

Long-Term, Open-Label, Safety Study of Edivoxetine as Adjunctive Treatment for Adult Patients with Major Depressive Disorder Who Were Partial Responders to Selective Serotonin Reuptake Inhibitor Treatment in Japan

Emel Serap Monkul¹, Mark Bangs¹, Keita Asato², Masashi Takahashi², Yasushi Takita², Mary Anne Dellva¹, Jonna Ahl¹, Celine Goldberger¹

¹Eli Lilly and Company, Indianapolis, IN, USA

²Eli Lilly Japan K.K. Office, Kobe, Japan

Email: nery_emel_serap_monkul@lilly.com

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Abstract

Edivoxetine is a highly selective norepinephrine reuptake inhibitor (NRI) that has been investigated in short-term studies as adjunctive therapy to selective serotonin reuptake inhibitor antidepressants (SSRIs) in patients with major depressive disorder (MDD) who were partial responders to their SSRIs. This 52-week open-label study investigated the safety and tolerability of long-term treatment with adjunctive edivoxetine in patients with MDD in Japan, who had completed one of two placebo-controlled acute studies of edivoxetine as adjunctive therapy to SSRIs. All patients continued on their stable dose of SSRI. Two hundred eighty-eight patients were enrolled and assessed for up to 1 year using standard safety and tolerability measures. Of these, 195 patients previously received only placebo in the parent study and, therefore, were first exposed to edivoxetine in this study. Approximately 46% of patients completed the study. The most frequently cited (>5%) reasons for discontinuation were sponsor decision (19.4%, which included patients discontinued due to early study termination), adverse event (17.4%) and subject decision (8.7%). Adverse events leading to discontinuation in more than 2 patients (>1%) were palpitations, vomiting, hepatic function abnormal, hypertension, nausea, and tachycardia. Treatment-emergent elevations in diastolic blood pressure and pulse were at least twice that reported in the literature for non-Asian patients. Twenty percent of patients had sustained elevations in pulse. Treatment-

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emergent changes in laboratory measures were small and not clinically meaningful. Assessment across all safety measures in this study indicated that the safety profile of edivoxetine was consistent with that expected for a selective NRI.

Keywords

Edivoxetine, Depression, SSRI, NRI, Japan, Adjunctive Therapy

1. Introduction

Major depressive disorder (MDD) is a chronic illness that is estimated to have 2.9% lifetime prevalence in Japan [1]. Although the prevalence rates for MDD are lower in Japan than those reported in western countries, suicide rates in Japan are among the highest in the world with 24.4 per 100,000 inhabitants [2]. In a psychological autopsy case-control study of suicide in Japan, MDD was the disorder that was the most strongly associated with suicide, as well as anxiety disorder, alcohol-related disorders, and brief psychotic disorder [1]. As in other countries, the societal cost of depression in Japan is enormous, and was estimated to be ¥2.0 trillion in 2005 [3].

Complete remission of symptoms is the treatment goal in MDD, but is unattainable for many patients, which puts them at risk for relapse [4] and suicide [5]. First-line therapy for MDD is the most frequent monotherapy with a selective serotonin reuptake inhibitor (SSRI), though individual differences in response to treatment can contribute to incomplete symptom resolution. One second-step treatment option would be to switch to or add on another antidepressant with a different mode of action [6], and the addition of an agent with selective norepinephrine reuptake inhibition (NRI) to an SSRI antidepressant may provide additional benefit [7].

Edivoxetine is a highly selective NRI that has been investigated as adjunctive therapy to SSRI antidepressants in several acute placebo-controlled trials [8]–[10] and one open-label long-term safety trial [11] in patients with MDD who were partial responders to SSRI treatment. However, these studies were conducted in predominantly white populations. Since racial/genetic variations can contribute to differences in metabolism of psychiatric medications, which can ultimately impact efficacy and safety outcomes [12], it is important to conduct analyses in specific racial/genetic populations [13]. Herein we report on the tolerability and safety of edivoxetine as adjunctive treatment to SSRI antidepressants in a year-long, open-label trial conducted in Japan in patients with MDD who were partial responders to SSRI treatment.

