Neuropsychiatric Disease and Treatment

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Factors impacting the efficacy of venlafaxine extended release 75–225 mg/day in patients with major depressive disorder: exploratory post hoc subgroup analyses of a randomized, double-blind, placebo-controlled study in Japan

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

Yoshinori Watanabe[1]
Yuko Asami[2]
Yoko Hirano[2]
Kazuhiko Kuribayashi[3]
Rio Itamura[4]
Takayuki Imaeda[4]

[1]Himorogi Psychiatric Institute, Tokyo, Japan; [2]Medical Affairs, Pfizer Essential Health, Pfizer Japan Inc., Tokyo, Japan; [3]Clinical Statistics, Pfizer Japan Inc., Tokyo, Japan; [4]Clinical Research, Pfizer Japan Inc., Tokyo, Japan

Purpose: To explore the potential factors impacting the efficacy of venlafaxine extended release (ER) and treatment differences between 75 mg/day and 75–225 mg/day dose in patients with major depressive disorder (MDD).

Methods: We performed exploratory post hoc subgroup analyses of a randomized, double-blind, placebo-controlled study conducted in Japan. A total of 538 outpatients aged 20 years or older with a primary diagnosis of MDD who experienced single or recurrent episodes were randomized into three groups: fixed-dose, flexible-dose, or placebo. Venlafaxine ER was initiated at 37.5 mg/day and titrated to 75 mg/day for both fixed-dose and flexible-dose group, and to 225 mg/day for flexible-dose group (if well tolerated). Efficacy endpoints were changes from baseline at Week 8 using the Hamilton Rating Scale for Depression–17 items ($HAM\text{-}D_{17}$) total score, Hamilton Rating Scale for Depression–6 items score, and Montgomery–Asberg Depression Rating Scale total score. The following factors were considered in the subgroup analyses: sex, age, $HAM\text{-}D_{17}$ total score at baseline, duration of MDD, duration of current depressive episode, history of previous depressive episodes, history of previous medications for MDD, and CYP2D6 phenotype. For each subgroup, an analysis of covariance model was fitted and the adjusted mean of the treatment effect and corresponding 95% CI were computed. Due to the exploratory nature of the investigation, no statistical hypothesis testing was used.

Results: Venlafaxine ER improved symptoms of MDD compared with placebo in most subgroups. The subgroup with a long duration of MDD (>22 months) consistently showed greater treatment benefits in the flexible-dose group than in the fixed-dose group.

Conclusion: These results suggest that a greater treatment response to venlafaxine ER (up to 225 mg/day) can be seen in patients with a longer duration of MDD. Further investigations are needed to identify additional factors impacting the efficacy of venlafaxine ER.

Keywords: venlafaxine, Hamilton Rating Scale for Depression, HAM-D, subgroup, major depressive disorder, MDD, Montgomery–Asberg Depression Rating Scale, MADRS

Introduction

Antidepressant medications such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (SNRIs) are the first-line treatments for patients with moderate to severe major depressive disorder (MDD).[1–3] In 1993, venlafaxine was approved by the US Food and Drug Administration as the first SNRI

Correspondence: Yuko Asami
Pfizer Japan Inc., 3-22-7 Yoyogi, Shibuya-ku, Tokyo 151-8589, Japan
Tel +81 80 4066 6065
Fax +81 3 5309 9064
Email yuko.asami@pfizer.com

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/NDT.S146428

for the treatment of MDD in adults,[4] and is now marketed in more than 90 countries. In 2015, venlafaxine extended release (ER) became the third SNRI to receive regulatory approval for the treatment of MDD in Japan, thereby driving interest in data specifically addressing Japanese patients treated with venlafaxine ER.

Higuchi et al[5] reported the primary results of an 8-week, double-blind, placebo-controlled, randomized, Phase III study of 538 patients conducted in Japan using fixed-dose (75 mg/day) and flexible doses (75–225 mg/day) of venlafaxine ER. The study findings showed a statistically significant difference in the change from baseline in Hamilton Rating Scale for Depression–17 items (HAM-D_{17}) total score[6] in the fixed-dose group (−10.76; P=0.031), but not in the flexible-dose group (−10.37; P=0.106), compared with the placebo group (−9.25). However, the flexible-dose group showed statistically significant treatment benefits compared with the placebo group ($P<0.05$) in several secondary endpoints, such as the Montgomery–Asberg Depression Rating Scale (MADRS)[7] and the Hamilton Rating Scale for Depression–6 items (HAM-D_6).[8,9] An examination of the HAM-D_{17} revealed poor improvement in sleep disturbance scores (items 4–6)[10] for the flexible-dose group after Week 4, possibly due to the norepinephrine effect of venlafaxine at high doses.

Given these results, we performed exploratory post hoc subgroup analyses in order to explore the potential factors that may impact the efficacy of venlafaxine ER and treatment differences between the fixed-dose (75 mg/day) and the flexible-dose (75–225 mg/day) in patients with MDD.

Materials and methods

Study design

The original study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase III 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 with placebo (ClinicalTrials.gov: NCT01441440).[5] After a 2-week screening period, eligible patients were randomized in a 1:1:1 ratio to each treatment group for 8 weeks, followed by a 2-week tapering period.

Subjects

Eligible patients included outpatients aged 20 years or older who had a primary diagnosis of MDD based on criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, and had experienced single (≥90 days) or recurrent episodes (≥28 days) of depression without psychotic features. At both screening and baseline, patients were required to have scored at least 26 on the MADRS questionnaire and the change in MADRS total score from screening to baseline was required not to have exceeded 25%. Finally, at both screening and baseline, patients were required to have a 16-item Quick Inventory of Depressive Symptomatology self-report version ($QIDS_{16}$-SR-J)[11] total score and a Clinical Global Impressions–Severity scale (CGI-S) score of at least 16 and 4, respectively.

Settings

The original study was conducted at 62 investigational sites from November 2011 to March 2014 in Japan. All applicable documentation including the study protocol was approved by the Institutional Review Board and Independent Ethics Committee at each site (Box S1). The study was conducted in agreement with all legal and regulatory requirements and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice, and the Declaration of Helsinki. Written informed consent was provided by all patients before study participation.

Treatment

The details of drug administration and dose titration have been reported elsewhere.[5] Initial dose of venlafaxine was 37.5 mg/day. In Week 1, the dose could be increased to 75 mg/day, and in Week 2, based on tolerability, it could be increased to 150 mg/day in the flexible-dose group. Further, in Week 3, the dose was force titrated to 225 mg/day in the flexible-dose group, in spite of an acceptable response at a lower dose. Dose reduction was allowed in case of intolerance to higher doses. We simply compared the point estimates among the subgroups to explore the potential factors that may impact the efficacy of venlafaxine ER and treatment differences between the fixed-dose (75 mg/day) and the flexible-dose (75–225 mg/day) groups.

