), that didn't exist in the other study. Another sponsor has argued that frequency of study visits may be one factor influencing placebo response. If this is true, it also seems possible that frequency of

study visits could influence rate of relapse. (The patients were aware of the purpose of the study, and each study visit might have been further suggestion that possibility of relapse was imminent.)

Note also that the peak (difference between drug and placebo) is slightly higher for the recurrence study than for the relapse study. If longer duration of preceding treatment truly increases the likelihood of patients continuing in the study (ie. not experiencing a recurrence or being censored for some other reason), one would expect that the peak would be much lower for the recurrence study and higher for the relapse study.

Proposed labeling changes regarding efficacy

The sponsor's changed labeling with regard to efficacy can be found in the appendix in the section entitled "Sponsor's proposed labeling changes relevant to efficacy". I copied this section electronically from the sponsor's proposed labeling. The sponsor supplied electronic labeling only for the non-annotated version. I compared this with the annotated versions for both NDAs, ie for both the IR and the XR formulation. The wording for the two formulations is essentially identical. Where they diverge, I have made annotations in brackets.

The key items the sponsor wishes to add to labeling are separate claims for prevention of relapse and prevention of recurrence. These claims rest upon the sponsor's definitions of these terms, which I will comment upon in the Conclusions section below. Here are the sponsor's definitions of relapse and recurrence:

I was unable to find in the submission a reference or rationale for these definitions.

Conclusions regarding efficacy

It appears that the sponsor has presented convincing evidence that venlafaxine, in both the IR and the XR formulation, is statistically superior to placebo in its ability to maintain a state of remission from a depressive episode. I word it this way in order to avoid using the terms "recurrence" and "relapse".

According to Stedman's Medical Dictionary, these two terms are synonymous. The sponsor's definitions of relapse ("return of the original symptoms of depression within 4-6 months of obtaining an initial treatment response") is based on the return of symptoms occurring within a specified time window. Key terms in the sponsor's definition of relapse

_____) are _____ and _____. Implicit in this distinction is that one is able to determine whether the asymptomatic period represents "an initial treatment response" or "recovery". It appears that the sponsor makes this distinction based on the duration of the asymptomatic periods.

Lacking in these definitions, in my opinion, is any consideration of the presence or absence of effective treatment. Unfortunately, the psychiatric literature on this subject does not seem to address this issue.

Let us look at an example from another disease category, hypertension. Suppose that Patient A with hypertension begins treatment with an antihypertensive and that this treatment is effective. After 8 weeks, Patient A stops the medication and his blood pressure goes back up. Patient B, on

the other hand, stays on his antihypertensive for 6 months (or 10 years, for that matter) before he, too, discontinues treatment and his blood pressure returns to its baseline elevated state. Let us add that, for these two patients, blood pressure returned to near baseline within a similar period of time. (I would suppose a few days in this example.) Would we say that Patient A suffered a relapse while Patient B suffered a recurrence? I would argue that both patients underwent similar phenomena and the duration of their normotension was simply a function of the duration of treatment.

Another example could be that of insulin-dependent diabetes mellitus (IDDM). Whether the patient receives insulin for 6 months or for a year, discontinuation of the insulin is followed (presumably) by an increase in blood glucose. Both IDDM and hypertension are generally recognized as chronic illnesses, so a counterargument could be made that this it is not fair to compare these illnesses to recurrent major depression, whose course is not only chronic but, by definition, one of waxing and waning.

In the case of the two studies reviewed here, continuation or discontinuation of venlafaxine (in either formulation) appears to make a clear difference in whether patients continue in the remitted state. Thus it appears that these depressed patients "need" venlafaxine just as hypertensive and diabetic patients "need" their treatments.

Now, how *long* to treat a depressive episode is a question of more practical relevance to practicing psychiatrists. Addressing this question is outside the scope of this review. However, it appears, at least from the XR study, that the answer to this question is greater than one year.

In conclusion, it appears that a relapse prevention claim is warranted by the results of these two studies. I would also agree that such a claim is justifiable for both the IR and the XR formulation. However, I find no evidence or convincing argument that a distinct claim for the prevention of recurrence is warranted.

SAFETY DATA

I have summarized the safety data from the two NDAs into the following table.

