PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO.: B2411263

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Venlafaxine ER in Adult Outpatients with Major Depressive Disorder

Study Center(s): 62 sites in Japan

Study Initiation Date and Final Completion Dates: 17 November 2011 and 15 March 2014

Phase of Development: Phase 3

Study Objective(s):

Primary objectives: To compare the antidepressant efficacy of venlafaxine extended release (ER) in major depressive disorder (MDD) subjects receiving fixed dose of 75 mg/day and flexible doses of 75 - 225 mg/day with those subjects receiving placebo.

Secondary objectives:

- To evaluate the safety and tolerability of venlafaxine ER in MDD subjects.
- To evaluate the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine (ODV).

METHODS

Study Design: This was a phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of venlafaxine ER 75 mg/day (fixed dose) and venlafaxine ER 75 - 225 mg/day (flexible dose), compared to placebo. This study consisted of a 2-week screening period, an 8-week treatment period and a 2-week tapering period. The follow-up visit was conducted 2 weeks after the last dose of the study drug.

Subjects, who provided written informed consent, were confirmed to be eligible to meet entry criteria at the screening visit (Visit 1), followed by a 2-week screening period. Subjects who continued to meet all study entry criteria at baseline (Visit 2) were randomized to 10

weeks of treatment with placebo, venlafaxine ER 75 mg/day (fixed dose), or venlafaxine ER 75 - 225 mg/day (flexible dose) in the ratio of 1:1:1.

The timetable of study procedures/evaluation is presented in Table 1.

Table 1. Timetable of Study Procedure/Evaluations

	Screening	Double-blind Phase								Follow-up [b]
		Treatment Phase							Tapering [a]	
No. of visits	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Time point	Week -2	0	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8 /Termination	Week 10	Week 12
Allowable windows (days)	± 4	baseline	± 3	± 3	± 3	± 3	± 3	± 3	± 3 [c]	± 3 [c]
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Subject registration	X									
Subject background	X									
Medical history /complications	X									
Prior treatments (drug and non-drug)	X									
Concomitant treatments	X	X	X	X	X	X	X	X	X	X
MINI	X									
DSM-IV-TR Diagnostic Criteria for MDD	X									
Height	X									
Weight		X				X		X	X	
Blood pressure/pulse rate (Sitting)	X	X	X	X	X	X	X	X	X	
Physical examination	X							(X) [f]	X	
Clinical laboratory test	X	X						(X) [f]	X	
Pregnancy test (serum) [d]	X	X [e]						(X) [f]	X	
ECG	X	X						X	X	
Adverse events [g]		X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X
SBQ-R	X									
HAM-D	X	X	X	X	X	X	X	X		
MADRS	X	X						X		
CGI-S	X	X	X	X	X	X	X	X		
CGI-I			X	X	X	X	X	X		
$QIDS_{16}$-SR-J	X	X						X		
Randomization		X								
Dispense DB treatment		X	X	X	X	X	X	X [h]		

Table 1. Timetable of Study Procedure/Evaluations

	Screening	Double-blind Phase								Follow-up [b]
		Treatment Phase							Tapering [a]	
No. of visits	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Time point	Week -2	0	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8 /Termination	Week 10	Week 12
Allowable windows (days)	± 4	baseline	± 3	± 3	± 3	± 3	± 3	± 3	± 3 [c]	± 3 [c]
Review dosage record			X	X	X	X	X	X	X [h]	
PK sampling/ CYP2D6 genotyping								(X) [i]		

C-SSRS = Columbia Suicide Severity Rating Scale, CGI-I = Clinical Global Impression-Improvement, CGI-S = Clinical Global Impression-Severity, DSM-IV-TR = Text Revision of the Diagnostic and Statistical Manual of Mental Disorders - IV, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Åsberg Depression Rating Scale, MINI = Mini-International Neuropsychiatric Interview, SBQ-R = Suicidal Behaviors Questionnaire-Revised, $QIDS_{16}$-SR-J = 16-item Quick Inventory of Depressive Symptomatology Self-Report Japanese version

a) Subjects who completed 8 weeks and did not transfer to long-term extension study (B2411264) were to move to tapering phase.
b) The follow-up visits were to occur after 2 weeks of last study medication dosing for all subjects, who received study drug regardless of the duration of treatment, except the subjects transferring to long term study (B2411264). The subjects who discontinued before Week 8 were to visit before Week 12 as follow-up.
c) Allowable window was based on Visit 8.
d) For only women of childbearing potential.
e) Baseline pregnancy test was performed by urine.
f) Performing in subjects who discontinued before Week 8 and subjects who transferred to long-term extension study (B2411264)
g) Safety confirmation was to be made for up to 28 days after last study medication 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.
h) For the subjects who completed 8 weeks and did not transfer to long-term extension study (B2411264).
i) Performed in subjects who signed informed consent for identification of CYP2D6 genotyping and pharmacokinetics sampling.

Number of Subjects (Planned and Analyzed): At least 178 subjects per treatment group, 534 subjects in total, were planned to be enrolled in the study. A total of 538 subjects were randomized; 184 subjects in the placebo group, 174 subjects in the venlafaxine ER 75 mg/day group, and 180 subjects in the venlafaxine ER 75 - 225 mg/day group study.

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 20 years or older, who were given a primary diagnosis of MDD single or recurrent episode without psychotic features based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision (DSM-IV-TR), and with depressive symptoms for at least 90 days in single episode and for at least 28 days in recurrent episode before the screening visit.

Study Treatment: "Prescription A" to "Prescription F" listed in Table 2 were administered orally 3 capsules once daily after dinner. Once-daily morning administration was allowed if there was any tolerability concern for evening administration, or if treatment compliance improved compared to evening administration. In this case, the reason was written in the document.

Table 2. Study Drug in Double-Blind Period

	Prescription A	Prescription B	Prescription C	Prescription D	Prescription E	Prescription F
Placebo	0 mg/day	0 mg/day	0 mg/day	0 mg/day	0 mg/day	0 mg/day
Venlafaxine ER 75 mg/day	37.5 mg/day	75 mg/day	75 mg/day	75 mg/day	37.5 mg/day	0 mg/day
Venlafaxine ER 75 - 225 mg/day	37.5 mg/day	75 mg/day	150 mg/day	225 mg/day	37.5 mg/day[a] 75 mg/day[b]	0 mg/day[a] 37.5 mg/day[b]

a. Subjects who took prescription B at Week 8
b. Subjects who took prescription C or prescription D at Week 8

Treatment period: 8 weeks

Subjects were randomized to study drug at Visit 2. Treatment started from "Prescription A" followed by dose increase to "Prescription B" at Week 1 (Visit 3), which continued for 1 week. If there was no tolerability concern at Week 2 (Visit 4) at the discretion of the Investigator(s), the dose was increased to "Prescription C", and continued for 1 week. If there was no tolerability concern at Week 3 (Visit 5) at the discretion of the Investigator(s), the dose was increased to "Prescription D" (forced dose increase). If there was any tolerability concern, subjects were given option to remain at the same dose at the discretion of the Investigator(s). In the case of intolerability after dose increase, subjects were given option to reduce dose. If the subjects could not take "Prescription B" or higher doses at Week 1 (Visit 3) and the following weeks, the treatment would be discontinued. No dose adjustment was allowed from Week 4 (Visit 6) onward.