2. Methods

This was a phase III, multicenter, open-label investigation of the long-term tolerability and safety of edivoxetine as adjunctive treatment in patients with MDD in Japan. The study was conducted at 27 sites in accordance with ethical principles that had their origin in the Declaration of Helsinki, and were consistent with Good Clinical Practices and applicable laws and regulations. The institutional review boards for each site approved the protocol and all patients provided written informed consent.

Enrollment began 2 August 2011 and the final visit occurred on 16 January 2014 (ClinicalTrials.gov identifier: NCT01370499). The study planned to enroll approximately 320 patients, but was closed early because the parent studies, H9P-MC-LNBQ (NCT01187407) and H9P-MC-LNBM (NCT01173601), did not meet the primary efficacy endpoint of a statistically significant difference between adjunctive edivoxetine and adjunctive placebo on the mean change from baseline to Week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) [14] total score. At the time of study closure, 288 patients had been enrolled and assessed for up to one year from baseline.

Patients were eligible to enter the parent studies if they had been taking an SSRI that had been approved for MDD at a dose within the labeling guidelines for Japan. Duration of SSRI treatment had to be ≥ 6 weeks before visit 2, with at least the last 4 weeks at a stable, optimized dose as determined by the investigator. Eligible patients were required to meet criteria for partial response at visits 1 and 2, as defined by the investigator's opinion that the patient had experienced at least a minimally clinically meaningful improvement with the SSRI treatment. Additionally, patients had to score ≥ 16 on the GRID 17-Item Hamilton Depression Rating Scale total score [15] and to rate $\leq 75\%$ improvement for their current SSRI by using the patient-rated Massachusetts General Hospital

Antidepressant Treatment Response Questionnaire-Modified Version [16] at visit 1.

Both parent studies included three periods: screening, an 11-week double-blind treatment period [3-week placebo lead-in and 8 weeks of acute therapy for randomized patients], and a discontinuation period of 1 - 2 weeks. Throughout all study periods, patients were required to take their SSRI at a stable dose. During the double-blind placebo lead-in, those patients who had <25% improvement on the MADRS total score and a MADRS total score ≥ 14 at the end of the 3 weeks were randomly assigned to receive adjunctive edivoxetine or adjunctive placebo for 8 weeks. Patients who did not meet randomization criteria were kept on adjunctive placebo plus their SSRI, and were continued in the study to maintain the blind.

The studies differed with respect to dosing and discontinuation of adjunctive edivoxetine. In the LNBQ study, patients meeting randomization criteria were randomly assigned to once daily (QD) doses of adjunctive edivoxetine 6 mg fixed-dose, adjunctive edivoxetine 12 - 18 mg flexible dose, or adjunctive placebo. At the end of the double-blind treatment period, patients were abruptly discontinued from adjunctive edivoxetine and received adjunctive placebo for one week. In the LNBQ study, patients meeting randomization criteria were randomly assigned to receive fixed doses of adjunctive edivoxetine 12 mg QD or 18 mg QD or placebo. At the end of double-blind treatment, study medication was discontinued over a 2-week period. Patients in both adjunctive edivoxetine groups were randomized to an abrupt or tapered discontinuation. The taper schedule was 12 mg for 4 days, 6 mg for 4 days, and placebo for 6 days. Patients randomly assigned to abrupt discontinuation received placebo for the entire 2 weeks. Patients who received placebo during the acute adjunctive treatment phase continued to receive placebo during the discontinuation period.

To be eligible for the current study, patients in Japan were to have completed one of the two acute phase III parent studies (including the discontinuation period and were no longer taking adjunctive medication), and were still taking the same SSRI at the optimized and stable dose as in the parent study. Since these patients had already met the inclusion and exclusion criteria at entry to the parent studies, they were not re-assessed prior to enrollment in this study. Both non-randomized and randomized patients from the parent studies were eligible.

At enrollment, all patients began treatment with oral adjunctive edivoxetine 12 mg QD. After 1 week, the dose could be adjusted up to 18 mg/day and then back down to 12 mg/day if needed, based on tolerability and efficacy. At week 12, the dose could not be adjusted for the remainder of the study. At week 52 or at early discontinuation, adjunctive edivoxetine was discontinued abruptly and patients were followed up one week later. All patients were maintained on their stable dose of SSRI throughout the study including follow up after abrupt discontinuation of adjunctive edivoxetine.