Assessments

The results of all efficacy endpoints in this study have been previously published.[5] In this report, HAM-D_{17}, HAM-D_6, and MADRS were used for subgroup analyses. The formula, Σ (items 1, 2, 7, 8, 10, and 13), was used to measure HAM-D_6 score.

Statistical analysis

As the current investigation was exploratory in nature, no statistical hypothesis testing was used. The following

efficacy endpoints were analyzed: change from baseline at Week 8 in the HAM-D_{17} total score, HAM-D_6 score, and MADRS total score. The following factors were considered for the subgroup analyses: sex (male/female); age (≤37/>37 years [median]); HAM-D_{17} total score at baseline (total score ≤22/total score >22 [median]); duration of MDD, defined as the duration of MDD since the occurrence of the first episode (≤22 months/>22 months [median], <12 months/≥12 months, and <48 months/≥48 months); duration of the current depressive episode (≤6.6 months/>6.6 months [median]); history of previous depressive episodes (0 [single]/≥1 [recurrence]); history of previous medications for MDD (0 [no medication]/≥1 [medicated]); and CYP2D6 phenotypes (ultra-rapid/extensive and intermediate/poor metabolizers). For each subgroup, an ANCOVA model with the treatment group as a factor and the baseline value of the respective efficacy endpoint as a covariate was fitted. Based on the ANCOVA model, the adjusted mean and its corresponding 95% CI of the treatment effect (defined as a difference from placebo) was computed for each active treatment group.

The full analysis set (FAS) was used throughout the analyses. The FAS was defined as all patients who received at least one dose of the study drug and had baseline measurement and at least one post-baseline measurement of the primary efficacy endpoint was used for the analysis. Missing values in the endpoints at Week 8 were imputed using the last observation carried forward (LOCF) algorithm. Assessments prior to the first dose of the study medication were not eligible to be carried forward.

Results

Patient disposition

Of 538 randomized patients, 537 patients received the study drug (fixed-dose group, 174; flexible-dose group, 179; placebo, 184). Overall, 475 patients completed the study period (fixed-dose, 151; flexible-dose, 158; placebo, 166). Patients in all groups had comparable demographic and baseline MDD characteristics. The mean (SD) age in the three treatment groups ranged from 38.3 (10.2) to 38.6 (11.1) years, and the mean (SD) duration of MDD ranged from 40.3 (50.0) to 52.6 (62.9) months. The mean (SD) baseline HAM-D_{17} total score and MADRS total score ranged from 22.4 (4.1) to 22.6 (4.1) and from 32.6 (4.4) to 33.2 (5.1), respectively. The distribution of the last dose during the 8-week treatment period was 4.5%, 4.5%, 10.6%, and 80.4% for 37.5 mg/day, 75 mg/day, 150 mg/day, and 225 mg/day, respectively, in the flexible-dose group.

Efficacy

Figures 1–3 show forest plots of the differences between each treatment group and the placebo group in the adjusted mean change from baseline at Week 8 (LOCF) in the HAM-D_{17} total score (Figure 1), HAM-D_6 score (Figure 2), and MADRS total score (Figure 3). Both venlafaxine ER groups showed greater treatment benefits compared with the placebo group for all efficacy measures in males than in females; in patients with a low HAM-D_{17} total score at baseline (≤22) than in those with a high HAM-D_{17} total score at baseline (>22); in patients with a long duration of MDD (>22 months) than a short duration (≤22 months); in patients with a short duration of current episode (≤6.6 months) than a long duration (>6.6 months); and in patients with one or more previous episodes than none (Figures 1–3). There were no consistent trends in the subgroup of patients with or without a history of previous medications for MDD, in the subgroup of patients in two age categories, and in the subgroup of patients with the two CYP2D6 phenotypes.

Although the flexible-dose group showed a favorable treatment effect compared with placebo in most subgroups, the flexible-dose group showed a relatively smaller treatment effect than the fixed-dose group in most subgroups. However, a greater treatment effect was seen in the flexible-dose group versus the fixed-dose group for all efficacy measures in subgroups of older patients (>37 years), and in patients with a long duration of MDD (>22 months), and a short duration of current depressive episode (≤6.6 months) (Figures 1–3). Similar trends were observed in duration of MDD in an analysis that divided the groups into durations of 12 months and 48 months (Figures 4 and 5, respectively).

Demographic and disease characteristics stratified by duration of MDD (≤22 months/>22 months) are presented in Table 1. Overall, demographic characteristics and baseline HAM-D_{17} and MADRS total scores were comparable between the subgroups in each treatment group. Patients with a long duration of MDD (>22 months) had more frequent previous depressive episodes and a longer duration of the current depressive episode than patients with a short duration of MDD (≤22 months).

Discussion

Although these were exploratory, post hoc subgroup analyses of a placebo-controlled clinical study, our results highlight several potential factors that may impact the efficacy of venlafaxine ER in Japanese populations.

As in comparison between subgroups regardless of the treatment groups, there was no meaningful difference in the