Tapering period: 2 weeks

"Prescription E" was to be administered for 1 week and then "Prescription F" for 1 week after Week 8 (Visit 8). Subjects who transferred to the long term study were dispensed the

study drug for long-term study at Week 8, and were not dispensed study drug for the tapering period.

Efficacy, Pharmacokinetic and Pharmacogenomics Endpoints:

Efficacy Endpoints

Primary endpoint:

- Change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D_{17}) total score at Week 8 (or early termination)

Secondary endpoints:

- Change from baseline to Week 8 (or early termination) in terms of Montgomery-Åsberg Depression Rating Scale (MADRS) total score, Clinical Global Impression-Severity (CGI-S), 6-item Hamilton Rating Scale for Depression (HAM-D_6, derived from HAM-D_{17}) total score, and 16-item Quick Inventory of Depressive Symptomatology-Self Report Japanese version ($QIDS_{16}$-SR-J) total score
- Clinical Global Impression-Improvement (CGI-I) score at Week 8 (or early termination) in treatment period

Pharmacokinetic and Pharmacogenomics Endpoint

- The trough plasma concentrations (C_{trough}) of venlafaxine and its metabolite ODV at steady state, and genetic polymorphism of CYP2D6

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 subject's written informed consent to 28 days after the last dosing of the study drug. Even after the completion of the period during which information was to be proactively collected, any serious adverse events discovered by Investigator(s) that were related to the study drug as reasonably determined by the Investigator(s) were subject to prompt reporting to Sponsor. Safety endpoints included laboratory findings, physical examinations, body weight, blood pressures, pulse rates, standard 12-lead electrocardiograms (ECGs), and Columbia Suicide Severity Rating Scale (C-SSRS).

Statistical Methods: The full analysis set (FAS) consisted of subjects randomly assigned to treatment who took at least one dose of the study drug in the double-blind period and who had both baseline and at least one post-baseline measurement of the primary efficacy variable. This was used as the primary analysis set for all efficacy analyses.

The per protocol set (PPS) consisted of subjects in the FAS excluding those with major protocol deviations such as violations of inclusion/exclusion criteria. This was secondarily used for the analyses of the primary efficacy endpoint.

The primary analysis was based on the FAS and the primary endpoint, which was the change from baseline in the HAM-D_{17} total score at Week 8 (or early termination). The Last Observation Carried Forward (LOCF) approach was used for Week 8 assessment for subjects with early termination. The primary analysis was pairwise comparisons in the mean of the primary efficacy variable (1) between venlafaxine ER 75 mg/day fixed dose and placebo, and (2) between venlafaxine ER 75 - 225 mg/day flexible dose against placebo. The comparison began with (1), and then followed by (2) only when statistical significance was observed in (1). The one-sided test of significance level of 0.025 based on an analysis of covariance (ANCOVA) model was employed with the treatment group as the factor and the baseline measurement of the HAM-D_{17} total score as the covariate.

As a secondary analysis, changes in HAM-D_{17} total score from baseline to each assessment time point were analyzed using a mixed-effect model for repeated measurement. This model included the treatment group, assessment time point, treatment-by-time point interaction, and HAM-D_{17} total score at baseline.

Secondary endpoints, which were mean changes in the MADRS total score, CGI-S, HAM-D_6 total score, and $QIDS_{16}$-SR-J total score from baseline to Week 8 (LOCF) were compared between treatment groups using an ANCOVA model with the treatment group as the factor, and the respective baseline measurement as the covariate. Mean score of the CGI-I at Week 8 (LOCF) was compared between treatment groups using an ANCOVA model with treatment group as the factor and baseline measurement as the covariate.

In the primary analysis, a closed testing procedure was used for multiplicity considerations. No adjustments were made for multiplicity in all other comparisons because they were secondarily performed to support the results of the primary analysis. In all secondary analyses, a two-sided test at a significance level of 0.05 was employed.

The pharmacokinetic analysis set included subjects in whom C_{trough} was appropriately measured. To characterize the pharmacokinetics, steady-state C_{trough} of venlafaxine and ODV were summarized for each dose (immediately before blood sampling) and each genetic polymorphism of CYP2D6. The C_{trough} of ODV was plotted against that of venlafaxine with the C_{trough} of ODV on the vertical axis and that of venlafaxine on the horizontal axis; scatter plots were created for dose (immediately before blood sampling) and CYP2D6 genotypes.

The safety analysis set consists of all subjects who received the study drug. Safety was analyzed based on the Pfizer data standard.

RESULTS

Subject Disposition and Demography: Disposition of subjects are as shown in Table 3. Reasons for subject discontinuations were presented in Table 4.

In this study, 538 subjects were randomized (184 subjects in the placebo group, 174 subjects in the venlafaxine ER 75 mg/day group, and 180 subjects in the venlafaxine ER 75 - 225 mg/day group), and of whom, 537 subjects received the study drug (184 subjects in the placebo group, 174 subjects in the venlafaxine ER 75 mg/day group, and 179 subjects in the venlafaxine ER 75 - 225 mg/day group).

The number of subjects who completed the double-blind period was 475 subjects (166 subjects in the placebo group, 151 subjects in the venlafaxine ER 75 mg/day group, and 158 subjects in the venlafaxine ER 75 - 225 mg/day group). The number of subjects who discontinued the study due to an adverse event was 2 subjects in the placebo group, 9 subjects in the venlafaxine ER 75 mg/day group, and 9 subjects in the venlafaxine ER 75 - 225 mg/day group (Table 4).

Meanwhile, 1 subject in the placebo group erroneously received venlafaxine ER 75 - 225 mg/day for two days. The subject later stopped receiving the study drug temporarily because of the onset of adverse events (nausea and vomiting) and eventually discontinued the study by withdrawing the informed consent. This subject was included in the placebo group for the efficacy analysis, and the venlafaxine ER 75 - 225 mg/day group for the safety analysis according to the statistical analysis plan.

