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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Effexor® XR / Efexor® XL / Venlafaxine hydrochloride

PROTOCOL NO.: B2411264

PROTOCOL TITLE: An Open-Label Long-Term Extension Study to Evaluate the Safety and Efficacy of Venlafaxine ER in Adult Outpatients with Major Depressive Disorder

Study Center(s): 27 sites in Japan

Study Initiation Date and Final Completion Dates: 31 January 2012 and 6 January 2014

Phase of Development: Phase 3

Study Objective(s): Primary objectives: To evaluate the safety, tolerability, and efficacy of 10-month administration of venlafaxine extended-release formulation (ER) (75 - 225 mg/day) in subjects with major depressive disorder (MDD) who have completed the preceding double-blind study (B2411263).

METHODS

Study Design: This was a multicenter, open-label, flexible dose study.

This study consisted of a 10-month treatment phase and a 1 to 3-week tapering phase. The follow-up visits were made 2 weeks and 4 weeks after the last dose of the study drug. The timetable of study procedures/evaluations is presented in Table 1.

Table 1. Timetable of Study Procedures/Evaluations

	Treatment Phase																Tapering[a)]	Follow-up[b)]	
No. of visits	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19
Time point (week)	baseline	1	2	3	4	6	8	12	16	20	24	28	32	36	40	44/TER	45/46/47	47/48/49	49/50/51
Allowable windows (days)	0	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 3 [c)]	± 3 [c)]	± 3 [c)]
Informed consent	X																		
Inclusion/exclusion criteria	X																		
Concomitant treatments	(X) [d)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	(X) [d)]				X		X	X	X	X	X	X	X	X	X	X	X		
BP/pulse rate (Sitting)	(X) [d)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Physical examination	(X) [d)]							X			X					(X) [e)]	X		
Clinical laboratory test	(X) [d)]							X			X					(X) [e)]	X		
Pregnancy test (serum) [f)]	(X) [d)]							X			X					(X) [e)]	X		
ECG	(X) [d)]							X			X					X	X		
Adverse events [g)]	(X) [d)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	(X) [d)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAM-D	(X) [d)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
CGI-S	(X) [d)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
CGI-I		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
$QIDS_{16}$-SR-J	(X) [d)]							X			X					X			
Dispense study treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Review dose record		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

C-SSRS = Columbia Suicide Severity Rating Scale, CGI-I = Clinical Global Impression-Improvement, CGI-S = Clinical Global Impression-Severity, HAM-D = Hamilton Rating Scale for Depression, $QIDS_{16}$-SR-J = 16-item Quick Inventory of Depressive Symptomatology Self-Report Japanese version, TER = Termination

a) Subjects took study drug for 1 - 3 weeks depending on the dosage at Week 44/TER. Subjects who had taken 225 mg/day at week 44 took the study drug of tapering for 3 weeks (150 mg/day for the 1st week, 75 mg/day for the 2nd week, and then 37.5 mg/day for the 3rd week). Subjects who had taken 150 mg/day at week 44 took the study drug of tapering for 2 weeks (75 mg/day for the 1st week and then, 37.5 mg/day for the 2nd week). Subjects who had taken 75 mg/day at week 44 took the study drug of tapering for 1 week (37.5 mg/day). Subjects who terminated early followed the same tapering procedure. In addition, investigators could skip or reduce the tapering phase in the case that the subjects needed to be treated immediately by another antidepressant due to the short duration of study drug.
b) The follow-up visits were to occur for all subjects who had received study drug regardless of the duration of treatment. The 2 follow-up visits were to be evaluated after 2 weeks and 4 weeks of last study drug dosing. The subjects who discontinued before Week 44 had the 1st follow-up visit before Week 47/48/49. For subjects who had taken 225 mg/day at Week 44, the follow-up visit was to occur at week 49 and week 51 after 3 week tapering phase. For subjects who had taken 150 mg/day at week 44, the follow-up visit was to occur at week 48 and week 50 after 2 week tapering phase. For subjects who had taken 75 mg/day at week 44, the follow-up visit was to occur at week 47 and week 49 after 1 week tapering phase.
c) Allowable window was based on Visit 16.
d) The data at Week 8 in the preceding double-blind study (B2411263) was used as the baseline data in the open-label long-term extension study.
e) Performing only in subjects who skipped the tapering phase.
f) For only women of childbearing potential.
g) Safety confirmation was to be made for up to 28 days after last study drug dosing (i.e. 28 days from last dosing +7 days) by means such as hospital visit, telephone, or FAX. This safety confirmation was not required if the subjects did not take any study mediation.