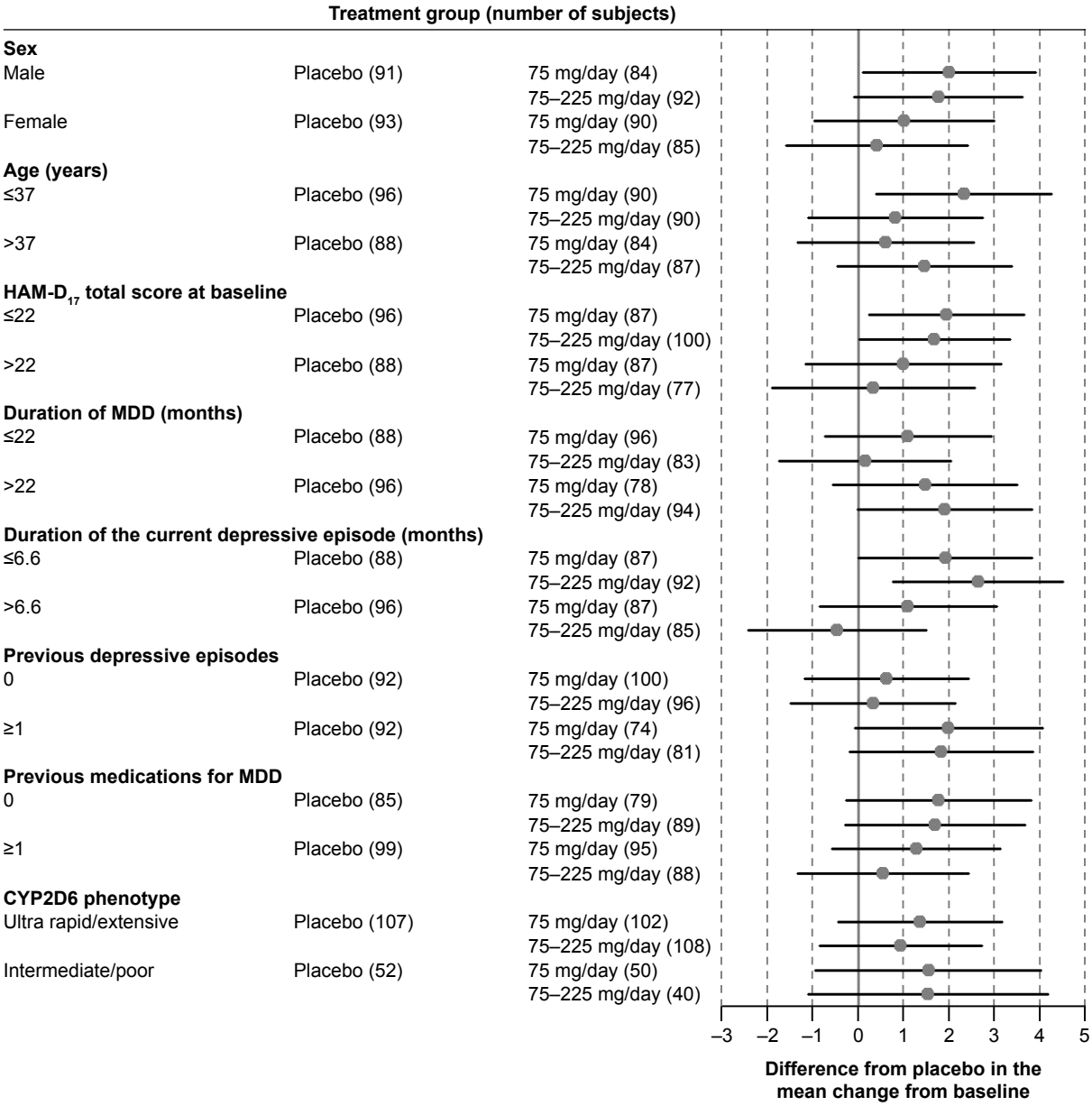

Figure 1 Forest plot of the HAM-D_{17} total score by subgroups: difference between venlafaxine ER treatment group and the placebo group in the adjusted mean change from baseline at Week 8 with 95% CIs (FAS, LOCF, ANCOVA model).

Abbreviations: FAS, full analysis set; HAM-D_{17}, Hamilton Rating Scale for Depression–17 items; LOCF, last observation carried forward; MDD, major depressive disorder.

effect of venlafaxine ER compared with placebo for different degrees of severity of depression at baseline. As shown in Figure 6, patients with more severe depression (HAM-D_{17} total score at baseline >22) showed a greater decrease in the mean change from baseline in the HAM-D_{17} total score among all groups, including the placebo group. While some studies have shown no relationship between severity of depression and treatment response to antidepressants in MDD,[12,13] others have shown greater antidepressant–placebo differences in patients with more severe depression.[14–17] This discrepancy is thought to be due to the extent of baseline score inflation.[18,19] In our study, patients were first screened with MADRS, $QIDS_{16}$-SR-J, and CGI-S to mitigate baseline score inflation, and a different score (HAM-D_{17}) was used as the primary efficacy measure, although previous studies have used the same score both as an inclusion criterion and the primary efficacy measure. Patients with low baseline HAM-D_{17} scores (≤22) showed greater treatment benefits than patients with high scores (>22) in both treatment groups compared with the placebo group, because placebo