Table 3. Subject Disposition

Number (%) of subjects		Placebo	Venlafaxine ER 75 mg/day	Venlafaxine ER 75 - 225 mg/day
Screened	635			
Assigned to Study Treatment		184	174	180
Treated		184	174	179[a]
Double-blind period				
Completed		166 (90.2)	151 (86.8)	158 (87.8)
Discontinued		18 (9.8)	23 (13.2)	21 (11.7)
Transition/Follow-up period				
Completed		179 (97.3)	168 (96.6)	174 (96.7)
Discontinued		5 (2.7)	6 (3.4)	5 (2.8)
Analyzed for efficacy				
FAS		184 (100.0)	174 (100.0)	177 (98.3)
PPS		175 (95.1)	170 (97.7)	175 (97.2)
Analyzed for safety				
Adverse events		183 (99.5)	174 (100.0)	180 (100.0)
Laboratory data		181 (98.4)	172 (98.9)	177 (98.3)

FAS = Full Analysis Set, PPS = Per Protocol Set
a. One subject who was randomized to the venlafaxine ER 75 - 225 mg/day group discontinued the study before receiving any study drug; thus, the total of 179 subjects received the study drug in this group.

Table 4. Reasons for Subject Discontinuation[a]

	Placebo N = 183	Venlafaxine ER 75 mg/day N = 174	Venlafaxine ER 75 - 225 mg/day N = 180
Double-blind period			
Subject died	1 (0.5)	0	1 (0.6)
Discontinuations	16 (8.7)	23 (13.2)	21 (11.7)
Lost to follow up	0	2 (1.1)	1 (0.6)
No longer willing to participate in study	11 (6.0)	9 (5.2)	8 (4.4)
Other	2 (1.1)	3 (1.7)	3 (1.7)
Withdrawn due to pregnancy	1 (0.5)	0	0
Adverse event (Related to study drug)	2 (1.1)	3 (1.7)	8 (4.4)
Adverse event (Not related to study drug)	0	6 (3.4)	1 (0.6)
Transition/Follow-up period			
Subject died	1 (0.5)	0	1 (0.6)
Discontinuations	4 (2.2)	6 (3.4)	4 (2.2)
Lost to follow up	3 (1.6)	3 (1.7)	2 (1.1)
No longer willing to participate in study	1 (0.5)	3 (1.7)	1 (0.6)
Other	0	0	1 (0.6)

a. Safety analysis set was used.

Demographic characteristics were presented in Table 5. There were no obvious differences in demographic characteristics among the 3 treatment groups.

Table 5. Demographic Characteristics

	Placebo	Venlafaxine ER 75 mg/day	Venlafaxine ER 75 - 225 mg/day	Total
Number (%) of subjects	184	174	179	537
Sex				
Male	91	84	93	268
Female	93	90	86	269
Age (years)				
< 18	0	0	0	0
18–44	130 (70.7)	126 (72.4)	137 (76.5)	393 (73.2)
45–64	50 (27.2)	41 (23.6)	38 (21.2)	129 (24.0)
≥65	4 (2.2)	7 (4.0)	4 (2.2)	15 (2.8)
Mean±SD	38.6±11.1	38.4±11.9	38.3±10.2	38.4±11.1
Range	20-75	20-76	21-72	20-76
Height (cm)				
Mean±SD	164.8±9.1	164.6±7.8	163.9±8.7	164.5±8.6
Range	143-186	147-185	144-187	143-187
Weight (kg)				
Mean±SD	61.7±16.0	61.8±14.4	62.4±14.3	62.0±14.9
Range	34-135	37-120	36-101	34-135
Body Mass Index (kg/m^2)				
Mean±SD	22.5±4.3	22.7±4.4	23.1±4.4	22.7±4.3
Range	13.3-40.3	14.3-38.8	16.0-36.2	13.3-40.3

Body Mass Index (kg/m^2) = Weight (kg) / (Height [cm]) × $0.01)^2$, SD = Standard Deviation

Baseline characteristics of disease severity were summarized in Table 6. There were no obvious differences in the results for HAM-D_{17}, MADRS, CGI-S and $QIDS_{16}$-SR-J at baseline among the 3 treatment groups.

Table 6. Baseline Characteristics of Disease Severity

	Placebo	Venlafaxine ER 75 mg/day	Venlafaxine ER 75 - 225 mg/day
Number of Subjects	184	174	179
HAM-D_{17}			
Number of Evaluated Subjects	184	174	179
Mean±SD	22.4±4.10	22.6±4.05	22.4±4.08
Range	12-33	12-35	12-33
Median	22.0	22.5	22.0
MADRS			
Number of Evaluated Subjects	184	174	179
Mean±SD	33.2±5.12	32.6±4.42	32.9±4.82
Range	26-49	26-48	26-48
Median	32.0	32.0	32.0
CGI-S			
Number of Evaluated Subjects	184	174	179
Mean±SD	4.5±0.69	4.5±0.62	4.5±0.63
Range	4-6	4-6	4-6
Median	4.0	4.0	4.0
$QIDS_{16}$-SR-J			
Number of Evaluated Subjects	184	174	179
Mean±SD	17.9±2.10	17.6±1.88	17.6±1.72
Range	16-25	16-24	16-23
Median	17.0	17.0	17.0

HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, SD = Standard Deviation, MADRS = Montgomery-Åsberg Depression Rating Scale, CGI-S = Clinical Global Impression-Severity, $QIDS_{16}$-SR-J = 16-item Quick Inventory of Depressive Symptomatology Self-Report Japanese version

Efficacy, Pharmacokinetic, and Pharmacogenomics Results:

Efficacy Results:

Primary Endpoint: Changes in HAM-D_{17} total score from baseline to Week 8 (or early termination) were summarized in Table 7.

Venlafaxine ER 75 mg/day was confirmed to be superior to placebo in terms of the primary endpoint, which was the change in HAM-D_{17} total score from baseline to Week 8 (or early termination). The mean change in HAM-D_{17} total score from baseline to Week 8 (or early termination) was -9.25 in the placebo group, -10.76 in the venlafaxine ER 75 mg/day group, and -10.37 in the venlafaxine ER 75 - 225 mg/day group. The difference in the primary endpoint compared to placebo was 1.50 and was statistically significant in the venlafaxine ER 75 mg/day group ($p = 0.031$) while it was 1.12 and was not statistically significant in the venlafaxine ER 75 - 225 mg/day group ($p = 0.106$).