Table 12. Summary of safety data for IR recurrence and XR relapse studies.

	IR Recurrence Study 0600A1-335-US/EU	XR Relapse Study 0600B1-370-US
Extent of exposure	<i>See Appendix Table 17. Extent of exposure in studies using IR formulation.</i>	<i>See Appendix Table 18. Extent of exposure for studies involving XR formulation.</i>
Deaths	<p>2 deaths:</p> <p>(1) — appears not to be drug-related in view of patient's history.</p> <p>(2) (2) "Cardiogenic shock", cannot judge drug-relatedness.</p> <p><i>See Appendix Table 19. Narrative of deaths occurring in IR study for details from narratives.</i></p>	none
SAEs and "events of clinical importance"	<p>All reported events either already in labeling or in proposed labeling as additions to Other Events listing. Many of these did not appear to be drug-related, either due to confounding conditions / medications or due to long duration of treatment prior to development of event.</p> <p>Selected narratives scanned in (using OCR) and pasted into appendix (see <i>Selected SAEs and events of clinical importance.</i></p>	<p>Again, all events listed already in labeling. Significant events include HTN, hallucinations, urinary retention, and thrombocytopenia (though at Day 240).</p>
Adverse dropouts	<p>Nausea (5% in open-label portion, 2% in double-blind drug group vs. <1% in pbo group)</p> <p>Dizziness (3% open but, in double-blind portion, < 1% for drug vs. 3% pbo)</p> <p>Insomnia, sweating, headache, somnolence, and nervousness all 2% in open-label and ≤ 2% in double-blind portion</p> <p>All other reasons for dropout ≤ 1%</p>	<p>In acute treatment period, asthenia, dizziness, somnolence caused withdrawal in 2% of patients. All other causes at frequency ≤ 1%.</p> <p>In double-blind relapse prevention, hypertension led to withdrawal of 2% of patients in venlafaxine ER group vs. 0% in placebo group. All other reasons for discontinuation in drug group at rate of ≤ 1%.</p> <p>Other AEs causing withdrawal in placebo group: dizziness (6%), nausea (3%), asthenia (2%), and headache (2%). All others at rates ≤ 1%.</p>

Proposed labeling changes regarding safety

The sponsor provided on diskette a non-annotated version of the proposed labeling. The only changes relevant to safety were to be found in the Other Adverse Events listing (a.k.a. "the laundry list"). The sponsor did not propose the deletion of any terms but did propose that some terms be added to the listing. I have edited the sponsor's version of the proposed listing so as to include only the terms to be added. This can be found in the appendix in the section entitled *Sponsor's proposed labeling changes relevant to safety*. I had only one comment, added as a bracketed comment, namely that _____

Conclusions regarding safety

The sponsor has proposed the addition of several terms to the Other Events listing, and I agree with their being added. Other than these, there appear to be no new safety issues raised by these two studies.

FINANCIAL DISCLOSURE INFORMATION

The sponsor provided financial disclosure information on both of the submitted studies. For the Effexor IR recurrence prevention study, the sponsor provided certification on 44 investigators in the US, 8 in Germany, and 6 in the UK (total = 58). The sponsor certified that it received no response from 73 investigators. The majority of these were listed as "no longer at site - cannot be located".

For the Effexor XR relapse prevention study, the sponsor provided certification on 39 investigators (all US). The sponsor certified that it had received no response from 86 investigators. 49 of these were listed as "has not responded to several requests". Another 38 were listed as "no longer employed by the site - forwarding address not provided".

From these numbers, it seems that there was significant noncompliance with the request for financial disclosure information. However, since these two studies reviewed here were double-blind (except for the open-label lead-in periods), and since an investigator was to break the blind for individual patients only in cases of emergency, I believe it is unlikely that financial interests on the part of certain investigators could have had a significant impact on the results.

Encl.

Orig NDA 20-151 and 20-699

Div file

cc: TLaughren, PDavid, ETurner

2-20-01

I agree that these supplements
are approvable. See
memo to file for more
detailed comments.

ISJ

TL, PDP

APPENDIX

Table 13: List of investigators: IR Study 0600A1-335-US/EU, page 1.