Number of Subjects (Planned and Analyzed): A total of 50 subjects were planned to be enrolled in the study. A total of 50 subjects were enrolled in the study, and received the study drug.

Diagnosis and Main Criteria for Inclusion: Subjects who have completed 8 weeks of double-blind study (B2411263) on an outpatient basis, without major protocol violations or tolerability concerns.

Study Treatment: Subjects orally received the study drug (Venlafaxine 37.5 mg capsule and Venlafaxine 75 mg capsule) once daily after dinner at a dosage within the predetermined range (75, 150, and 225 mg/day). Once-daily morning administration was allowed if there was any tolerability concern for evening administration, or if treatment compliance improved compared to evening administration.

Subjects, who provided written informed consent, commenced study treatment at the dosage of 37.5 mg/day, and after 1 week (Visit 2), increased the dosage to 75 mg/day and continued treatment for 1 week. If no tolerability issue was observed after 2 weeks (Visit 3) by the judgment of the investigators, the dosage was increased to 150 mg/day and continued for 1 week. Furthermore, if no tolerability issue was observed after 3 weeks (Visit 4) by the judgment of the investigators, the dosage was increased to 225 mg/day (forced-dose escalation).

Subjects were able to remain at the same dose by the judgment of investigators if there was any tolerability concern from dose escalation. In addition, dose reduction was allowed upon occurrence of tolerability concern following dose escalation. Subjects were to discontinue receiving the study drug if a dose of 75 mg/day or more was not tolerable any time after Visit 2.

Efficacy Endpoints:

The primary endpoint of this study was related to safety. Secondary efficacy endpoints were as follows:

- 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) total score
- Clinical Global Impression-Severity (CGI-S)
- Clinical Global Impression-Improvement (CGI-I): CGI-S at Week 8 of the preceding double-blind study (B2411263) was used as the baseline value to evaluate CGI-I.
- 16-item Quick Inventory of Depressive Symptomatology Self-Report Japanese version ($QIDS_{16}$-SR-J) total score

Safety Evaluations: The reporting period for adverse events in each subject was from the first dose of the study drug to the completion of final visit. The reporting period for serious adverse events was from the time the subject signed the informed consent form to 28 days after the last dosing of the study drug. Any serious adverse events that came to the attention of the investigator after the adverse event reporting period were to be promptly reported to

the sponsor if the investigator judged the serious adverse event to be related to the study drug. Safety endpoints other than the above included laboratory findings, body weight, blood pressures, pulse rates, standard 12-lead electrocardiograms (ECGs), and the Columbia Suicide Severity Rating Scale (C-SSRS).

Statistical Methods: The efficacy analysis set was the full analysis set (FAS) of whom at least one dose of the study drug was administered in this study, and who had at least one evaluable HAM-D_{17} score after Week 8 of the preceding Study B2411263.

Changes in HAM-D_{17} total score, $QIDS_{16}$-SR-J total score, and CGI-S score at each assessment time point from baseline in this study, which was Week 8 assessment of the preceding Study B2411263, were descriptively summarized. The CGI-I score at each assessment time point was also descriptively summarized. In addition, the HAM-D_{17} total score was computed for the proportion of subjects whose score at each assessment time point decreased by 50% or more compared to baseline (responders) and the proportion of subjects whose score became below 7 points at each time point compared to baseline (remission).

The safety analysis set was comprised of subjects who received at least one dose of the study drug in this study.

Adverse events were encoded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. Safety was analyzed based on the Pfizer Data Standards; for which, adverse events, body weight, vital signs, 12-lead ECGs, laboratory findings, and the C-SSRS were summarized. Changes in variables other than the C-SSRS at each assessment time point compared to baseline, which was Week 8 assessment of the preceding Study B2411263, were descriptively summarized. The C-SSRS result at baseline of Study B2411263 was used as the baseline C-SSRS for this study.