Table 7. Analysis of Changes in HAM-D_{17} Total Score From Baseline to Week 8 (or Early Termination) Using ANCOVA (FAS-LOCF)

Treatment group	Number of Evaluated Subjects	Adjusted Mean of Total Score	Changes from Baseline		Adjusted Mean Difference[a] (95% CI)	p-value[b]
			Adjusted Mean	Standard Error		
Placebo	184	13.22	-9.25	0.48		
Venlafaxine ER 75 mg/day	174	11.71	-10.76	0.50	1.50 (0.14, 2.87)	0.031
Venlafaxine ER 75 - 225 mg/day	177	12.10	-10.37	0.49	1.12 (-0.24, 2.48)	0.106

HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, FAS = Full Analysis Set, LOCF = Last Observation Carried Forward, CI = Confidence Interval, ANCOVA = Analysis of Covariance
a. Adjusted mean difference = Placebo group - Active treatment group
b. Two-sided p-value from an analysis of covariance model including treatment as a factor and baseline as a covariate.

Secondary Endpoints: Changes in MADRS total score, CGI-S, HAM-D_6 total score, and $QIDS_{16}$-SR-J total score from baseline to Week 8 (or early termination) were summarized in Table 8, Table 9, Table 10, and Table 11 respectively. CGI-I score at Week 8 (or early termination) were summarized in Table 12.

The difference in terms of secondary endpoints, including mean changes in MADRS total score, CGI-S, and HAM-D_6 total score from baseline to Week 8 (or early termination) compared to placebo was statistically significant in the venlafaxine ER 75 mg/day and the venlafaxine ER 75 - 225 mg/day groups. Meanwhile, the difference in terms of the mean change in $QIDS_{16}$-SR-J total score from baseline to Week 8 (or early termination) compared to the placebo group was statistically significant in the venlafaxine ER 75 mg/day group while it was not in the venlafaxine ER 75 - 225 mg/day group. The difference in terms of CGI-I score at Week 8 (or early termination) compared to the placebo group was statistically significant in the venlafaxine ER 75 - 225 mg/day group while it was not in the venlafaxine ER 75 mg/day group.

Table 8. Analysis of Changes in MADRS Total Score From Baseline to Week 8 (or Early Termination) Using ANCOVA (FAS-LOCF)

Treatment group	Number of Evaluated Subjects	Adjusted Mean of Total Score	Changes from Baseline		Adjusted Mean Difference[a] (95% CI)	p-value[b]
			Adjusted Mean	Standard Error		
Placebo	182	20.39	-12.41	0.75		
Venlafaxine ER 75 mg/day	172	17.51	-15.30	0.77	2.88 (0.77, 5.00)	0.008
Venlafaxine ER 75 - 225 mg/day	176	17.75	-15.05	0.76	2.64 (0.54, 4.74)	0.014

MADRS = Montgomery-Åsberg Depression Rating Scale, FAS = Full Analysis Set, LOCF = Last Observation Carried Forward, CI = Confidence Interval, ANCOVA = Analysis of Covariance
a. Adjusted mean difference = Placebo group - Active treatment group
b. Two-sided p-value from an analysis of covariance model including treatment as a factor and baseline as a covariate.

Table 9. Analysis of Changes in CGI-S From Baseline to Week 8 (or Early Termination) Using ANCOVA (FAS-LOCF)

Treatment group	Number of Evaluated Subjects	Adjusted Mean	Changes from Baseline		Adjusted Mean Difference[a] (95% CI)	p-value[b]
			Adjusted Mean	Standard Error		
Placebo	184	3.21	-1.31	0.08		
Venlafaxine ER 75 mg/day	174	2.95	-1.57	0.08	0.26 (0.03, 0.49)	0.025
Venlafaxine ER 75 - 225 mg/day	177	2.96	-1.56	0.08	0.25 (0.02, 0.48)	0.032

CGI-S = Clinical Global Impression-Severity, FAS = Full Analysis Set, LOCF = Last Observation Carried Forward, CI = Confidence Interval, ANCOVA = Analysis of Covariance
a. Adjusted mean difference = Placebo group - Active treatment group
b. Two-sided p-value from an analysis of covariance model including treatment as a factor and baseline as a covariate.

Table 10. Analysis of Changes in HAM-D_6 Total Score From Baseline to Week 8 (or Early Termination) Using ANCOVA (FAS-LOCF)

Treatment group	Number of Evaluated Subjects	Adjusted Mean of Total Score	Changes from Baseline		Adjusted Mean Difference[a] (95% CI)	p-value[b]
			Adjusted Mean	Standard Error		
Placebo	184	6.85	-4.92	0.28		
Venlafaxine ER 75 mg/day	174	5.67	-6.10	0.29	1.18 (0.39, 1.97)	0.004
Venlafaxine ER 75 - 225 mg/day	177	5.79	-5.99	0.29	1.06 (0.28, 1.85)	0.008

HAM-D_6 = 6-item Hamilton Rating Scale for Depression, FAS = Full Analysis Set, LOCF = Last Observation Carried Forward, CI = Confidence Interval, ANCOVA = Analysis of Covariance
a. Adjusted mean difference = Placebo group - Active treatment group
b. Two-sided p-value from an analysis of covariance model including treatment as a factor and baseline as a covariate.

Table 11. Analysis of Changes in $QIDS_{16}$-SR-J Total Score From Baseline to Week 8 (or Early Termination) Using ANCOVA (FAS-LOCF)

Treatment group	Number of Evaluated Subjects	Adjusted Mean of Total Score	Changes from Baseline		Adjusted Mean Difference[a] (95% CI)	p-value[b]
			Adjusted Mean	Standard Error		
Placebo	182	11.18	-6.50	0.36		
Venlafaxine ER 75 mg/day	172	9.68	-8.00	0.37	1.50 (0.48, 2.53)	0.004
Venlafaxine ER 75 - 225 mg/day	175	10.41	-7.27	0.37	0.77 (-0.25, 1.79)	0.137

$QIDS_{16}$-SR-J = 16-item Quick Inventory of Depressive Symptomatology Self-Report Japanese version, FAS = Full Analysis Set, LOCF = Last Observation Carried Forward, CI = Confidence Interval, ANCOVA = Analysis of Covariance
a. Adjusted mean difference = Placebo group - Active treatment group
b. Two-sided p-value from an analysis of covariance model including treatment as a factor and baseline as a covariate.

Table 12. Analysis of CGI-I Score at Week 8 (or Early Termination) Using ANCOVA (FAS-LOCF)

Treatment group	Number of Evaluated Subjects	Adjusted Mean of Score	Adjusted Mean Difference[a] (95% CI)	p-value[b]
Placebo	184	2.53		
Venlafaxine ER 75 mg/day	174	2.32	0.21 (-0.02, 0.45)	0.073
Venlafaxine ER 75 - 225 mg/day	177	2.28	0.25 (0.02, 0.48)	0.034

CGI-I = Clinical Global Impression-Improvement, FAS = Full Analysis Set, LOCF = Last Observation Carried Forward, CI = Confidence Interval, ANCOVA = Analysis of Covariance
a. Adjusted mean difference = Placebo group - Active treatment group
b. Two-sided p-value from an analysis of covariance model including treatment as a factor and baseline of CGI-S as a covariate.