The primary safety and tolerability assessments included: discontinuation rates, treatment-emergent adverse events (TEAEs), vital signs, weight, electrocardiograms (ECGs), and laboratory analysis. Secondary safety and tolerability measures included serious adverse events, adverse events that were reported as a reason for discontinuation, dose reduction, or were associated with discontinuation of adjunctive edivoxetine; suicidal ideation/behavior assessed with the Columbia-Suicide Severity Rating Scale (CSSR-S) [17], changes in sexual function assessed with the Arizona Sexual Experiences (ASEX) scale [18]; and cognitive and physical function assessed using the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (MGH-CPFQ) [19].

The C-SSRS [17] captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred.

The ASEX [18] is a patient-rated assessment of sexual interest, arousal, response, ability to achieve orgasm, and satisfaction with orgasm that uses a 6-point scale, ranging from “extremely” (score = 1) to “never” or “no” (score = 6). Patients were categorized as having sexual dysfunction if they had an ASEX total score of ≥ 19 , a score of ≥ 5 on any item; or a score of ≥ 4 on any 3 items.

The MGH-CPFQ [19] is a patient-rated questionnaire consisting of 7 questions pertaining to a patient’s cognitive and physical well-being in which each question is rated on a 6-point scale, with scores ranging from “greater than normal” (score = 1) to “normal” (score = 2), to “totally absent” (score = 6). The MGH-CPFQ total score ranges from 7 to 42, and higher scores were associated with less cognitive and physical well-being. The scale assesses symptoms that may be either residual to the depressive illness or associated with TEAEs of antidepressant therapies for the previous month.

Triplicate measures of blood pressure and single measures of pulse were taken at each study visit in the sitting position. The three blood pressure measures were averaged for use in the analyses. Elevated blood pressure was

defined as: systolic blood pressure (SBP) ≥ 140 mm Hg and an increase of ≥ 20 mm Hg from baseline; or diastolic blood pressure (DBP) ≥ 90 mm Hg and an increase of ≥ 10 mm Hg from baseline. Elevated pulse was defined as > 100 beats per minute (bpm) and an increase of ≥ 15 bpm from baseline. Sustained elevations in blood pressure and pulse were defined by the above criteria that occurred at three consecutive visits. Potentially clinically significant changes in blood pressure were defined as: SBP ≥ 180 mm Hg and an increase ≥ 20 mm Hg from baseline; or DBP ≥ 105 mm Hg and an increase ≥ 15 mm Hg from baseline.

The safety analyses were conducted on all enrolled patients who took at least one dose of adjunctive edivoxetine. For those patients who received placebo in the parent studies, this study was the first time that they received adjunctive edivoxetine, so the safety results were summarized for all patients and by the adjunctive treatment assignments in the parent studies. Patients who received adjunctive placebo in the parent studies comprised the placebo/edivoxetine (PBO/EDX) group, and those patients who received adjunctive edivoxetine in the parent studies comprised the edivoxetine/edivoxetine (EDX/EDX) group. Safety outcomes were evaluated based on adjunctive treatment assignment in the parent study. There were baseline differences between patients with prior exposure to edivoxetine (EDX/EDX) and those who had no prior exposure (PBO/EDX); however, no statistical comparisons were made between these two groups. Categorical variables were summarized with counts and percentages. Analyses of covariance (ANCOVA) models were used to analyze continuous variables, and the model contained the main effect of pooled investigative site and the baseline value as a covariate. Type III sum-of-squares were used to calculate the least-squares (LS) means from the ANCOVA model. For continuous analyses, a separate model was fit for each group defined by the adjunctive treatment phase assignments from the parent studies.

3. Results

Patient characteristics, illness severity, and SSRI treatment are summarized in [Table 1](#). Twice as many patients comprised the PBO/EDX group because it included patients from the parent study lead-in period who remained on placebo, in addition to those patients who were randomized to adjunctive placebo. Approximately 46% of the patients completed the study. The most frequently cited ($> 5\%$) reasons for discontinuation were sponsor decision (19.4%, which included patients discontinued due to early study termination), adverse event (17.4%) and subject decision (8.7%).

Over the course of the study, 88.9% of all patients reported at least one TEAE and there were no deaths. The most common ($> 5\%$ frequency) TEAEs are summarized in [Table 2](#). Most of the TEAEs were mild or moderate in severity.