LIST OF INVESTIGATORS

The number of patients in the open-label period are shown in parentheses; the number of patients in the double-blind period are shown in brackets.

Jay D. Amsterdam, MD (33501)
Depression Research Unit
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104, USA
(n = 24) [n = 13]

Colin Barrett, MD (33516)
Rutherglen Health Center
130 Stone Law Drive
Rutherglen 673 2 PQ
Glasgow, UK
(n = 9) [n = 3]

A. S. Boyd, MD (33517)
Dumbarton Health Centre
Station Road Dumbarton
Dumbarton - Glasgow, UK
(n = 4) [n = 1]

Gerhard Buchkremer, MD (33537)
Psychiatrische Universitätsklinik
Osiander Strasse 22
72076 Tübingen, Germany
Dobler str. 27
72074 Tübingen, Germany
(n = 1) [n = 0]

John Carman, MD (33502)
Psychiatry and Research P.C.
4015 South Cobb Drive, Suite 245
Smyrna, GA 30080, USA
(n = 24) [n = 14]

Lynn Cunningham, MD (33503)

(n = 24) [n = 15]

Bruce Diamond, PhD (33504)
Clinical Therapeutics Section
520 Shartom Drive Biotech Park
Augusta, GA 30907, US
1021 15th Street, Suite 7
Augusta, GA 30901, USA
(n = 23) [n = 10] (See Section 6.8)

Karl Heinz Ditzler, MD (33524)

(n = 8) [n = 5]

John Feighner, MD (33505)
Feighner Research Institute
5375 Mira Sorrento Place
East Tower Building, Suite 210
San Diego, CA 92121, USA
(n = 24) [n = 13]

James Ferguson, MD (33506)
Pharmacology Research Institute
448 East 6400 South, Suite 350
Salt Lake City, UT 84107, USA
(n = 23) [n = 8]

Gerd Jürgen Fischer, MD (33525)

(n = 2) [n = 1]

William Henderson, MD (33519)
Dr. Chong and Henderson

Community Pharmacology Services Ltd
11 Hume Street
Clydebank G81 1XL Glasgow, UK
(n = 7) [n = 2]

<p>Yvonne Hoffmann, MD (33526)</p> <hr/> <p>(n = 9) [n = 2]</p> <p>Wolfgang Kafferlein, MD (33527)</p> <hr/> <p>(n = 10) [n = 0]</p> <p>Ronald Landbloom, MD (33510) St. Paul-Ramsey Medical Center 640 Jackson Street St. Paul, MN 55101-2595, USA (n = 24) [n = 14]</p> <p>Roderick Macleod, MD (33520)</p> <hr/> <p>(n = 8) [n = 1]</p> <p>Abdolveza Madiderey, MD (33529)</p> <hr/> <p>(n = 28) [n = 13]</p> <p>Manssur Mir Haschemi, MD (33530)</p> <hr/> <p>(n = 23) [n = 14]</p> <p>Gary Post, MD (33508) Roger Patrick, PhD Denver Drug Research Associates 8200 E. Belleview, Suite 280 Englewood, CO 80111, USA (n = 24) [n = 15]</p> <p>A. Rennie, MD (33521) Thornliebank Health Centre Thornliebank Hall Main St. Glasgow, UK (n = 2) [n = 1]</p>	<p>Robert Riesenber, MD (33509) Bio Behavioral Research Center 625 De Kalb Industrial Way Decatur, GA 30033, USA (n = 23) [n = 11]</p> <p>Eugen Schlegel, MD (33533)</p> <hr/> <p>(n = 6) [n = 3]</p> <p>Ram Shrivastava, MD (33511) Eastside Comprehensive Medical Services 133 East 73rd Street New York, NY 10021, USA (n = 24) [n = 12]</p> <p>Jeffrey S. Simon, MD (33512) Northbrooke Hospital 4600 West Schroeder Drive Brown Deer, WI 53223, USA (n = 25) [n = 16]</p> <p>Ward Smith, MD (33513) Clinical Trial Systems 2212 Lloyd Center Portland, OR 97232, USA (n = 25) [n = 12]</p> <p>Steven Targum, MD (33507)</p> <hr/> <p>(n = 24) [n = 16]</p> <p>Harold D. Udelman, MD (33514) Biomedical Stress Research Foundation Ltd. 45 East Osborn Road Phoenix, AZ 85012, USA (n = 20) [n = 7]</p>
<p>Alan Wade, MD (33522) Community Pharmacology Services LTD 11 Hume Street Clydebank G81 1XL Glasgow, UK and Clydebank Health Centre Kilbowie Road Clydebank G28 2TQ Glasgow, UK (n = 17) [n = 4]</p>	<p>Elke Wieden, MD (33534)</p> <hr/> <p>(n = 4) [n = 3]</p> <p>John M. Zajecka, MD (33515) The Woman's Board Depression Treatment and Research Center 1725 West Harrison Street, Suite 955 Chicago, IL 60612, USA (n = 14) [n = 6]</p>