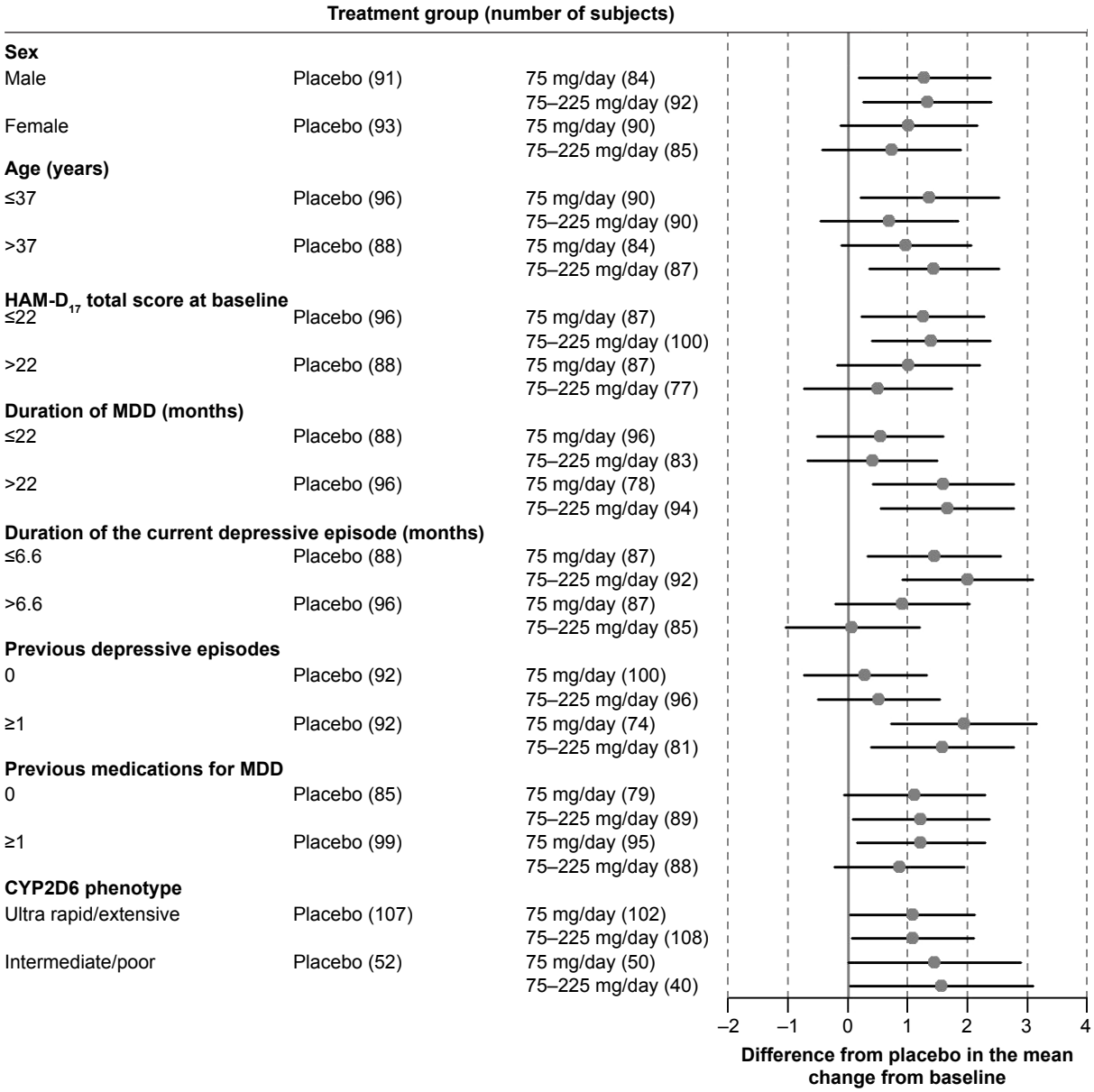

Figure 2 Forest plot of the HAM-D_6 score by subgroups: difference between venlafaxine ER treatment group and the placebo group in the adjusted mean change from baseline at Week 8 with 95% CIs (FAS, LOCF, ANCOVA model).

Abbreviations: FAS, full analysis set; HAM-D_6, Hamilton Rating Scale for Depression–6 items; HAM-D_{17}, Hamilton Rating Scale for Depression–17 items; LOCF, last observation carried forward; MDD, major depressive disorder.

response was much higher in patients with a high baseline HAM-D_{17} score (>22), particularly in changes from baseline in HAM-D_{17} and MADRS total scores, which contributed to smaller differences between each treatment group and the placebo group in those patients.

Patients with a long duration of MDD (>22 months) showed greater treatment benefits than those with a short duration of MDD (≤22 months) in both venlafaxine ER treatment groups compared with the placebo group. Placebo response was much smaller in patients with a long duration of MDD (Figure 4); these results were consistent with a meta-analysis of ten clinical trials[13] as well as other prior studies.[20,21] A small placebo response in patients with a long duration of MDD may have contributed to the larger differences observed between each treatment group and the placebo group. Similar trends were seen in an analysis that divided the groups at 12 months and 48 months (Figures 4 and 5, respectively).

Comparing the effect between the treatment groups in each subgroup, greater treatment effect was seen in the

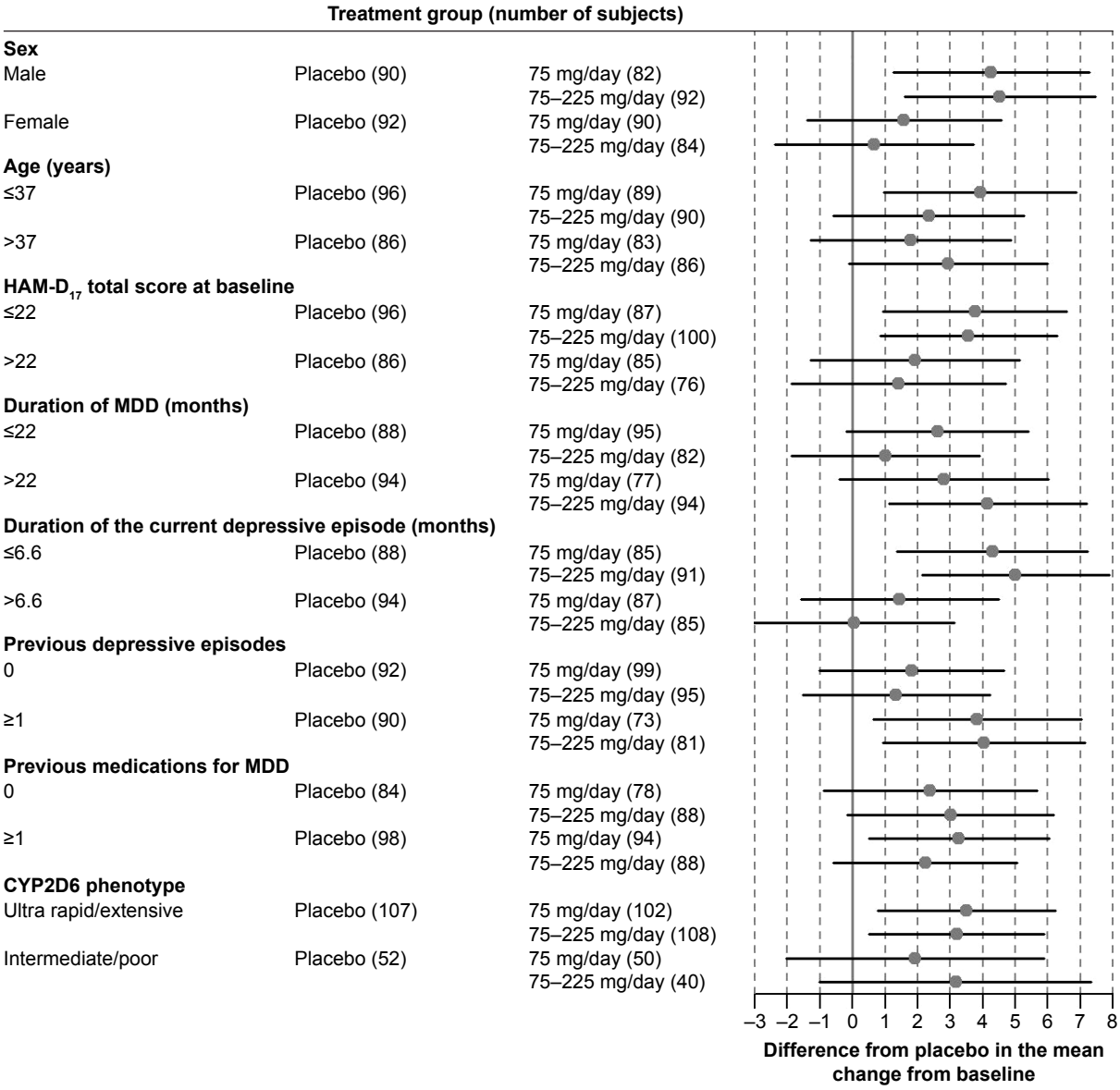

Figure 3 Forest plot of the MADRS total score by subgroups: difference between venlafaxine ER treatment group and the placebo group in the adjusted mean change from baseline at Week 8 with 95% CIs (FAS, LOCF, ANCOVA model).