SAEs were reported by 2 patients in the EDX/EDX group (contusion and hyperglycemia) and 1 patient in the PBO/EDX group reported an SAE of subdural hygroma. None of these events were considered by the investigator to be associated with the investigational product or study procedure.

Table 1. Patient demographics, baseline illness severity, and selective serotonin reuptake inhibitor treatment.

Variable	PBO/EDX N = 195	EDX/EDX N = 93	All Patients N = 288
Age (years), mean (SD), range	39.3, (9.4), 21.2 - 77.8	37.4, (9.2), 20.6 - 64.9	38.7, (9.4), 20.6 - 77.8
Males, n (%)	107 (54.9)	48 (51.6)	155 (53.8)
Females, n (%)	88 (45.1)	45 (48.4)	133 (46.2)
Japanese, n (%)	195 (100)	93 (100)	288 (100)
Weight (kg), mean (SD)	66.3, (15.5)	64.5, (14.4)	65.7, (15.1)
SSRI, n (%)			
Sertraline	80 (41.0)	36 (38.7)	116 (40.3)
Paroxetine	57 (29.2)	21 (22.6)	78 (27.1)
Fluvoxamine	35 (18.0)	20 (21.5)	55 (19.1)
Escitalopram	23 (11.8)	16 (17.2)	39 (13.5)

Abbreviations: PBO = placebo; EDX = edivoxetine; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor.

Table 2. Treatment-emergent adverse events that were reported by at least 5% of all patients.

Variable, n (%)	Placebo/Edivoxetine N = 195	Edivoxetine/Edivoxetine N = 93	All Patients N = 288
Patients with at least one TEAE	176 (90.3)	79 (85.9)	255 (88.9)
Nasopharyngitis	56 (28.7)	29 (31.5)	85 (29.6)
Tachycardia	62 (31.8)	17 (18.5)	79 (27.5)
Hyperhidrosis	33 (16.9)	16 (17.4)	49 (17.1)
Palpitations	36 (18.5)	12 (13.0)	48 (16.7)
Nausea	26 (13.3)	8 (8.7)	34 (11.9)
Heart rate increased	25 (12.8)	7 (7.6)	32 (11.2)
Constipation	19 (9.7)	7 (7.6)	26 (9.1)
Dizziness	21 (10.8)	4 (4.4)	25 (8.7)
Headache	17 (8.7)	7 (7.6)	24 (8.4)
Vomiting	14 (7.2)	3 (3.3)	17 (5.9)

Abbreviation: TEAE = treatment-emergent adverse event.

Adverse events leading to study discontinuation in $\geq 2\%$ patients in the PBO/EDX group were palpitations ($n = 6$, 3.1%), vomiting ($n = 5$, 2.6%), and hypertension ($n = 4$, 2.1%); in the EDX/EDX group only palpitations was reported by at least 2% of the patients.

Longitudinal changes in blood pressure and pulse are shown in **Figure 1**. Across the study, changes in blood pressure and pulse were numerically greater in the PBO/EDX group. At the end of 52 weeks of adjunctive treatment, LS mean (SE) changes from baseline in blood pressure and pulse measures in the PBO/EDX and EDX/EDX groups, respectively, were: 6.7 (0.9) mm Hg and 3.7 (1.3) mm Hg for SBP; 7.6 (5.9) mm Hg and 6.3 (1.0) mm Hg for DBP; and 17.0 (1.2) bpm and 11.0 (1.5) bpm for pulse. A week after abrupt discontinuation of adjunctive edivoxetine LS mean (SE) changes in blood pressure and pulse measures in the PBO/EDX and EDX/EDX groups (respectively) were 0.9 (0.7) mm Hg and 0.3 (1.0) mm Hg for SBP; -2.2 (0.6) mm Hg and -2.7 (0.9) mm Hg for DBP; and -8.1 (0.7) bpm and -8.3 (1.0) bpm for pulse.

Categorical treatment-emergent changes in blood pressure and pulse are summarized in **Table 3**. These changes were more frequently noticed in DBP and pulse. The percentage of patients who met criteria for an elevation in these measures at any time was higher (27% and 50%, respectively), than that observed for sustained elevations (11% and 20%). Potentially clinically significant elevations were only noted for DBP in 3% of the patients.