Table 14: Number of patients discontinuing during each time period by reason and by drug group.

Reason	Days																												
	1-30		31-60		61-90		91-120		121-150		151-180		181-210		211-240		241-270		271-300		301-330		331-360		>360				
	P ^a	V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	
Adverse reaction	2	0	3	0	2	0	0	0	0	0	1	0	1	0	1	0	0	0	2	0	1	0	0	1	0	0	0	0	0
Failed to return	2	3	2	3	0	0	0	0	0	3	0	0	1	1	0	0	0	0	1	1	2	1	0	1	1	0	0	1	
Patient request	4	1	0	1	1	0	0	0	0	1	1	1	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	
Unsatisfactory response - efficacy	16	5	14	6	9	2	7	4	4	2	2	2	1	1	0	1	2	1	1	1	0	2	1	0	0	0	0	0	
Protocol violation	1	1	0	0	1	0	0	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	
Other medical event	0	0	1	1	1	0	0	0	1	0	1	0	0	1	0	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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Total - number (%)	25 (20)	10 (9)	20 (16)	11 (10)	14 (11)	2 (2)	7 (6)	5 (4)	9 (7)	4 (4)	5 (4)	4 (4)	4 (3)	6 (5)	0 (0)	2 (2)	2 (2)	5 (4)	2 (2)	3 (3)	2 (2)	3 (2)	2 (2)	2 (2)	1 (<1)	0 (0)	1 (<1)	0 (0)	

a: P = placebo; V = venlafaxine.

Table 15. List of investigators for Effexor XR relapse study # 0600B1-370-US CSR-36951

<p>Barry Bauml, MD</p> <p>_____</p> <p>_____</p> <p>_____</p>	<p>Arifulla Khan, MD Northwest Psychiatric Institute Hambleton Professional Building 10126 NE 132nd, Suite B Kirkland, WA 98034</p>	<p>Robert Riesenber, MD Bio-Behavioral Research Center 625 DeKalb Industrial Way Decatur, GA 30033</p>
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Table 16. Demographic and baseline characteristics for all patients in relapse prevention study of XR formulation.

Characteristic	Placebo (n = 157)	Venlafaxine ER (n = 161)	p-value	Statistical Test ^b
Age (years)			0.15	F
Mean	41.0	42.6		
SD	±10.6	±9.8		
Range	19 to 66	21 to 75		
Sex n (%)			0.69	C
Female	99 (63)	105 (65)		
Male	58 (37)	56 (35)		
Ethnic origin, n (%)			0.29	C
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)		
Body weight (kg)			0.72	F
Mean	79.5	80.4		
SD	±21.6	±23.4		
Range	46 to 142	44 to 148		
Duration of Current Episode (days)			0.70	F
Mean	167	154		
SD	±306	±274		
Range	5 to 2038	4 to 2444		
Duration of Current Episode, n (%)			1.00	C
< 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 Episodes (within past 5 years)			0.27	F
Mean	1.1	1.0		
SD	±1.3	±1.0		
(Range)	0 to 12	0 to 5		
Baseline Scores^c				
HAM-D Total			0.78	F
Mean	6.4	6.5		
SD	±3.0	±2.9		
Range	0 to 20	0 to 13		

Characteristic	Placebo (n = 157)	Venlafaxine ER (n = 161)	p-value	Statistical Test ^b
MADRS Total			0.70	F
Mean	7.2	7.4		
SD	±4.7	±4.6		
Range	0 to 21	0 to 21		
CGI - Severity			0.44	C
1	67 (43)	58 (36)		
2	51 (32)	61 (38)		
3	38 (24)	42 (26)		
4	1 (1)	0 (0)		

a: Patients who qualified to enter the double-blind treatment period at the day 56 evaluation and who provided data thereafter.
b: C and F indicate p-value for chi-square or F-test, respectively.
c: Study day 56.