Abbreviations: FAS, full analysis set; HAM-D_{17}, Hamilton Rating Scale for Depression–17 items; LOCF, last observation carried forward; MADRS, Montgomery–Asberg Depression Rating Scale; MDD, major depressive disorder.

flexible-dose group versus the fixed dose group in the subgroup with a long duration of MDD. These results may prove the hypothesis that a greater treatment response to venlafaxine ER (up to 225 mg/day) can be seen in patients with a longer duration of MDD. A similar observation was seen in patients in age subgroups. In the older patient (>37 years) subgroup, the effect in the flexible-dose group was greater than that in the fixed-dose group. This result may be considered to be associated with the fact that the mean duration of MDD in the >37 years subgroup was longer than that in the ≤37 years subgroup (data not shown).

Furthermore, in both venlafaxine ER treatment groups, patients with recurrent depressive episodes showed greater treatment benefits than those with a single depressive episode compared with the placebo group. The placebo response was much smaller in patients with recurrent episodes (Figure 7), which corresponds with the results of a meta-analysis of seven clinical trials.[22] A small placebo response may have contributed to the larger differences between the venlafaxine ER groups and the placebo group in patients with recurrent depressive episodes. These results were similar to those for duration of MDD reported previously (Figure 4), as patients with a long duration of MDD (>22 months) experienced more depressive episodes (Table 1).

Interestingly, patients with a long duration of the current depressive episode (>6.6 months) versus a short duration

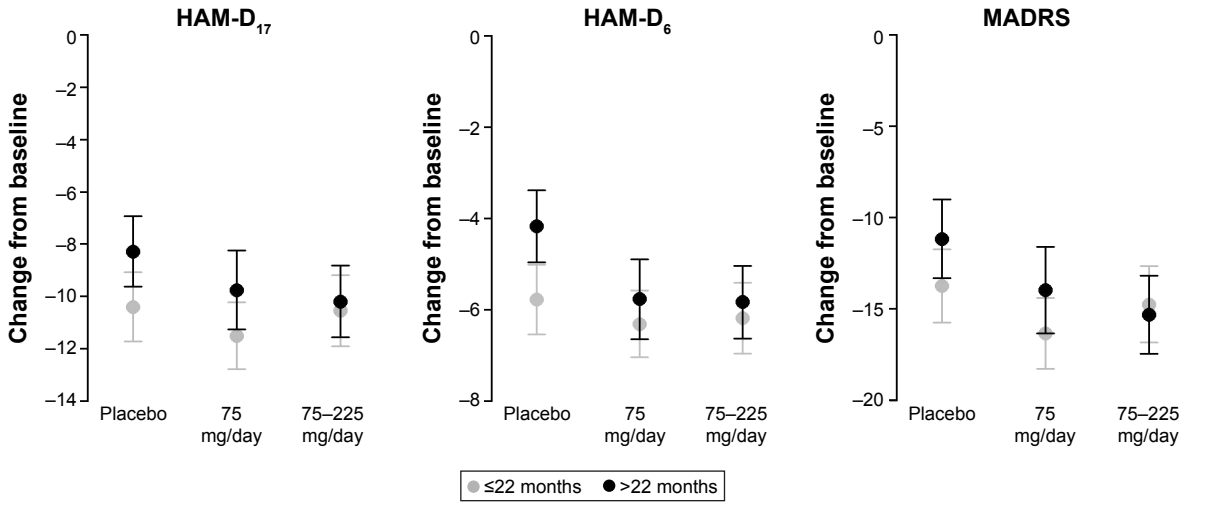

Figure 4 Adjusted mean change from baseline at Week 8 with 95% CIs by duration of MDD (≤22 months/>22 months) in each efficacy endpoint (FAS, LOCF, ANCOVA model).
Abbreviations: FAS, full analysis set; HAM-D_6, Hamilton Rating Scale for Depression–6 items; HAM-D_{17}, Hamilton Rating Scale for Depression–17 items; LOCF, last observation carried forward; MADRS, Montgomery–Asberg Depression Rating Scale; MDD, major depressive disorder.