Pharmacokinetic and Pharmacogenomics Results:

Descriptive summary of C_{trough} of venlafaxine and ODV by dose and CYP2D6 genotype were presented in Table 13. Scatterplots of C_{trough} of venlafaxine and ODV by dose and CYP2D6 genotype were presented in Figure 1.

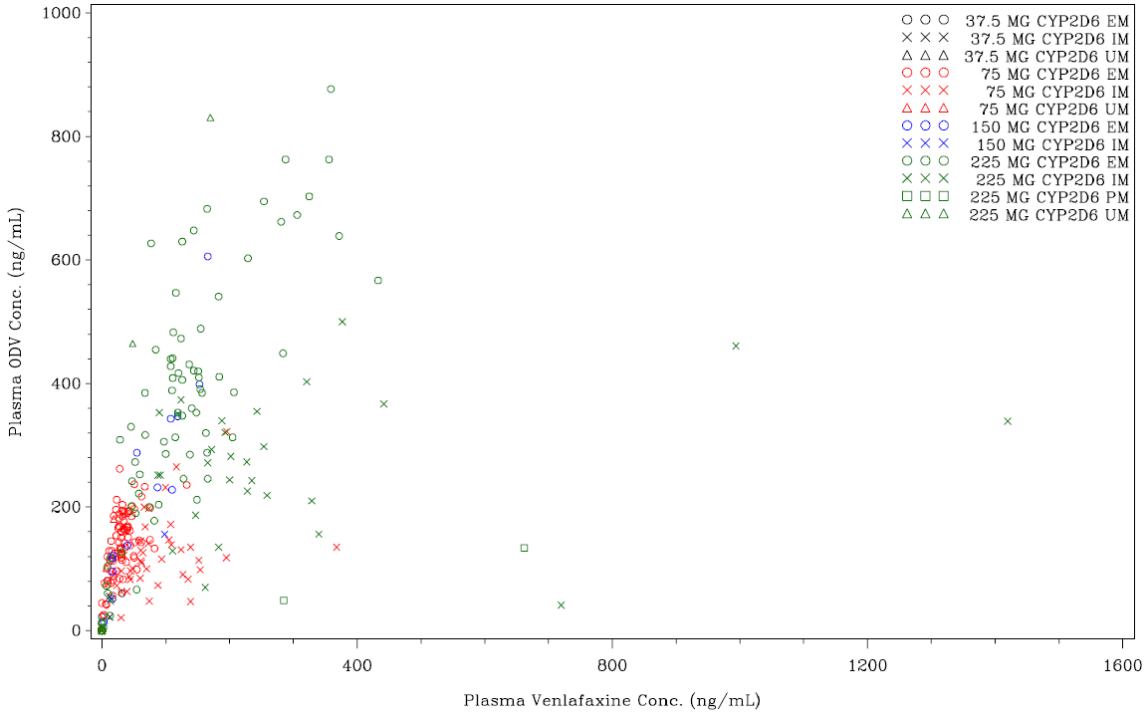
C_{trough} of venlafaxine and ODV immediately following administration of venlafaxine ER tended to dose-dependently increase in the subgroup of patients with the same genotype of CYP2D6. In the active treatment group, 2 subjects were categorized as CYP2D6 poor metabolizer (PM), and 4 subjects were categorized as CYP2D6 ultra-rapid metabolizer (UM). The concentration of venlafaxine tended to be higher and that of ODV tended to be lower in patients with lower CYP2D6 activity than those with higher CYP2D6 activity given the same dose immediately before measurement. The blood concentration of venlafaxine tended to be lower and that of ODV tended to be higher in patients with higher CYP2D6 activity than those with lower CYP2D6 activity (Table 13). Meanwhile, there were overlaps between UM and extensive metabolizer (EM), between EM and intermediate metabolizer (IM), and between IM and PM in terms of the distribution of plasma drug concentration (Figure 1).

Table 13. Descriptive Summary of the Trough Concentration of Venlafaxine and O-Desmethylvenlafaxine at Week 8 (or Early Termination) by Dose and CYP2D6 Genotype

	C_{trough}, Mean±Standard deviation (Number of Evaluated Subjects)			
CYP2D6 genotype	**37.5 mg**	**75 mg**	**150 mg**	**225 mg**
Venlafaxine				
UM	- (1)	12.72±8.32 (2)	-	109.15±86.05 (2)
EM	9.53±12.68 (6)	27.09±22.34 (102)	63.65±58.97 (14)	117.17±99.79 (83)
IM	8.17±7.07 (3)	74.12±67.71 (49)	56.35±59.47 (2)	254.08±286.03 (34)
PM		-	-	473.50±266.58 (2)
ODV				
UM	- (1)	141.00±56.57 (2)	-	648.00±258.80 (2)
EM	37.77±31.32 (6)	118.54±70.23 (102)	209.23±174.82 (14)	328.81±223.56 (83)
IM	25.73±27.67 (3)	99.82±71.05 (49)	103.75±73.89 (2)	235.13±137.26 (34)
PM	-	-	-	91.45±60.17 (2)

ODV = O-desmethylvenlafaxine, UM = Ultra-rapid Metabolizer, EM = Extensive Metabolizer, IM = Intermediate Metabolizer, PM = Poor Metabolizer

Figure 1. Scatterplots of Trough Concentration of Venlafaxine and O-Desmethyl-Venlafaxine by Dose and CYP2D6 Genotype



Safety Results:

Adverse events occurred in the entire study (treatment, tapering, and follow-up periods) were as summarized in Table 14.

In the entire study, all-causality adverse events occurred in 123 subjects (67.2%) in the placebo group, 131 subjects (75.3%) in the venlafaxine ER 75 mg/day group, and 147

subjects (81.7%) in the venlafaxine ER 75 - 225 mg/day group. Treatment-related adverse events in the entire study period occurred in 74 subjects (40.4%) in the placebo group, 96 subjects (55.2%) in the venlafaxine ER 75 mg/day group, and 126 subjects (70.0%) in the venlafaxine ER 75 - 225 mg/day group.