3 page(s) of revised draft labeling has been redacted from this portion of the review.

Table 17. Extent of exposure in studies using IR formulation.

NUMBER OF PATIENTS EXPOSED TO VENLAFAXINE DISTRIBUTION BY MEAN DAILY DOSE RANGE AND TIME - OPEN-LABEL PERIOD							
Period Time Interval (days)	Mean Daily Dose Range of Venlafaxine (mg) (n = 483)					All	Daily Dose (mean ± SD, mg)
	0-50	51-100	101-150	151-200	>200		
1-7	38	440	5	0	0	483	74.2 ± 25.9
8-14	11	61	362	18	0	452	132.5 ± 29.8
15-21	2	60	298	74	0	434	145.4 ± 32.4
22-28	3	66	267	92	0	428	147.8 ± 32.8
29-56	1	65	226	124	0	416	150.9 ± 37.4
57-90	2	55	196	119	1	373	152.6 ± 38.2
91-120	3	62	165	112	0	342	151.9 ± 40.7
121-150	4	57	147	104	1	313	152.4 ± 39.9
151-180	4	55	147	92	0	298	149.6 ± 41.9
>180	15	43	77	28	1	164	119.6 ± 48.5

NUMBER OF PATIENTS EXPOSED TO VENLAFAXINE DISTRIBUTION BY MEAN DAILY DOSE RANGE AND TIME - DOUBLE-BLIND PERIOD							
Period Time Interval (days)	Mean Daily Dose Range of Venlafaxine (mg) (n=112)					All	Daily Dose (mean ± SD, mg)
	0-50	51-100	101-150	151-200	>200		
1-30	0	15	66	31	0	112	151.5 ± 37.3
31-60	1	19	54	28	0	102	149.7 ± 40.1
61-90	1	20	48	23	0	92	145.8 ± 43.3
91-120	3	15	48	24	0	90	144.6 ± 44.6
121-150	2	17	47	19	0	85	144.5 ± 42.5
151-180	4	15	47	17	0	83	138.9 ± 45.5
181-210	3	19	41	15	0	78	141.7 ± 43.0
211-240	1	17	37	16	0	71	142.0 ± 41.2
241-270	2	19	33	15	0	69	139.2 ± 43.5
271-300	2	17	33	13	0	65	139.9 ± 43.9
301-330	1	14	34	12	0	36	140.5 ± 42.2
331-360	3	14	31	11	0	32	132.2 ± 48.4
>360	17	24	9	0	0	21	79.5 ± 59.2

Table 18. Extent of exposure for studies involving XR formulation.

NUMBER OF PATIENTS EXPOSED TO VENLAFAXINE ER: DISTRIBUTION BY MEAN DAILY DOSE RANGE AND TIME - ACUTE-TREATMENT PERIOD							
Period	Mean Daily Dose Range of Venlafaxine (mg) (n = 488) ^a					Daily Dose	
Time Interval (days)	0-50	51-100	101-200	201-300	>300	All	(mean ± SD, mg)
1-7	235	253	0	0	0	488	58.2 ± 19.8
8-14	4	447	24	0	0	475	81.4 ± 26.7
15-21	4	81	367	2	1	455	134.0 ± 37.6
22-28	7	70	371	3	0	451	142.0 ± 43.6
29-35	6	41	154	237	2	440	185.6 ± 61.1
36-42	9	35	133	254	1	432	188.0 ± 63.1
43-49	11	27	129	258	1	426	191.5 ± 61.0
50-56	9	26	123	257	1	416	190.5 ± 62.7
>56	9	40	54	62	0	165	111.2 ± 82.0

a: Data were not available for 2 patients.