RESULTS

Subject Disposition and Demography: Details of subject disposition and subjects analyzed were as shown in Table 2.

In this long-term study, 50 subjects were enrolled, and they all received the study drug. Thirty eight subjects (76.0%) completed treatment and tapering phases, and 12 subjects (24.0%) discontinued study during the treatment and tapering phases. The reason for discontinuation was adverse events in 8 subjects, no longer willing to participate in study in 2 subjects, and others in 2 subjects. Forty six subjects (92.0%) completed follow-up phase, and 4 subjects (8.0%) discontinued study during the follow-up phase. The reason for discontinuation was adverse events in 2 subjects, and others in 2 subjects.

Table 2. Subject Disposition and Subjects Analyzed [Number (%) of Subjects]

	Venlafaxine ER 75-225 mg/day Flexible	
Assigned to study treatment	50	
Treated	50	
	<Treatment/tapering phase>	<Follow-up phase>
Completed	38 (76.0)	46 (92.0)
Discontinued	12 (24.0)	4 (8.0)
	<Treatment/tapering phase>	<Follow-up phase>
Discontinuation	12 (24.0)	4 (8.0)
Reason for discontinuation		
Adverse events		
Related to the study drug	6 (12.0)	2 (4.0)
Not related to the study drug	2 (4.0)	-
No longer willing to participate in study	2 (4.0)	-
Others	2 (4.0)	2 (4.0)
Analyzed for Efficacy		
Full Analysis Set	50 (100.0)	
Analyzed for Safety		
Adverse Events	50 (100.0)	
Laboratory Data	49 (98.0)	

Demographic characteristics were summarized in Table 3.

Of the 50 subjects who received the study drug in the long-term study, 24 were males and 26 were females; the mean age was 43.7 years (range: 24 to 72 years), and the mean Body Mass Index (BMI) was 23.2 kg/m^2 (range: 15.4 to 40.3 kg/m^2). The number of subjects aged 65 years or older was 8.

Table 3. Demographic Characteristics [Number (%) of Subjects]

	Total N=50	Male N=24	Female N=26
Age (years)			
<18	0	0	0
18 – 44	30 (60.0)	16 (66.7)	14 (53.8)
45 – 64	12 (24.0)	6 (25.0)	6 (23.1)
≥65	8 (16.0)	2 (8.3)	6 (23.1)
Mean±SD	43.7±13.6	41.5±10.6	45.8±15.9
Range	24-72	27-67	24-72
Height (cm)			
Mean±SD	164.0±8.9	170.4±6.9	158.0±5.9
Range	148-187	158-187	148-170
Weight (kg)			
Mean±SD	62.9±16.3	71.6±17.4	54.8±10.1
Range	37-135	49-135	37-83
BMI (kg/m^2)			
Mean±SD	23.2±4.8	24.6±5.3	22.0±4.0
Range	15.4-40.3	16.0-40.3	15.4-35.5

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation

Efficacy Results:

The HAM-D_{17} total score at each assessment time point and changes from baseline (secondary endpoints) were as shown in Table 4.

The mean change in HAM-D_{17} total score from baseline to Week 44 was -7.1; the mean HAM-D_{17} total score gradually decreased from baseline to Week 44, showing a sustained efficacy of venlafaxine in subjects who were available for continuous administration of venlafaxine.

Table 4. Summary of HAM-D_{17} Total Score and Change From Baseline Based on Observed Cases

	N	Mean Total Score	SD	Changes From Baseline			
				Mean	SD	Minimum	Maximum
Baseline	50	12.0	6.10	NA	NA	NA	NA
Week 1	50	11.0	5.86	-1.0	2.00	-7	4
Week 2	50	10.5	5.18	-1.5	3.47	-8	10
Week 3	50	9.9	5.49	-2.2	4.76	-15	18
Week 4	50	9.2	5.06	-2.9	4.55	-17	7
Week 6	47	8.8	4.26	-3.4	4.39	-14	5
Week 8	48	8.4	4.59	-3.9	4.61	-14	4
Week 12	47	8.3	5.14	-4.1	5.41	-19	17
Week 16	46	7.8	6.25	-4.4	7.06	-21	30
Week 20	45	6.3	4.62	-6.2	4.93	-21	7
Week 24	44	6.8	5.46	-5.7	5.08	-21	5
Week 28	42	6.4	5.23	-6.1	5.67	-21	6
Week 32	41	6.2	5.30	-6.4	5.81	-21	4
Week 36	41	6.1	5.62	-6.5	5.85	-21	7
Week 40	40	5.9	6.20	-6.4	6.55	-21	11
Week 44	40	5.7	6.00	-7.1	5.98	-21	7

HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, N = Number of Subjects, NA = Not Applicable, SD = Standard Deviation

Responder and remission rate based on HAM-D_{17} total score were summarized in Table 5.