Table 14. Summary of Adverse Events (The Entire Study)

Number (%) of subjects:	All-Causality			Treatment-Related		
	Placebo N = 183	Venlafaxine ER 75 mg/day N = 174	Venlafaxine ER 75 - 225 mg/day N = 180	Placebo N = 183	Venlafaxine ER 75 mg/day N = 174	Venlafaxine ER 75 - 225 mg/day N = 180
Number of adverse events	269	351	428	148	241	321
Subjects with adverse events	123 (67.2)	131 (75.3)	147 (81.7)	74 (40.4)	96 (55.2)	126 (70.0)
Subjects with serious adverse events	2 (1.1)	1 (0.6)	1 (0.6)	1 (0.5)	0	1 (0.6)
Subjects with severe adverse events	2 (1.1)	4 (2.3)	2 (1.1)	1 (0.5)	2 (1.1)	2 (1.1)
Subjects discontinued due to adverse events	3 (1.6)	9 (5.2)	10 (5.6)	3 (1.6)	3 (1.7)	9 (5.0)
Subjects with dose reduced or temporary discontinuation due to adverse events	4 (2.2)	8 (4.6)	16 (8.9)	4 (2.2)	8 (4.6)	14 (7.8)

Non-serious treatment emergent adverse events are summarized in Table 15.

Overall, all-causality adverse events that occurred in not less than 5% of subjects in any of the treatment groups (the placebo group, the venlafaxine ER 75 mg/day group, and the venlafaxine ER 75 - 225 mg/day group) included nausea (13.1%, 22.4%, 29.4%), nasopharyngitis (22.4%, 20.1%, 17.8%), somnolence (8.2%, 12.1%, 17.2%), headache (7.7%, 9.2%, 10.0%), thirst (7.7%, 6.3%, 10.0%), constipation (4.4%, 9.8%, 9.4%), dizziness (2.7%, 5.7%, 10.0%), heart rate increased (2.2%, 5.7%, 7.2%), malaise (2.7%, 5.2%, 6.1%), abdominal discomfort (2.2%, 4.0%, 6.1%), and hyperhidrosis (1.1%, 1.7%, 8.3%). Treatment-related adverse events that occurred in not less than 5% of subjects in any of the treatment groups (the placebo group, the venlafaxine ER 75 mg/day group, and the venlafaxine ER 75 - 225 mg/day group) included nausea (9.8%, 19.5%, 27.8%), somnolence (7.1%, 11.5%, 15.6%), thirst (7.7%, 6.3%, 10.0%), constipation (3.3%, 9.2%, 8.9%), headache (2.7%, 6.3%, 8.3%), dizziness (2.2%, 4.0%, 8.9%), heart rate increased (1.6%, 5.2%, 6.7%), malaise (2.2%, 4.0%, 6.1%), abdominal discomfort (1.6%, 3.4%, 5.0%), and hyperhidrosis (0.5%, 1.7%, 7.8%). The severity of these adverse events was mostly mild or moderate.

Table 15. Treatment-Emergent non-Serious Adverse Events[a]

Number (%) of Subjects with Adverse Events by: MedDRA System Organ Class Preferred Term (version 16.1)	All-Causality			Treatment-Related		
	Placebo	Venlafaxine ER 75 mg/day	Venlafaxine ER 75 - 225 mg/day	Placebo	Venlafaxine ER 75 mg/day	Venlafaxine ER 75 - 225 mg/day
	N = 183	N = 174	N = 180	N = 183	N = 174	N = 180
Cardiac disorders						
Palpitations	5 (2.7)	8 (4.6)	6 (3.3)	5 (2.7)	7 (4.0)	6 (3.3)
Tachycardia	0	4 (2.3)	7 (3.9)	0	4 (2.3)	7 (3.9)
Ear and labyrinth disorders						
Ear discomfort	0	0	2 (1.1)	0	0	2 (1.1)
Tinnitus	1 (0.5)	2 (1.1)	1 (0.6)	0	2 (1.1)	0
Vertigo	2 (1.1)	4 (2.3)	6 (3.3)	2 (1.1)	4 (2.3)	3 (1.7)
Eye disorders						
Vision blurred	0	0	2 (1.1)	0	0	2 (1.1)
Gastrointestinal disorders						
Abdominal discomfort	4 (2.2)	7 (4.0)	11 (6.1)	3 (1.6)	6 (3.4)	9 (5.0)
Abdominal distension	2 (1.1)	1 (0.6)	1 (0.6)	2 (1.1)	1 (0.6)	1 (0.6)
Abdominal pain upper	7 (3.8)	5 (2.9)	0	4 (2.2)	4 (2.3)	0
Constipation	8 (4.4)	17 (9.8)	17 (9.4)	6 (3.3)	16 (9.2)	16 (8.9)
Diarrhoea	7 (3.8)	6 (3.4)	8 (4.4)	4 (2.2)	4 (2.3)	6 (3.3)
Dry mouth	1 (0.5)	5 (2.9)	7 (3.9)	1 (0.5)	5 (2.9)	7 (3.9)
Dyspepsia	1 (0.5)	2 (1.1)	0	1 (0.5)	2 (1.1)	0
Eructation	0	2 (1.1)	0	0	2 (1.1)	0
Nausea	24 (13.1)	39 (22.4)	53 (29.4)	18 (9.8)	34 (19.5)	50 (27.8)
Stomatitis	0	1 (0.6)	2 (1.1)	0	0	0
Toothache	2 (1.1)	1 (0.6)	0	1 (0.5)	0	0
Vomiting	7 (3.8)	5 (2.9)	4 (2.2)	4 (2.2)	5 (2.9)	3 (1.7)
General disorders and administration site conditions						
Asthenia	0	1 (0.6)	2 (1.1)	0	1 (0.6)	2 (1.1)
Chest discomfort	0	1 (0.6)	2 (1.1)	0	1 (0.6)	2 (1.1)
Feeling abnormal	0	2 (1.1)	4 (2.2)	0	2 (1.1)	3 (1.7)
Irritability	3 (1.6)	3 (1.7)	1 (0.6)	3 (1.6)	3 (1.7)	0
Malaise	5 (2.7)	9 (5.2)	11 (6.1)	4 (2.2)	7 (4.0)	11 (6.1)
Pyrexia	2 (1.1)	0	3 (1.7)	0	0	1 (0.6)
Thirst	14 (7.7)	11 (6.3)	18 (10.0)	14 (7.7)	11 (6.3)	18 (10.0)
Hepatobiliary disorders						
Hepatic function abnormal	2 (1.1)	3 (1.7)	3 (1.7)	1 (0.5)	2 (1.1)	2 (1.1)
Infections and infestations						
Enteritis infectious	1 (0.5)	0	2 (1.1)	0	0	0

Table 15. Treatment-Emergent non-Serious Adverse Events[a]