NUMBER OF PATIENTS EXPOSED TO VENLAFAXINE ER: DISTRIBUTION BY MEAN DAILY DOSE RANGE AND TIME DOUBLE-BLIND TREATMENT PERIOD							
Period	Mean Daily Dose Range of Venlafaxine (mg) (n=161)					Daily Dose	
Time Interval	0-50	51-100	101-200	201-300	All	(mean ± SD, mg)	
Long-term							
Week 1	0	12	54	95	161	191.1 ± 53.1	
Week 2	1	14	52	93	160	187.7 ± 57.1	
Month 1	7	15	55	81	158	178.3 ± 63.3	
Month 2	6	11	56	65	138	177.4 ± 64.3	
Month 3	9	8	46	60	123	177.4 ± 64.3	
Month 4	3	10	42	55	110	180.8 ± 62.1	
Month 5	6	9	31	56	102	181.4 ± 64.2	
Month 6	8	13	52	13	86	143.5 ± 81.0	
>Month 6	29	13	1	0	43	29.5 ± 42.6	

Table 19. Narrative of deaths occurring in IR study

- (1) 63 y.o. man, MI after 158 days (5 mos.) @ 150 mg/d. H/o MI 10 years prior. Admitted to hospital w/ CHF, dx'd w/ severe aortic valve stenosis and mod. mitral valve insuff. by echo.
- (2) 59 y.o. man, cardiogenic shock after 40 days @ 100 mg/d. Pt was smoker with normal BP and VS at screening, but cholesterol = 297 and glucose = 180. Last seen by investigator study day 29; unknown if pt cont'd to take medication. Study day 40 consulted his FP for nausea and diarrhea and collapsed in doctor's office. CPR unsuccessful. "Died of cardiogenic shock in hospital. Acute MI suspected, but no autopsy performed."

Selected SAEs and events of clinical importance

Selected SAEs from IR study

Syncope with seizure

This 18-year-old woman with a history of hypoglycemia began taking venlafaxine on 14 Jan 1993. On 6 Feb 1993 (study day 24) she called the study site to report that she had experienced a seizure. She stated that she had three similar previous episodes, beginning on 4 Feb 1993 (study day 22). The dose of study medication at that time was 150 mg/day and she did not take any doses after 4 Feb 1993. She stated that on 4 Feb 1993 she had been having a disagreement with her roommate, and when she got up to walk, she fell to the floor. She remembers losing consciousness. She denied any headache or bowel and bladder incontinence. She also stated that she had a subsequent episode on the following day, 5 Feb 1993. At that time, she was playing cards with friends when she lost consciousness and fell to the floor. Again, there was no injury or loss of bowel or bladder control. That same day, while cleaning her house, she fell over her vacuum cleaner and scratched her ankle. She was seen by the investigator on _____. Diagnoses considered at that time were: seizures of unknown origin, episodes of fainting because of rapid weight loss, or hysterical seizures. _____ she was admitted to the emergency room for a neurologic evaluation. She was found to have a normal neurologic exam. A non-contrast computerized tomography scan of the brain, as well as a sleep-deprived EEG, were reported as normal. The impression of the neurology consultant was that the history of episodes was most compatible with syncope. A seizure disorder was doubted at that time. Subsequently, she did not return to the site for follow-up, even after phone contact and a registered letter was sent. In the opinion of the investigator, this study event was of moderate severity and not related to study drug.

Hallucinations

This 32-year-old woman with a history of major depression, but no history of psychosis,

began taking venlafaxine on 23 Mar 1993. On _____ she reported to a community mental health center that she was hearing voices telling her she was going to die in June 1993. At the community mental health center, Zoloft and Trilafon were prescribed. The center subsequently notified the study site of her clinic visit and she was instructed to stop study drug. The last dose of study medication (150 mg) was taken on 27 May 1993 (study day 66). On 1 Jun 1993, she was evaluated at the study site and withdrawn from the study. At that time, she denied suicidal ideation or intent. In the opinion of the investigator, this study event was of moderate severity and possibly related to study drug.