The responder rate based on the HAM-D_{17} total score gradually increased from 6.0% at Week 1 to 62.5% at Week 44, with the peak at Week 20. The remission rate gradually increased from 32.0% at Week 1 to 75.0% at Week 44. These results suggest that the efficacy of venlafaxine was sustainable in subjects who tolerated continued treatment with venlafaxine.

Table 5. Responder and Remission Rate Based on HAM-D_{17} Total Score [Number (%) of Subjects Based on Observed Cases]

	Responder	Remission
Week 1	3/50 (6.0)	16/50 (32.0)
Week 2	3/50 (6.0)	16/50 (32.0)
Week 3	12/50 (24.0)	19/50 (38.0)
Week 4	12/50 (24.0)	18/50 (36.0)
Week 6	11/47 (23.4)	19/47 (40.4)
Week 8	15/48 (31.3)	24/48 (50.0)
Week 12	19/47 (40.4)	23/47 (48.9)
Week 16	20/46 (43.5)	26/46 (56.5)
Week 20	29/45 (64.4)	28/45 (62.2)
Week 24	23/44 (52.3)	29/44 (65.9)
Week 28	23/42 (54.8)	27/42 (64.3)
Week 32	23/41 (56.1)	29/41 (70.7)
Week 36	24/41 (58.5)	26/41 (63.4)
Week 40	25/40 (62.5)	30/40 (75.0)
Week 44	25/40 (62.5)	30/40 (75.0)

HAM-D_{17} = 17-item Hamilton Rating Scale for Depression

CGI-S score at each assessment time point and changes from baseline were summarized in Table 6. CGI-I score at each assessment time point was summarized in Table 7. $QIDS_{16}$-SR-J total score at each assessment time point and changes from baseline were summarized in Table 8.

As a result of other secondary endpoints including CGI-S, CGI-I, and $QIDS_{16}$-SR-J, a sustained efficacy of venlafaxine was shown in subjects who were available for continuous administration of venlafaxine in the long-term study.

Table 6. Summary of CGI-S Score and Change From Baseline Based on Observed Cases

	N	Mean Score	SD	Changes From Baseline			
				Mean	SD	Minimum	Maximum
Baseline	50	3.1	1.13	NA	NA	NA	NA
Week 1	50	3.0	1.05	-0.1	0.46	-1	1
Week 2	50	2.8	1.01	-0.3	0.63	-2	2
Week 3	50	2.7	1.05	-0.3	0.87	-3	3
Week 4	50	2.6	1.05	-0.4	0.81	-3	2
Week 6	47	2.5	0.88	-0.6	0.77	-3	1
Week 8	48	2.5	0.92	-0.6	0.91	-3	1
Week 12	47	2.3	0.96	-0.8	1.20	-5	3
Week 16	46	2.2	1.05	-0.9	1.34	-5	5
Week 20	45	2.0	0.82	-1.2	0.98	-5	1
Week 24	44	2.0	0.96	-1.1	1.01	-5	1
Week 28	42	1.9	0.93	-1.2	1.07	-5	1
Week 32	41	1.9	1.00	-1.2	1.11	-5	1
Week 36	41	1.9	1.10	-1.2	1.19	-5	1
Week 40	40	1.9	1.11	-1.2	1.23	-5	1
Week 44	40	1.8	1.08	-1.3	1.12	-5	1

CGI-S = Clinical Global Impression-Severity, N = Number of Subjects, NA = Not Applicable, SD = Standard Deviation