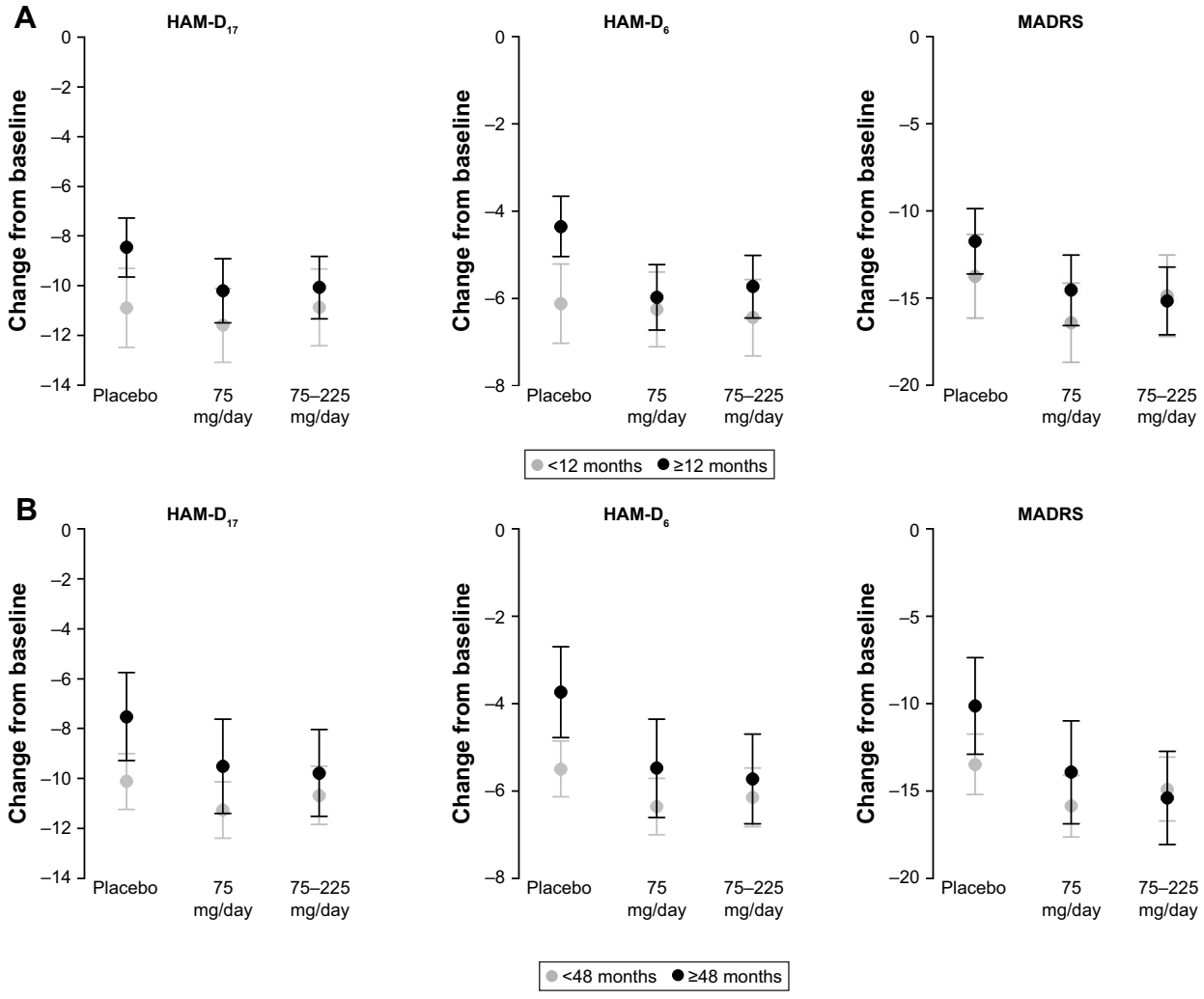

Figure 5 Adjusted mean change from baseline in each efficacy endpoint at Week 8 with 95% CIs by duration of MDD (**A**) <12 months/≥12 months, and (**B**) <48 months/≥48 months (FAS, LOCF, ANCOVA model).
Abbreviations: FAS, full analysis set; HAM-D_6, Hamilton Rating Scale for Depression–6 items; HAM-D_{17}, Hamilton Rating Scale for Depression–17 items; LOCF, last observation carried forward; MADRS, Montgomery–Asberg Depression Rating Scale; MDD, major depressive disorder.

Table 1 Demographic and disease characteristics by duration of MDD (≤22 months/>22 months) (FAS)

	Duration of MDD (months)			
	≤22 months (n=267)		>22 months (n=268)	
Sex	Male	Female	Male	Female
Placebo	43 (48.9)	45 (51.1)	48 (50.0)	48 (50.0)
Venlafaxine ER 75 mg/day	48 (50.0)	48 (50.0)	36 (46.2)	42 (53.8)
Venlafaxine ER 75–225 mg/day	41 (49.4)	42 (50.6)	51 (54.3)	43 (45.7)
Age, years				
Placebo	39.2 (12.0)		38.0 (10.2)	
Venlafaxine ER 75 mg/day	37.8 (12.6)		39.2 (10.8)	
Venlafaxine ER 75–225 mg/day	38.0 (10.3)		38.4 (10.3)	
Weight, kg				
Placebo	62.6 (17.2)		60.8 (14.8)	
Venlafaxine ER 75 mg/day	61.4 (14.1)		62.2 (14.7)	
Venlafaxine ER 75–225 mg/day	60.8 (12.9)		63.7 (15.5)	
BMI, kg/m^2				
Placebo	22.8 (4.5)		22.2 (4.0)	
Venlafaxine ER 75 mg/day	22.3 (4.1)		23.1 (4.6)	
Venlafaxine ER 75–225 mg/day	22.6 (4.0)		23.5 (4.7)	
Duration of MDD, months				
Placebo	9.8 (5.2)		75.7 (50.1)	
Venlafaxine ER 75 mg/day	9.3 (5.2)		78.5 (53.9)	
Venlafaxine ER 75–225 mg/day	7.9 (4.0)		89.7 (64.3)	
Duration of the current depressive episode, months				
Placebo	8.1 (4.8)		14.1 (18.7)	
Venlafaxine ER 75 mg/day	7.9 (4.8)		17.3 (24.2)	
Venlafaxine ER 75–225 mg/day	7.3 (4.0)		16.3 (22.3)	
Number of previous depressive episodes				
Placebo	0.2 (0.4)		1.3 (1.0)	
Venlafaxine ER 75 mg/day	0.1 (0.3)		1.6 (1.7)	
Venlafaxine ER 75–225 mg/day	0.1 (0.2)		1.4 (1.4)	
Baseline HAM-D$_{17}$ total score				
Placebo	22.0 (3.5)		22.8 (4.6)	
Venlafaxine ER 75 mg/day	22.8 (3.8)		22.5 (4.3)	
Venlafaxine ER 75–225 mg/day	22.4 (3.9)		22.3 (4.1)	
Baseline MADRS total score				
Placebo	32.8 (4.9)		33.5 (5.3)	
Venlafaxine ER 75 mg/day	32.6 (4.2)		32.7 (4.7)	
Venlafaxine ER 75–225 mg/day	32.5 (4.7)		33.0 (4.8)	

Notes: Sex is described as number of patients (%); all other parameters are described as mean (SD).

Abbreviations: BMI, body mass index; FAS, full analysis set; HAM-D$_{17}$, Hamilton Rating Scale for Depression–17 items; MADRS, Montgomery–Asberg Depression Rating Scale; MDD, major depressive disorder.

(≤6.6 months) showed smaller treatment benefits in both venlafaxine ER treatment groups compared with the placebo group. Treatment benefit of venlafaxine 75–225 mg/day was nearly absent in patients with a long duration of the current depressive episode (Figure 8). Since the inclusion criteria for the original study required a current depressive episode (≥90 days, single episode; ≥28 days, recurrent episode) before the screening visit, patients with more severe or treatment-resistant depression with a single episode may have been included in the subgroup. However, patients with a short duration of the current depressive episode consistently showed greater treatment benefits in the flexible-dose group than the fixed-dose group compared with the placebo group, which was also consistent with the findings observed in patients with a long duration of MDD (>22 months) (Figure 4).

Finally, in recent years, the response to placebo observed in studies of antidepressants for MDD has increased.[23] Placebo response also increases as the number of active medication arms,[24] investigational sites,[25] and study visits[26] increase, and as the number of academic sites[27] decreases. The number of study visits influences dropout rate rather than treatment response;[28] that is, an increasing number of study visits increases the dropout rate. Additionally, site ratings, not centralized ratings, increase placebo response.[29] The present study had two active medication arms, seven visits during the 8-week treatment phase, and was conducted with the site rating method at 62 investigational sites. These factors might have contributed considerably to the high placebo response in this study. In addition, it is important