Discontinuation symptoms

Case 1 of discontinuation symptoms

This 29-year-old man began taking venlafaxine on 11 Dec 1992. He was titrated to a dose of 150 mg/day and completed the open-label phase on 26 May 1993. He was randomized to the placebo group and began taper as per protocol on the following day. On 6 Jun 1993, the first day on placebo, he began experiencing poor concentration and dizziness (both severe). On 8 Jun 1993 he began experiencing visual distortions (mild in severity), hypoacusis, and hyperacusis (both of moderate severity). The taper period was extended for a few days and the symptoms improved. However, on 11 Jun 1993, when taking 25 mg/day, he began experiencing poor short-term memory (severe). It was recommended that he be withdrawn from the study and that a slow taper be instituted. In the opinion of the investigator, these study events were probably related to study drug. The patient also experienced an increased SGOT. On 30 Nov 1992, at baseline, his SGOT was 21 Units (normal 11 to 36 Units) and on 26 May 1993, at the end of the open-label phase, the SGOT was 25 Units. On 16 June 1993, at study termination, 4 days after the last dose of study medication, his SGOT was 148 Units. No follow-up was provided.

Case 2 of discontinuation symptoms

This 53-year-old man started taking venlafaxine on 30 Sep 1993. He was titrated to a daily dose of 100 mg and completed the open-label phase on 4 May 1994. He was randomized to the placebo group and began a 5-day venlafaxine taper as per protocol on the following day. On 19 May 1994 (double-blind study day 15; ie, after 10 days on placebo, he reported experiencing severe aggression, restlessness, and sleep disturbance. From 19 May 1994 to 10 Jun 1994, and again on 12 Jun 1994, he took fluvoxamine. He was withdrawn from the study on 16 Jun 1994, because of lack of efficacy and the above-mentioned study events. On that day, the investigator commented that the patient had felt quite well with the study medication since Mar 1994. However, after taking double-blind medication, the patient started experiencing restlessness and difficulties with his wife. In the investigator's opinion, the events were definitely related to the study drug.

Case 3 of discontinuation symptoms

This 39-year-old man began taking venlafaxine on 2 Aug 1993. He completed the open-label phase on 26 Jan 1994 and was randomized to continue on venlafaxine (150 mg/day). On 12 Oct 94, after 443 days of venlafaxine therapy he decided to withdraw from the study because of decreased libido. Taper was initiated. The last dose of study medication (50 mg/day) was taken on 22 Oct 1994. Two days later, he experienced brief

syncope episodes, In the opinion of the investigator, the event was of mild severity and possibly related to study drug.

Dissecting aortic aneurysm

This 63-year-old woman began taking venlafaxine on 12 May 1993 and completed the open-label phase on 28 Oct 1993. She was randomized to continue venlafaxine therapy in the double-blind phase. On _____ after receiving venlafaxine for 485 days, she experienced a sudden onset of acute substernal chest pain and presented to the emergency room. In the emergency room, a computerized tomography scan showed a dissecting aortic aneurysm. She was admitted to the hospital and underwent emergency surgery to correct the aneurysm. The dose of study medication at the time of the event was venlafaxine 100 mg/day. She recovered and was discharged from the hospital on _____. She was withdrawn from the trial. She took her last full dose of study drug on 7 Sep 1994; she had taken only her morning dose on 8 Sep 1994. In the opinion of the investigator, this study event was severe and not related to study drug.

Rash, arthrosis, and arthralgia

This 26-year-old woman began taking venlafaxine on 16 Jul 1993 and completed the open-label phase on 20 Jan 1994. She was randomized to continue venlafaxine. On 2 Nov 1994, after 475 days of venlafaxine treatment, she experienced dry, itchy skin on her right index finger and was subsequently seen by a dermatologist on 30 Nov 1994. At that time, a biopsy demonstrated possible lupus. However, blood studies were inconclusive; ANA was negative and ESR was 25 mm/hour (normal range 0 to 20 mm/hour). The dose of study medication at the time of the event was venlafaxine 150 mg/day. On 10 Dec 1994, she developed a rash on her face that was treated with tetracycline and prednisone. Subsequently, she developed dryness and sores on the mucous membrane of her mouth and tongue that were accompanied by facial swelling. This was treated with two cortisone injections. On 30 Dec 1994, the dermatologist prescribed ciprofloxacin for 10 days and the mouth sores resolved. On 5 Jan 1995, she experienced swelling of her large and small joints (severe) accompanied by pain (moderate in severity), as well as swollen hands (severe) and an elbow rash (moderate). On 9 Jan 1995, she was seen by her family doctor who diagnosed Lyme disease. Ibuprofen was prescribed. On 13 Jan 1995, she experienced increased swelling of her hands at which time doxycycline was prescribed and she was referred to a rheumatologist. On 18 Jan 1995, the rheumatologist prescribed Rhumatex and additional laboratory tests were obtained. The rheumatologist made a provisional diagnosis of Lyme disease, lupus, rheumatoid arthritis, and dermatosclerosis. She completed the study and took her last dose of study medication (150 mg of venlafaxine) on 5 Jan 1995. In the opinion of the investigator, these study events were possibly related to study drug.