Table 7. Summary of CGI-I Score Based on Observed Cases

	N	Mean Score	SD	Minimum	Maximum
Week 1	50	3.8	0.62	2	5
Week 2	50	3.5	0.81	2	5
Week 3	50	3.3	1.05	1	6
Week 4	50	3.1	1.05	1	5
Week 6	47	2.9	0.91	1	5
Week 8	48	2.9	0.96	1	5
Week 12	47	2.6	1.06	1	6
Week 16	46	2.4	1.20	1	7
Week 20	45	2.1	0.97	1	4
Week 24	44	2.2	1.05	1	4
Week 28	42	2.2	1.09	1	4
Week 32	41	2.1	1.14	1	4
Week 36	41	2.2	1.18	1	5
Week 40	40	2.1	1.25	1	5
Week 44	40	2.0	1.15	1	5

CGI-I = Clinical Global Impression-Improvement, N = Number of Subjects, SD = Standard Deviation

Table 8. Summary of $QIDS_{16}$-SR-J Total Score and Change From Baseline Based on Observed Cases

	N	Mean Total Score	SD	Changes From Baseline			
				Mean	SD	Minimum	Maximum
Baseline	49	11.2	4.06	NA	NA	NA	NA
Week 4	2	5.0	1.41	-2.5	2.12	-4	-1
Week 12	47	8.7	4.68	-2.7	4.97	-17	14
Week 16	1	15.0	–	11.0	–	11	11
Week 20	1	2.0	–	-8.0	–	-8	-8
Week 24	44	7.5	4.79	-3.8	4.45	-18	5
Week 28	1	13.0	–	-1.0	–	-1	-1
Week 44	40	6.4	4.60	-4.7	4.73	-18	3

N = Number of Subjects, NA = Not Applicable, SD = Standard Deviation, $QIDS_{16}$-SR-J = 16-item Quick Inventory of Depressive Symptomatology Self-Report Japanese version

Safety Results:

A summary of adverse events in the long-term study were as shown in Table 9. All-causality adverse events occurred in 49 of the 50 subjects in the entire study, 48 of the 50 subjects in the treatment phase, and 24 of the 48 subjects in the tapering/follow-up phase. Treatment-related adverse events occurred in 41 of the 50 subjects in the entire study, 38 of the 50 subjects in the treatment phase, and 16 of the 48 subjects in the tapering/follow-up phase.

No death was reported in this study. Adverse events that occurred in this study were mostly mild or moderate in severity; the only severe adverse event, which occurred in 1 subject, was crime (theft and sexual abuse).

Table 9. Summary of Adverse Events

Number (%) of Subjects	All-Causality			Treatment-Related		
	Entire study N=50	Treatment phase N=50	Tapering/ Follow-up phase N=48	Entire study N=50	Treatment phase N=50	Tapering/ Follow-up phase N=48
Number of adverse events	257	198	62	138	106	34
Subjects with adverse events	49 (98.0)	48 (96.0)	24	41 (82.0)	38 (76.0)	16
Subjects with serious adverse events [a]	3 (6.0)	1 (2.0)	2	1 (2.0)	1 (2.0)	0
Subjects with severe adverse events	1 (2.0)	1 (2.0)	0	1 (2.0)	1 (2.0)	0
Subjects discontinued due to adverse events	7 (14.0)	5 (10.0)	2	5 (10.0)	4 (8.0)	1
Subjects with dose reduced or temporary discontinuation due to adverse events	15 (30.0)	15 (30.0)	0	14 (28.0)	14 (28.0)	0

a. One subject had a serious adverse event occurring after the completion of the follow-up phase.

A summary of treatment emergent non-serious adverse events in the entire study is presented in Table 10.