Number (%) of Subjects with Adverse Events by: MedDRA System Organ Class Preferred Term (version 16.1)	All-Causality			Treatment-Related		
	Placebo	Venlafaxine ER 75 mg/day	Venlafaxine ER 75 - 225 mg/day	Placebo	Venlafaxine ER 75 mg/day	Venlafaxine ER 75 - 225 mg/day
	N = 183	N = 174	N = 180	N = 183	N = 174	N = 180
Gastroenteritis	2 (1.1)	1 (0.6)	1 (0.6)	1 (0.5)	0	1 (0.6)
Gingivitis	3 (1.6)	1 (0.6)	0	1 (0.5)	0	0
Nasopharyngitis	41 (22.4)	35 (20.1)	32 (17.8)	1 (0.5)	0	0
Oral herpes	2 (1.1)	1 (0.6)	0	0	1 (0.6)	0
Pharyngitis	0	0	2 (1.1)	0	0	0
Upper respiratory tract infection	0	2 (1.1)	0	0	0	0
Injury, poisoning and procedural complications						
Contusion	3 (1.6)	0	1 (0.6)	0	0	0
Investigations						
Alanine aminotransferase increased	0	4 (2.3)	2 (1.1)	0	3 (1.7)	0
Aspartate aminotransferase increased	0	2 (1.1)	0	0	2 (1.1)	0
Blood pressure increased	2 (1.1)	4 (2.3)	5 (2.8)	2 (1.1)	4 (2.3)	5 (2.8)
Gamma-glutamyltransferase increased	1 (0.5)	2 (1.1)	3 (1.7)	1 (0.5)	0	3 (1.7)
Heart rate increased	4 (2.2)	10 (5.7)	13 (7.2)	3 (1.6)	9 (5.2)	12 (6.7)
Liver function test abnormal	0	2 (1.1)	2 (1.1)	0	2 (1.1)	1 (0.6)
Weight decreased	1 (0.5)	3 (1.7)	2 (1.1)	1 (0.5)	1 (0.6)	1 (0.6)
Weight increased	2 (1.1)	1 (0.6)	1 (0.6)	2 (1.1)	1 (0.6)	1 (0.6)
Metabolism and nutrition disorders						
Decreased appetite	1 (0.5)	4 (2.3)	4 (2.2)	1 (0.5)	3 (1.7)	3 (1.7)
Hyperlipidaemia	2 (1.1)	2 (1.1)	0	2 (1.1)	2 (1.1)	0
Musculoskeletal and connective tissue disorders						
Back pain	1 (0.5)	3 (1.7)	2 (1.1)	0	0	0
Pain in extremity	0	1 (0.6)	2 (1.1)	0	0	1 (0.6)
Nervous system disorders						
Dizziness	5 (2.7)	10 (5.7)	18 (10.0)	4 (2.2)	7 (4.0)	16 (8.9)
Dizziness postural	1 (0.5)	2 (1.1)	5 (2.8)	1 (0.5)	2 (1.1)	5 (2.8)
Headache	14 (7.7)	16 (9.2)	18 (10.0)	5 (2.7)	11 (6.3)	15 (8.3)
Hypoaesthesia	2 (1.1)	1 (0.6)	1 (0.6)	1 (0.5)	1 (0.6)	1 (0.6)
Somnolence	15 (8.2)	21 (12.1)	31 (17.2)	13 (7.1)	20 (11.5)	28 (15.6)
Psychiatric disorders						
Agitation	1 (0.5)	2 (1.1)	2 (1.1)	1 (0.5)	1 (0.6)	2 (1.1)
Depression	2 (1.1)	2 (1.1)	1 (0.6)	0	1 (0.6)	1 (0.6)
Emotional disorder	2 (1.1)	0	0	2 (1.1)	0	0
Insomnia	6 (3.3)	4 (2.3)	8 (4.4)	5 (2.7)	3 (1.7)	6 (3.3)

Table 15. Treatment-Emergent non-Serious Adverse Events[a]

Number (%) of Subjects with Adverse Events by: MedDRA System Organ Class Preferred Term (version 16.1)	All-Causality			Treatment-Related		
	Placebo	Venlafaxine ER 75 mg/day	Venlafaxine ER 75 - 225 mg/day	Placebo	Venlafaxine ER 75 mg/day	Venlafaxine ER 75 - 225 mg/day
	N = 183	N = 174	N = 180	N = 183	N = 174	N = 180
Major depression	3 (1.6)	0	1 (0.6)	0	0	0
Sleep disorder	1 (0.5)	2 (1.1)	1 (0.6)	1 (0.5)	2 (1.1)	1 (0.6)
Renal and urinary disorders						
Dysuria	0	0	2 (1.1)	0	0	2 (1.1)
Haematuria	2 (1.1)	0	0	1 (0.5)	0	0
Pollakiuria	0	2 (1.1)	5 (2.8)	0	2 (1.1)	5 (2.8)
Respiratory, thoracic and mediastinal disorders						
Oropharyngeal pain	0	1 (0.6)	2 (1.1)	0	1 (0.6)	1 (0.6)
Yawning	0	2 (1.1)	2 (1.1)	0	2 (1.1)	2 (1.1)
Skin and subcutaneous tissue disorders						
Eczema	1 (0.5)	1 (0.6)	2 (1.1)	0	0	1 (0.6)
Hyperhidrosis	2 (1.1)	3 (1.7)	15 (8.3)	1 (0.5)	3 (1.7)	14 (7.8)
Night sweats	1 (0.5)	1 (0.6)	2 (1.1)	0	1 (0.6)	2 (1.1)
Rash	1 (0.5)	1 (0.6)	2 (1.1)	0	1 (0.6)	1 (0.6)
Vascular disorders						
Hot flush	2 (1.1)	1 (0.6)	2 (1.1)	2 (1.1)	1 (0.6)	2 (1.1)
Hypertension	0	1 (0.6)	2 (1.1)	0	1 (0.6)	2 (1.1)

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.

In this study, 1 case of death occurred in the placebo group and the venlafaxine ER 75 - 225 mg/day group respectively. These deaths were due to suicide; causal relationship with the study drug could not be ruled out for both events (Table 16).

Table 16. Individual Listing of Deaths

Sex	Age[a]	Dose at death	Day of death[b]	Action taken (Study drug)	Event with fatal outcome MedDRA version 16.1 Preferred term (Verbatim term)	Cause of Death MedDRA version 16.1 Preferred term (Verbatim term)
Placebo						
Male	43	0 mg	25	Unknown	Completed suicide (Suicide)	Major depression (major depressive disorder aggravated) Completed suicide (death by hanging)
Venlafaxine ER 75 - 225 mg/day						
Male	49	37.5 mg	7	Dose not changed	Completed suicide (Completed suicide)	Abdominal injury (intra-abdominal organ injury) Completed suicide (Completed suicide)

a. Age at death
b. Day of death is calculated as death date minus first active therapy date plus one.