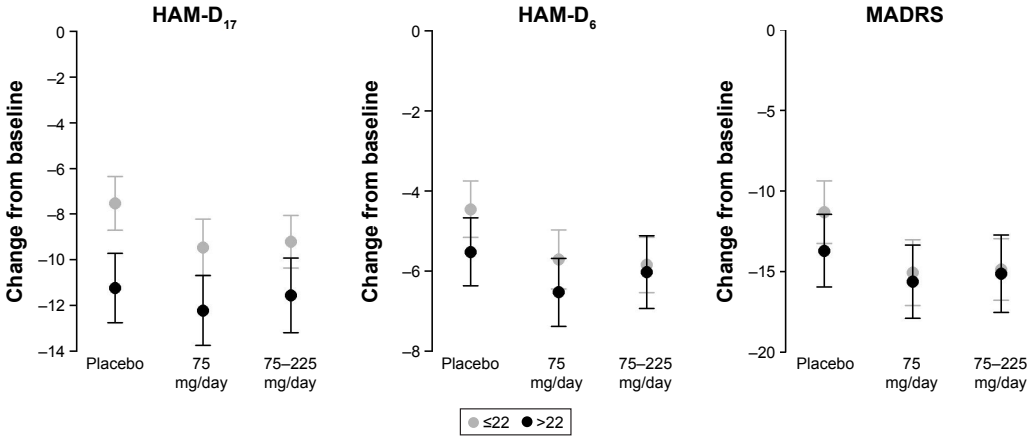

Figure 6 Adjusted mean change from baseline at Week 8 with 95% CIs by HAM-D_{17} total score at baseline (total score ≤22/total score >22) in each efficacy endpoint (FAS, LOCF, ANCOVA model).
Abbreviations: FAS, full analysis set; HAM-D_6, Hamilton Rating Scale for Depression–6 items; HAM-D_{17}, Hamilton Rating Scale for Depression–17 items; LOCF, last observation carried forward; MADRS, Montgomery–Asberg Depression Rating Scale.

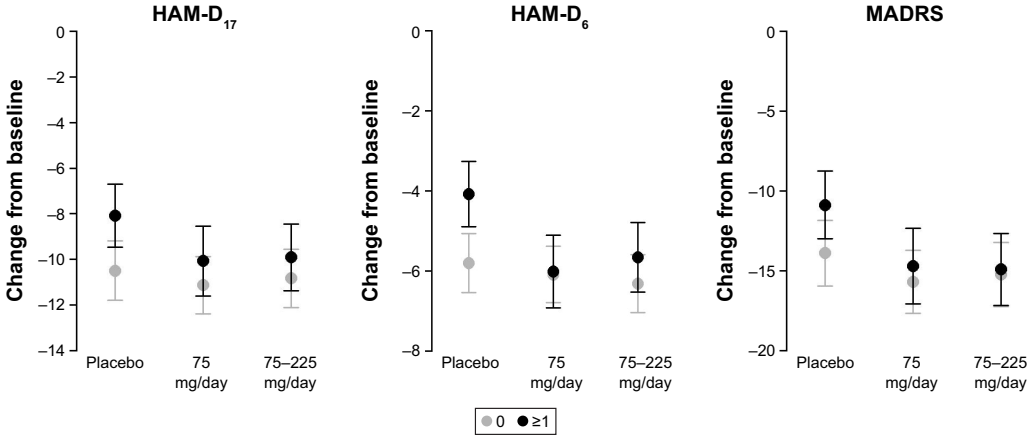

Figure 7 Adjusted mean change from baseline at Week 8 with 95% CIs by history of previous depressive episodes (0 [single episode]/≥1 [recurrent episodes]) in each efficacy endpoint (FAS, LOCF, ANCOVA model).
Abbreviations: FAS, full analysis set; HAM-D_6, Hamilton Rating Scale for Depression–6 items; HAM-D_{17}, Hamilton Rating Scale for Depression–17 items; LOCF, last observation carried forward; MADRS, Montgomery–Asberg Depression Rating Scale.

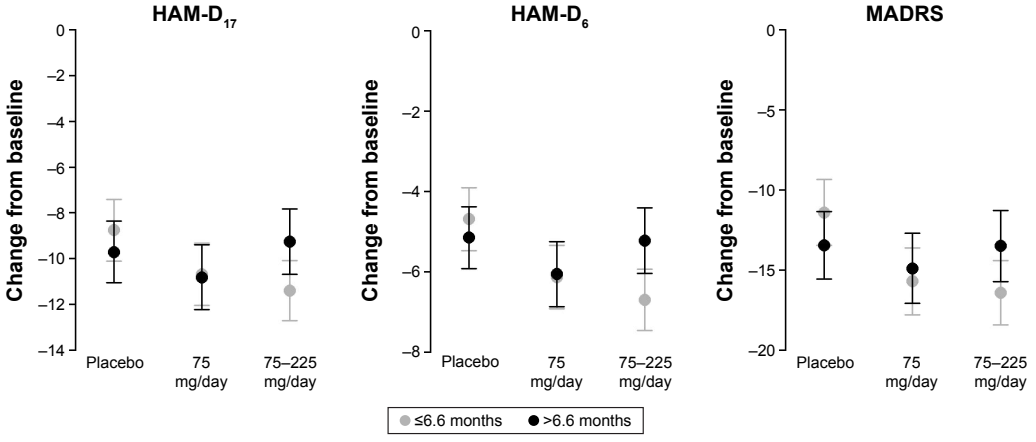

Figure 8 Adjusted mean change from baseline at Week 8 with 95% CIs by duration of current depressive episode (≤6.6 months/>6.6 months) in each efficacy endpoint (FAS, LOCF, ANCOVA model).
Abbreviations: FAS, full analysis set; HAM-D_6, Hamilton Rating Scale for Depression–6 items; HAM-D_{17}, Hamilton Rating Scale for Depression–17 items; LOCF, last observation carried forward; MADRS, Montgomery–Asberg Depression Rating Scale.

to remember that drug adherence is often low among MDD outpatients. In this study, drug adherence was determined through capsule-counting procedures and patient–physician interviews at follow-up visits.

In conclusion, despite a high placebo response, venlafaxine ER improved symptoms of MDD compared with placebo among most subgroups. It is hypothesized that patients with a longer duration of MDD may have a greater treatment response at a higher dose of venlafaxine ER (up to 225 mg/day). Further investigation in real-world settings in Japan is needed to evaluate patient groups that require higher doses of venlafaxine ER.

Data sharing statement

Anonymized patient-level data will be available through the Pfizer Inc. data access request site: http://www.pfizer.com/research/clinical_trials/trial_data_and_results/data_request.

Acknowledgments

This study was sponsored by Pfizer Inc. Editorial support was provided by Pearl Gomes of Cactus Communications and was funded by Pfizer Inc. We are grateful for the contributions of trial participants, principal investigators, and all other medical personnel to this study. Full control of the manuscript content was retained by all authors.

Disclosure

YA, YH, RI, and TI are employees of Pfizer Japan Inc. KK was an employee of Pfizer Japan Inc. at the time of the study. YW has received speaker's honoraria from Pfizer Japan Inc., GlaxoSmithKline K.K., Otsuka Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Meiji Seika Pharma Co., Ltd, Eli Lilly Japan K.K., MSD K.K. a subsidiary of Merck & Co., Inc., Takeda Pharmaceutical Co., Ltd., and Mochida Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corp., and Sumitomo Dainippon Pharma Co., Ltd., within the past 5 years. The authors report no other conflicts of interest in this work.