The percentage of patients with treatment-emergent changes in weight ($\geq 7\%$ loss at any time) was 15% (17% and 10% in the PBO/EDX and EDX/EDX groups, respectively). The overall frequency of treatment-emergent weight gain $\geq 7\%$ was 6% (5% and 9%, respectively).

Treatment-emergent changes in ECG parameters included rates of PR < 120 ms in 2.1% of patients overall (1.6% of PBO/EDX and 3.3% of EDX/EDX patients); the overall rate was 1.1% for QTC Fridericia changes that were > 450 ms in males and > 470 ms in females (1.0% of PBO/EDX and 1.1% of EDX/EDX patients), and none of the patients had QTc > 500 ms. Changes in heart rate > 100 bpm and an increase ≥ 15 bpm from baseline were observed in 29.0% of patients overall (32.5% of PBO/EDX and 21.7% of EDX/EDX patients). No clinically significant changes from baseline were observed in any of the other ECG parameters in either adjunctive treatment group.

Mean changes from baseline to each visit during the open-label adjunctive treatment phase were statistically significant for various chemistry, hematology, and urinalysis analytes. However, the mean changes were small and not considered clinically meaningful. During the study, 15% of the patients overall reported an adverse event as a reason for a dose reduction, and the most common events (≥ 5 patients) were tachycardia ($n = 11$, 3.8%) and palpitations ($n = 5$, 1.7%), both of which occurred more frequently in the PBO/EDX group ($n = 9$, 4.6%; and $n = 4$, 2.1%).