Serious adverse events other than death included anaemia which occurred in 1 subject in the placebo group and Meniere's disease which occurred in 1 subject in the venlafaxine ER 75 mg/day group; causal relationship with the study drug was denied for both events (Table 17).

Table 17. Treatment-Emergent Serious Adverse Events

Number (%) of Subjects with Adverse Events by: MedDRA System Organ Class Preferred Term(version 16.1)	All-Causality			Treatment-Related		
	Placebo	Venlafaxine ER 75 mg/day	Venlafaxine ER 75 - 225 mg/day	Placebo	Venlafaxine ER 75 mg/day	Venlafaxine ER 75 - 225 mg/day
	N = 183	N = 174	N = 180	N = 183	N = 174	N = 180
Blood and lymphatic system disorders						
Anaemia	1 (0.5)	0	0	0	0	0
Ear and labyrinth disorders						
Meniere's disease	0	1 (0.6)	0	0	0	0
Psychiatric disorders						
Completed suicide	1 (0.5)	0	1 (0.6)	1 (0.5)	0	1 (0.6)

Subjects are only counted once per treatment for each row.
Includes all data collected during study.
MedDRA = Medical Dictionary for Regulatory Activities

A summary of withdrawals due to adverse events is presented in Table 18.

Table 18. Summary of Withdrawals due to Adverse Events (All-Causality)

Number (%) of Subjects with Adverse Events by: MedDRA System Organ Class Preferred Term (version 16.1)	Placebo	Venlafaxine ER 75 mg/day	Venlafaxine ER 75 - 225 mg/day
	N = 183	N = 174	N = 180
Cardiac disorders			
Atrial fibrillation	0	1 (0.6)	0
Palpitations	0	0	1 (0.6)
Gastrointestinal Disorders			
Abdominal discomfort	0	0	1 (0.6)
Abdominal pain upper	0	1 (0.6)	0
Nausea	0	2 (1.1)	2 (1.1)
General disorders and administration site conditions			
Asthenia	0	0	1 (0.6)
Malaise	2 (1.1)	1 (0.6)	0
Infections and infestations			
Gastroenteritis	0	0	1 (0.6)
Metabolism and nutrition disorders			
Decreased appetite	0	1 (0.6)	0
Nervous system disorders			
Somnolence	0	1 (0.6)	0
Psychiatric disorders			
Agitation	0	1 (0.6)	0
Completed suicide	1 (0.5)	0	1 (0.6)
Depression	0	2 (1.1)	1 (0.6)
Flashback	0	0	1 (0.6)
Insomnia	0	0	1 (0.6)
Major depression	0	0	1 (0.6)

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

Regarding laboratory findings, major laboratory test abnormalities occurred in not less than 10% of subjects in any of the treatment groups (the placebo group, the venlafaxine ER 75 mg/day group, and the venlafaxine ER 75 - 225 mg/day group) were urinary occult blood positive (13.8%, 10.5%, 11.3%), low density lipoprotein cholesterol increased (7.2%, 11.1%, 7.3%), and triglyceride increased (6.6%, 9.4%, 10.7%). There was no major difference between treatment groups in the incidence of these events.

There was no clear dose response in the mean blood pressure, pulse rate, and body weight. The proportion of subjects that met the criteria for sustained hypertension was evaluated; the proportion of such subjects was low in all of the treatment groups.

Pertinent to ECG findings, there were 4 subjects in the placebo group whose change in QT interval from baseline was at least 60 msec (measured value, 376 to 439 msec; change from baseline, 61 to 77 msec), and there was 1 subject in the venlafaxine ER 75 mg/day group whose change in the corrected QT interval using Bazett's corrections from baseline was at least 60 msec (measured value, 455 msec; change from baseline, 60 msec). No subjects had at least 60 msec of a change from baseline in the corrected QT interval using Fridericia's corrections. One subject each in the placebo and the venlafaxine ER 75 mg/day groups

reported an adverse event of a QT prolongation in ECG. There was no significant issue regarding the results of physical examinations.

In the C-SSRS evaluation at baseline, suicidal behaviour or self injurious behaviour was not confirmed in any of the subjects. After the commencement of study treatment, completed suicide was confirmed in 1 subject each in the placebo and the venlafaxine ER 75 - 225 mg/day groups. Self injurious behaviour was confirmed in 1 subject in the venlafaxine ER 75 mg/day group, who discontinued study due to agitation which occurred concurrently with the self injurious behaviour. All these events were reported as adverse events.

At baseline, suicidal ideation was confirmed in 39 subjects (21.3%) in the placebo group, 41 subjects (23.6%) in the venlafaxine ER 75 mg/day group, and 47 subjects (26.1%) in the venlafaxine ER 75 - 225 mg/day group. The number of subjects in whom suicidal ideation was not confirmed at baseline, but occurred after the commencement of study treatment was 21 subjects (11.5%) in the placebo group, 7 subjects (4.0%) in the venlafaxine ER 75 mg/day group, and 13 subjects (7.3%) in the venlafaxine ER 75 - 225 mg/day group.

CONCLUSION(S):

- The superiority to the placebo group was shown in the venlafaxine ER 75 mg/day group but not in the venlafaxine ER 75 - 225 mg/day group in terms of the primary endpoint, which was the mean change in HAM-D_{17} total score from baseline to Week 8 (or early termination). The efficacy in the venlafaxine ER 75 mg/day group was demonstrated by using the pre-specified closed testing procedure. In addition, the venlafaxine ER 75 mg/day group was more effective than the placebo group in all secondary endpoints, which supported the results of the primary analysis.

- The venlafaxine ER 75 - 225 mg/day group showed numerically better results than the placebo group in the primary endpoint and all secondary endpoints although the differences in the primary endpoint and one of the secondary endpoints were not statistically significant. The difference between the venlafaxine ER 75 - 225 mg/day group and the placebo group was statistically significant in terms of the secondary endpoints of the mean changes in MADRS total score, CGI-S, HAM-D_6 total score, and CGI-I score, suggesting the efficacy of the venlafaxine ER 75 - 225 mg/day group.

- Venlafaxine ER has an acceptable safety and tolerability profiles; there was no new safety issue found in the study. The major adverse events occurred in this study were not different from the established safety profile. Most adverse events were either mild or moderate. One case of death due to suicide occurred in the placebo group and the venlafaxine ER 75 - 225 mg/day group respectively; causal relationship with the study drug could not be ruled out for both events.

- Interindividual variability in terms of the pharmacokinetics of venlafaxine and ODV following administration of this product was confirmed to be mainly attributable to the gene polymorphism of CYP2D6.