Table 10. Treatment-Emergent Non-Serious Adverse Events[a] in the Entire Study

	Venlafaxine ER 75-225 mg/day Flexible	
	All-Causality	Treatment-Related
Number (%) of Subjects with Adverse Events by: MedDRA System Organ Class Preferred Term (version 16.1)	**N=50**	**N=50**
Cardiac disorders		
Palpitations	5 (10.0)	5 (10.0)
Ear and labyrinth disorders		
Tinnitus	4 (8.0)	3 (6.0)
Vertigo	2 (4.0)	2 (4.0)
Gastrointestinal Disorders		
Abdominal pain upper	2 (4.0)	2 (4.0)
Constipation	7 (14.0)	7 (14.0)
Diarrhoea	2 (4.0)	1 (2.0)
Gastrooesophageal reflux disease	3 (6.0)	2 (4.0)
Nausea	7 (14.0)	5 (10.0)
Stomatitis	2 (4.0)	0
Vomiting	3 (6.0)	2 (4.0)
General disorders and administration site conditions		
Chest discomfort	2 (4.0)	1 (2.0)
Chest pain	2 (4.0)	1 (2.0)
Feeling abnormal	6 (12.0)	5 (10.0)
Irritability	2 (4.0)	0
Malaise	2 (4.0)	1 (2.0)
Thirst	4 (8.0)	4 (8.0)
Hepatobiliary disorders		
Hepatic function abnormal	3 (6.0)	2 (4.0)
Immune system disorders		
Seasonal allergy	3 (6.0)	0
Infections and infestations		
Gastroenteritis	2 (4.0)	0

Table 10. Treatment-Emergent Non-Serious Adverse Events[a] in the Entire Study

	Venlafaxine ER 75-225 mg/day Flexible	
	All-Causality	Treatment-Related
Number (%) of Subjects with Adverse Events by: MedDRA System Organ Class Preferred Term (version 16.1)	**N=50**	**N=50**
Nasopharyngitis	20 (40.0)	0
Injury, poisoning and procedural complications		
Fall	3 (6.0)	2 (4.0)
Investigations		
Alanine aminotransferase increased	2 (4.0)	2 (4.0)
Aspartate aminotransferase increased	2 (4.0)	2 (4.0)
Blood cholesterol increased	2 (4.0)	1 (2.0)
Blood pressure increased	7 (14.0)	7 (14.0)
Electrocardiogram QT prolonged	2 (4.0)	2 (4.0)
Gamma-glutamyltransferase increased	2 (4.0)	2 (4.0)
Weight decreased	3 (6.0)	1 (2.0)
Weight increased	5 (10.0)	5 (10.0)
Metabolism and nutrition disorders		
Diabetes mellitus	3 (6.0)	1 (2.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	2 (4.0)	0
Musculoskeletal stiffness	2 (4.0)	1 (2.0)
Myalgia	3 (6.0)	0
Pain in extremity	2 (4.0)	0
Nervous system disorders		
Dizziness	11 (22.0)	8 (16.0)
Headache	13 (26.0)	11 (22.0)
Hypoaesthesia	5 (10.0)	2 (4.0)
Somnolence	9 (18.0)	7 (14.0)
Psychiatric disorders		
Agitation	2 (4.0)	2 (4.0)
Depression	2 (4.0)	1 (2.0)
Insomnia	6 (12.0)	4 (8.0)
Respiratory, thoracic and mediastinal disorders		
Asthma	2 (4.0)	0
Skin and subcutaneous tissue disorders		
Hyperhidrosis	2 (4.0)	2 (4.0)
Pruritus	5 (10.0)	4 (8.0)
Vascular disorders		
Hypertension	6 (12.0)	2 (4.0)

Subjects are only counted once per treatment for each row.
Includes all data collected during study.
MedDRA = Medical Dictionary for Regulatory Activities
a. All causality adverse events occurred in ≥ 2 subjects are presented in this table.

A summary of treatment emergent serious adverse events is provided in Table 11.

Table 11. Treatment-Emergent Serious Adverse Events

	Venlafaxine ER 75-225 mg/day Flexible	
	All-Causality	Treatment-Related
Number (%) of Subjects with Serious Adverse Events by: MedDRA System Organ Class Preferred Term (v16.1)	**N=50**	**N=50**
General disorders and administration site Conditions		
Pyrexia	1 (2.0)	0
Social circumstances		
Crime	1 (2.0)	1 (2.0)

MedDRA = Medical Dictionary for Regulatory Activities

A summary of withdrawals due to adverse events is presented in Table 12.