References

1. American Psychiatric Association. *Practice guideline for the treatment of patients with major depressive disorder 3*rd *edition*. American Psychiatric Association; 2010. Available from: http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed March 12, 2018.
2. Nutt DJ, Davidson JR, Gelenberg AJ, et al. International consensus statement on major depressive disorder. *J Clin Psychiatry*. 2010; 71 Suppl E1:e08.
3. Japanese Society of Mood Disorders. [*Guideline for treatment of major depressive disorder by the Japanese Society of Mood Disorders*.] Japanese Society of Mood Disorders; 2013. Available from: http://www.secretariat.ne.jp/jsmd/mood_disorder/img/130924.pdf. Accessed March 12, 2018. Japanese.
4. Papakostas GI. Serotonin norepinephrine reuptake inhibitors: spectrum of efficacy in major depressive disorder. *Prim Psychiatry*. 2009;16: 5 Suppl 4:16–24.
5. Higuchi T, Kamijima K, Nakagome K, et al. A randomized, double-blinded, placebo-controlled study to evaluate the efficacy and safety of venlafaxine extended release and a long-term extension study for patients with major depressive disorder in Japan. *Int Clin Psychopharmacol*. 2016;31(1):8–19.
6. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56–62.
7. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
8. Bech P, Gram LF, Dein E, et al. Quantitative rating of depressive states. *Acta Psychiatr Scand*. 1975;51(3):161–170.
9. Bech P, Allerup P, Gram LF, et al. The Hamilton depression scale. Evaluation of objectivity using logistic models. *Acta Psychiatr Scand*. 1981;63(3):290–299.
10. Cleary P, Guy W. Factor analysis of the Hamilton depression scale. *Drugs under Experimental and Clinical Research*. 1977;1:115–120.
11. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573–583.
12. Shelton RC, Prakash A, Mallinckrodt CH, et al. Patterns of depressive symptom response in duloxetine-treated outpatients with mild, moderate or more severe depression. *Int J Clin Pract*. 2007;61(8):1337–1348.
13. Nelson JC, Delucchi KL, Schneider LS. Moderators of outcome in late-life depression: a patient-level meta-analysis. *Am J Psychiatry*. 2013; 170(6):651–659.
14. Elkin I, Shea MT, Watkins JT, et al. National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. *Arch Gen Psychiatry*. 1989;46(11): 971–982.
15. Khan A, Leventhal RM, Khan SR, Brown WA. Severity of depression and response to antidepressants and placebo: an analysis of the Food and Drug Administration database. *J Clin Psychopharmacol*. 2002; 22(1):40–45.
16. Khan A, Brodhead AE, Kolts RL, Brown WA. Severity of depressive symptoms and response to antidepressants and placebo in antidepressant trials. *J Psychiatr Res*. 2005;39(2):145–150.
17. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA*. 2010;303(1):47–53.
18. Rutherford BR, Roose SP. A model of placebo response in antidepressant clinical trials. *Am J Psychiatry*. 2013;170(7):723–733.
19. Mancini M, Wade AG, Perugi G, Lenox-Smith A, Schacht A. Impact of patient selection and study characteristics on signal detection in placebo-controlled trials with antidepressants. *J Psychiatr Res*. 2014; 51:21–29.
20. Posternak MA, Zimmerman M, Keitner GI, Miller IW. A reevaluation of the exclusion criteria used in antidepressant efficacy trials. *Am J Psychiatry*. 2002;59(2):191–200.
21. Cohen D, Consoli A, Bodeau N, et al. Predictors of placebo response in randomized controlled trials of psychotropic drugs for children and adolescents with internalizing disorders. *J Child Adolesc Psychopharmacol*. 2010;20(1):39–47.
22. Bialik RJ, Ravindran AV, Bakish D, Lapierre YD. A comparison of placebo responders and nonresponders in subgroups of depressive disorder. *J Psychiatry Neurosci*. 1995;20(4):265–270.
23. Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*. 2002;287(14):1840–1847.

24. Sinyor M, Levitt AJ, Cheung AH, et al. Does inclusion of a placebo arm influence response to active antidepressant treatment in randomized controlled trials? Results from pooled and meta-analyses. *J Clin Psychiatry*. 2010;71(3):270–279.
25. Bridge JA, Birmaher B, Iyengar S, Barbe RP, Brent DA. Placebo response in randomized controlled trials of antidepressants for pediatric major depressive disorder. *Am J Psychiatry*. 2009;166(1):42–49.
26. Posternak MA, Zimmerman M. Therapeutic effect of follow-up assessments on antidepressant and placebo response rates in antidepressant efficacy trials: meta-analysis. *Br J Psychiatry*. 2007;190:287–292.
27. Dunlop BW, Thase ME, Wun CC, et al. A meta-analysis of factors impacting detection of antidepressant efficacy in clinical trials: the importance of academic sites. *Neuropsychopharmacology*. 2012;37(13):2830–2836.
28. Rutherford BR, Cooper TM, Persaud A, et al. Less is more in antidepressant clinical trials: a meta-analysis of the effect of visit frequency on treatment response and dropout. *J Clin Psychiatry*. 2013;74(7):703–715.
29. Kobak KA, Leuchter A, DeBrota D, et al. Site versus centralized raters in a clinical depression trial: impact on patient selection and placebo response. *J Clin Psychopharmacol*. 2010;30(2):193–197.

Supplementary material

Box S1 List of approving institutional review boards and ethics committees

1	Shinagawa East One Medical Clinic institutional review board (IRB)
2	Yokohama Minoru Clinic IRB
3	Omuta Memorial Hospital IRB
4	Nippon Medical School, Chiba Hokusoh Hospital IRB
5	Hayakawa Clinic IRB
6	Suzuki Hospital IRB
7	Imazato Gastroenteric Hospital IRB
8	Riverside Clinic IRB
9	Tokyo-Eki Center Building Clinic IRB
10	Yuge Hospital IRB
11	Shinagawa Clinic IRB
12	National Hospital Organization central review board
13	Haradoi Hospital IRB
14	Sakayori Clinic IRB
15	Miki Mental Clinic IRB
16	Tokyo Women's Medical University Hospital IRB
17	Himorogi Psychiatric Institute IRB
18	Tokyo Kosei Nenkin Hospital IRB
19	Aino Clinic IRB
20	Eda Memorial Hospital IRB
21	Warakukai Akasaka Clinic IRB
22	Himeno Tomomi Clinic IRB
23	Mizuo Clinic IRB
24	Suzuki Internal & Circulatory Medical Clinic IRB
25	Yutaka Clinic IRB
26	Kayaba Dermatology Clinic IRB