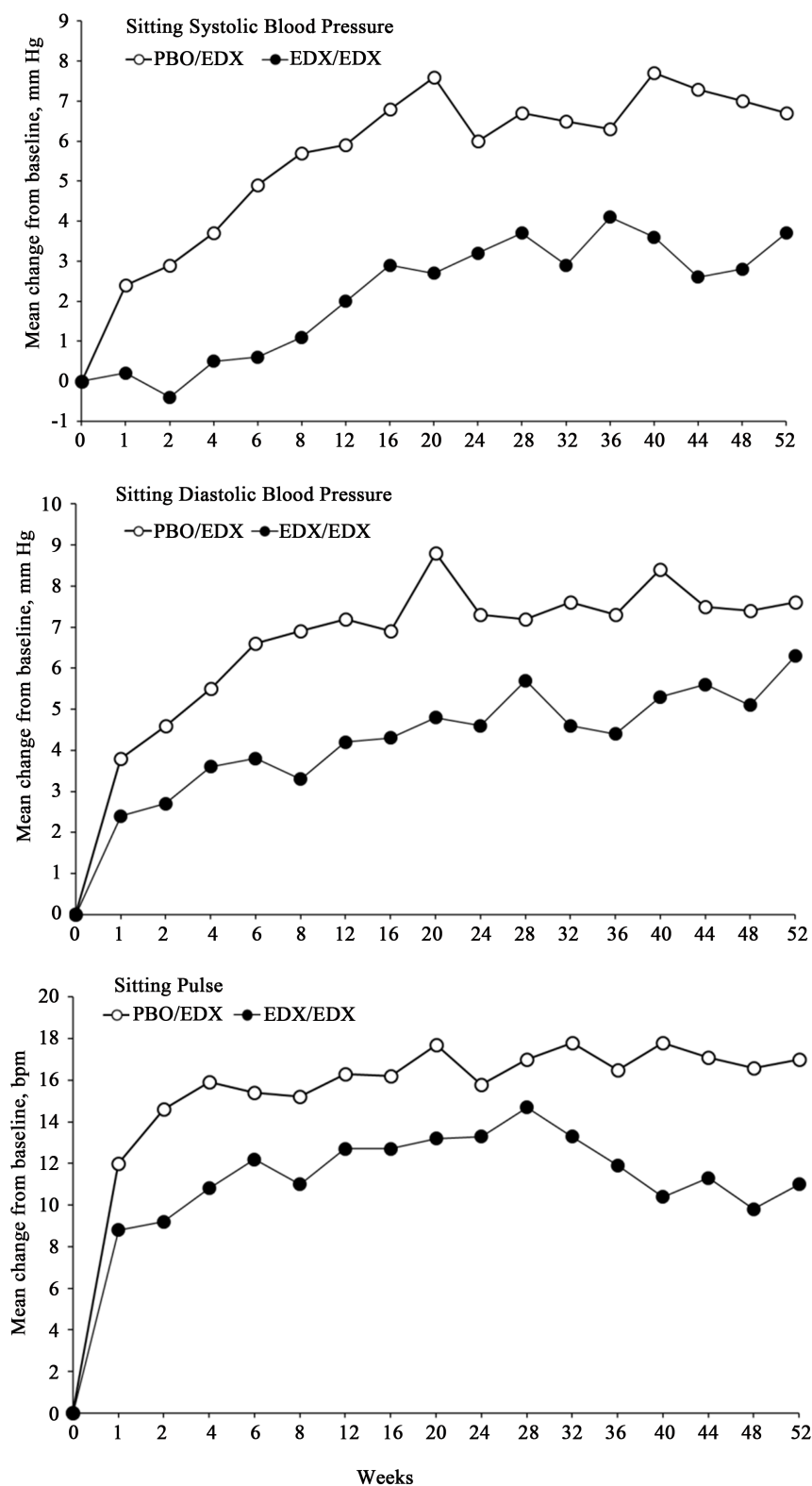


Figure 1. Least-squares mean changes from baseline in systolic blood pressure (top), diastolic blood pressure (middle) and pulse (bottom) taken while sitting at each study visit. Abbreviations: PBO = placebo; EDX = edivoxetine; mm Hg = millimeters of mercury; bpm = beats per minutes.

Table 3. Treatment-emergent elevations in sitting blood pressure and pulse.

Measure (Unit)/Criteria	Placebo/Edivoxetine		Edivoxetine/Edivoxetine		All Patients	
	N	n (%)	N	n (%)	N	n (%)
Elevated Any Time						
SDP of ≥ 140 mm Hg and an increase of ≥ 20 mm Hg from baseline	195	20 (10.3)	92	4 (4.4)	287	24 (8.4)
DBP of ≥ 90 mm Hg and an increase of ≥ 10 mm Hg from baseline	195	54 (27.7)	92	24 (26.1)	287	78 (27.2)
Pulse > 100 beats per minute (bpm) and an increase of ≥ 15 bpm from baseline.	195	109 (55.9)	92	35 (38.0)	287	144 (50.2)
Sustained Elevation at 3 Consecutive Visits						
SDP of ≥ 140 mm Hg and an increase of ≥ 20 mm Hg from baseline	185	2 (1.1)	86	0	271	1 (0.7)
DBP of ≥ 90 mm Hg and an increase of ≥ 10 mm Hg from baseline	185	22 (11.9)	86	8 (9.3)	271	30 (11.1)
Pulse > 100 beats per minute (bpm) and an increase of ≥ 15 bpm from baseline	185	46 (24.9)	86	8 (9.3)	271	54 (20.0)
Potentially Clinically Significant, Any Time						
SDP of ≥ 180 mm Hg and an increase of ≥ 20 mm Hg from baseline	195	0	92	0	287	0
DBP of ≥ 105 mm Hg and an increase of ≥ 15 mm Hg from baseline	195	6 (3.1)	92	2 (2.2)	287	2 (2.8)

Abbreviations: SDP = systolic blood pressures; DBP = diastolic blood pressure; mm Hg = millimeters of mercury; bpm = beats per minute.

Treatment-emergent suicidal ideation or behavior as assessed by the C-SSRS was reported by 9.8% of patients overall and there was one interrupted suicide attempt in the PBO/EDX group.

The majority of patients met criteria for sexual dysfunction at baseline based on the ASEX scores: 79.6% (121/152) of male patients and 90.2% of female patients (119/132). For patients who met criteria for sexual dysfunction at baseline, most continued to meet criteria at endpoint (88.4% of males and 90.8% of females). For patients who did not meet sexual dysfunction at baseline, 35.5% of male patients and 61.5% of female patients worsened and met dysfunction criteria at endpoint.