Table 12. Summary of Withdrawals due to Adverse Events (All-Causality)

	Venlafaxine ER 75-225 mg/day Flexible
Number (%) of Subjects with Adverse Events by: MedDRA System Organ Class Preferred Term (v16.1)	**N=50**
General disorders and administration site conditions	2 (4.0)
Feeling abnormal	1 (2.0)
Gait disturbance	1 (2.0)
Hepatobiliary disorders	1 (2.0)
Hepatic function abnormal	1 (2.0)
Investigations	1 (2.0)
Gamma-glutamyltransferase increased	1 (2.0)
Metabolism and nutrition disorders	1 (2.0)
Diabetes mellitus	1 (2.0)
Nervous system disorders	2 (4.0)
Hypoaesthesia	1 (2.0)
Somnolence	1 (2.0)
Psychiatric disorders	1 (2.0)
Depression	1 (2.0)
Skin and subcutaneous tissue disorders	2 (4.0)
Hyperhidrosis	1 (2.0)
Pruritus	1 (2.0)
Social circumstances	1 (2.0)
Crime	1 (2.0)

Includes all data collected during study.
MedDRA = Medical Dictionary for Regulatory Activities

Laboratory Test Abnormalities

Major laboratory abnormalities (which occurred in not less than 10% of subjects) were LDL cholesterol increased (24.5%), urine occult blood positive (20.4%), and triglyceride increased (16.3%).

Vital Signs

The mean change in systolic or diastolic blood pressure, or pulse rate from baseline did not substantially fluctuate up to the end of the study. Of 50 subjects, 3 had sustained systolic hypertension, 4 had sustained diastolic hypertension, and 1 had sustained pulse rate increased.

ECGs

There was no subject in whom the maximum QT interval exceeded 480 msec while there were 5 subjects (10.2%) in whom the maximum QT interval exceeded 450 msec. The number of subjects in whom Bazett-corrected QT interval exceeded 500, 480, and 450 msec was 1 (2.0%), 4 (8.2%), and 17 (34.7%), respectively. The number of subjects in whom Fridericia-corrected QT interval exceeded 500 msec was none, and that exceeded 480 and 450 msec was 1 (2.0%) and 8 (16.3%), respectively.

Body Weight

The mean change in body weight tended to increase slightly until the study completion. As all-causality adverse events, mild weight decrease occurred in 3 subjects, and mild weight increase occurred in 5 subjects. Weight decrease in 1 subject and weight increase in 5 subjects was determined as events to which causal relationship with the study drug could not be ruled out.

Columbia Suicide Severity Scale (C-SSRS)

Post-baseline suicidal ideation occurred in 5 subjects, of whom 3 had been in the venlafaxine group of the preceding study and 2 in the placebo group. All 5 subjects had already had suicidal ideation at the baseline, and thus, none was reported as an adverse event. No other events of the Columbia-Classification Algorithm of Suicide Assessment (C-CASA) were reported either before or after baseline.

CONCLUSION(S):

This study was performed to evaluate the safety, tolerability, and efficacy of long-term (10 month) treatment with venlafaxine ER at doses from 75 to 225 mg/day in 50 MDD subjects who have completed study treatment for 8 weeks (Treatment Phase) in the preceding Phase 3 study (Protocol Number: B2411263) designated to demonstrate the superiority in the antidepressive effect of venlafaxine ER 75 mg/day (fixed dose) and venlafaxine ER 75 to 225 mg/day (flexible dose) to placebo.

There were no safety or tolerability concerns regarding long-term administration of venlafaxine ER, nor were there any other safety concerns confirmed in the study. Adverse events were mostly mild or moderate in severity. Serious adverse events occurred in 3 subjects (theft and sexual abuse in 1 subject, pyrexia in 1 subject, and chest pain in 1 subject [after the completion of the follow-up phase]). Of these serious adverse events, theft and sexual abuse was determined as an event to which causal relationship with the study drug could not be ruled out; the outcome of the event was unknown. There was no reporting of death.

Among the secondary endpoints, the mean HAM-D_{17} total score gradually decreased from baseline (at the start of the long-term study) through Week 44 (at the completion of the treatment phase of the long-term study). The mean CGI-S score gradually decreased through Week 20, followed by a slight decrease up to Week 44. The mean CGI-I score gradually decreased through Week 20 and then remained stable up to Week 44. Furthermore, the mean

$QIDS_{16}$-SR-J total score gradually decreased through Week 44. Based on these results, the efficacy of venlafaxine was shown to sustain in subjects who were available for continuous administration of venlafaxine.