Thrombocytopenia

This 72-year-old woman began taking venlafaxine on 8 Jun 1993. She completed the open-label phase on 22 Nov 1993 and was randomly assigned to continue on venlafaxine. During the study, she experienced increasing pain in the right hip that led to

hospitalization on _____. On _____ she underwent elective right total hip replacement for progressive coxarthrosis. She was perioperatively anticoagulated with heparin 7500 IU subcutaneously twice daily from 20 Jun 1994 to 11 Jul 1994. She developed severe heparin-induced [reviewer's emphasis] thrombocytopenia (platelets were 430 g/L on 14 Jun 1994; 63 g/L on 6 Jul 1994) with subcutaneous bleedings and necroses at her left thigh and forearm. The patient was referred to the university hospital on _____. From _____, she was anticoagulated with warfarin. She improved and was re-referred on _____. She underwent rehabilitation, and the remainder of her course was unremarkable. She was discharged from the hospital on _____. She recovered and completed the study on 24 Dec 1994. In the investigator's opinion, neither event was related to the study drug. She also had an increase in cholesterol at the end of the study. At initial screening, on 23 May 1993, her cholesterol was 254 mg%, on 22 Nov 1993, it was 241 mg%, and on 20 Dec 1994, it was 324 mg%.

Allergic reaction

This 57-year-old woman with a medical history of rough skin, asthmatic complaints, shortness of breath, and with no known allergies, began taking venlafaxine on 25 Oct 1993. On _____ (_____) she was hospitalized for a nonspecific allergic reaction consisting of itching, paresthesia, and shortness of breath. A specialist in allergy and pneumology confirmed the diagnosis of asthma and prescribed a 10-day course of prednisone 5 mg/day, as well as Salbutamol and beclomethasone by inhalation. Study medication (150 mg/day) was stopped from 20 Mar 1994 to 8 Apr 1994. The symptoms had improved by 18 Apr 1994. She completed the open-label phase on 24 May 1994 and she was randomized to venlafaxine in the double-blind phase. On _____ after being treated with venlafaxine for 280 days, she was admitted to the hospital because of vertigo and an episode of unconsciousness (details unknown). No remarkable findings were discovered during her stay in the hospital. She recovered and was discharged on _____. Study medication was discontinued from 26 Jul 1994 to 7 Aug 1994. On _____ after being treated with venlafaxine for 396 days, she was again admitted to the hospital, this time because of a fracture of the costal process of the third lumbar vertebra. This fracture had followed another brief episode of unconsciousness that resulted in a fall. She improved without surgery. She underwent extensive cardiovascular investigations. No significant findings were discovered and hypotensive dysregulation was suspected. Blood pressure readings from that time are not available. Norfenefrine ER 15 mg/day was started on 1 Dec 1994. Because of the second episode of unconsciousness, she was withdrawn from the study on 8 Dec 1994 after 410 days of venlafaxine treatment. Sulpiride was started on 11 Dec 1994. She was discharged from the hospital on _____. At follow-up, on 5 Jan 1995, she had fully recovered. In the investigator's opinion, the nonspecific allergic reaction was not study-drug related, while the unconsciousness was possibly related to the study drug. Supine systolic/diastolic values (mm Hg) are provided.

/s/

Erick Turner
2/20/01 11:24:59 AM
MEDICAL OFFICER

Thomas Laughren
2/20/01 02:11:07 PM
MEDICAL OFFICER

I agree that these supplements are approvable. See memo to file for more detailed comments.--TPL