At baseline, the mean (SD) MGH-CPFQ total score was 23.8 (6.6) in the PBO/EDX group and was 25.2 (6.0) in the EDX/EDX group. At the end of the study, cognitive and physical well-being was improved with LS mean changes (SE) from baseline that were statistically significant ($p \leq 0.001$) from zero in both groups: -4.02 (0.5) and -2.53 (0.8), respectively.

4. Discussion

This is the first long-term safety study of edivoxetine as adjunctive therapy to SSRI antidepressants inpatients with MDD in Japan, who were partial responders to their SSRI treatment. Long-term treatment with adjunctive edivoxetine in Japanese patients with MDD did not reveal safety and tolerability concerns that differed substantially from the outcomes of short-term (1 phase II and 3 phase III) adjunctive edivoxetine trials [8] [10] and a 1-year open-label safety and tolerability study [11]. In addition, there were no deaths during this study.

Discontinuation due to adverse events in this study (17.4%) was higher than in the short-term adjunctive edivoxetine studies (4.9% - 5.4%) [8] [10], but was similar to the rate reported in the other long-term study of adjunctive edivoxetine (17.0%) [11]. The most common adverse events ($\geq 2\%$ frequency) leading to early discontinuation were palpitations, vomiting and hypertension in this study; the other long-term study reported hypertension (2.0%) [11]. The most common ($\geq 5\%$) TEAEs reported in this study were similar to those reported in the previous studies: nasopharyngitis, tachycardia, hyperhidrosis, nausea, palpitations, and increased heart rate [8] [10]. Adverse events (≥ 5 patients) that led to a dose reduction were palpitations and tachycardia in this study; and erectile dysfunction, nausea, and hyperhidrosis in the other long-term study [11].

Mean increases in blood pressure and pulse were observed across visits during this study. These increases were observed in the previous adjunctive edivoxetine studies [8] [10], and were expected given the mechanism of action of edivoxetine as a norepinephrine reuptake inhibitor. However, the mean increases in pulse rate and DBP was higher in this study as compared with the previous short- and long-term studies of adjunctive edivox-

etine [8] [10] [11]. In a pooled analysis of the three phase III trials [10], there was a significant treatment-by-geographic region interaction (across Japan, the UK and the US) with adjunctive edivoxetine that was observed with changes in DBP and pulse. The interaction suggested that the hemodynamic response to NRIs as adjunctive treatment to SSRIs in Japanese patients may be different from that in non-Japanese. However, in the 1-year open-label safety study, ethnic differences in vital sign changes were not observed probably because the study population was mostly comprised of Caucasian patients [11].

It is unclear why treatment with edivoxetine as adjunctive treatment to SSRI antidepressants would be associated with higher increases in DBP and pulse in Japanese patients than that observed in Caucasian patients. In a short-term safety study of edivoxetine given as single or multiple doses that was conducted in healthy adult male Japanese and Caucasian patients (unpublished), greater increases in pulse and blood pressure were observed in the Japanese patients relative to the Caucasian patients. However, the trends of the changes were similar between the groups, and there were no significant differences between the Japanese and Caucasian patients in pharmacokinetics (PK) or pharmacodynamic (PD) evaluations (unpublished). However, PK and PD evaluations were not done in this study, so it was not known if the outcome of these measures would be different when edivoxetine was given with SSRI antidepressants.

There are few long-term studies of treatment with NRI drugs in Japan. However, there is one long-term (58 weeks) safety study of treatment with the NRI atomoxetine that is conducted in adult Japanese patients with attention deficit hyperactivity disorder (ADHD) [20]. Similarly, this study reported treatment-emergent increases in pulse (9 bpm), and systolic and diastolic blood pressure (4 mm Hg and 5 mm Hg, respectively). Because these vital sign changes were similar to those reported in long-term studies in North American adults with ADHD [21]–[23], they were considered to be consistent with the known NRI mode of action.

The open-label study design and lack of control group limit the interpretation of observed changes that may have been associated with non-treatment effects. In addition, there were no statistical comparisons performed between groups and only categorical variables were summarized with counts and percentages. However, the open-label design mirrored clinical practice and provided a description of key clinically relevant safety outcomes in Japanese patients.

In conclusion, the assessment across all safety measures in the long-term treatment with edivoxetine as adjunctive therapy to SSRI antidepressants in Japanese patients with MDD indicated that the safety profile of edivoxetine was consistent with that expected for a selective NRI.

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