

## ORIGINAL PAPER

**Results of a Real-World Study of Vortioxetine in Patients with Major Depressive Disorder in South East Asia (REVIDA): Subgroup Analysis of Malaysian Patients**

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**Abstract**

**Objective:** This subgroup analysis of the real-world REVIDA study aimed to evaluate depressive symptom progression, cognitive function, and work productivity in Malaysian patients with major depressive disorder (MDD) treated with vortioxetine over 3 months. **Methods:** The REVIDA study was conducted from August 2016 to April 2017. Overall, 76 patients (aged 18–65 years, inclusive) with an active MDD episode were recruited in Malaysia. Vortioxetine was initiated on the first visit and patients were followed for 3 months. Depression severity was assessed by patients (PHQ-9 questionnaire) and physicians (CGI-S scale); cognitive function was assessed with the PDQ-D questionnaire; work productivity and activity impairment were assessed using the WPAI questionnaire. **Results:** In eligible Malaysian patients, mean (SD) baseline PHQ-9 and CGI-S scores decreased from 20.6 (4.7) [severe depression] and 4.6 (0.6) [moderately to markedly ill] to 4.3 (4.5) [none–mild depression] and 2.1 (0.9) (borderline ill) at Month 3, respectively. During the 3-month treatment period, mean (SD) PDQ-D scores decreased from 48.4 (17.6) to 11.2 (11.5). During the same period, work productivity loss decreased from 83.2% to 30.3%, activity impairment decreased from 80.5% to 21.8%, and absenteeism decreased from 70.3% to 17.1%. By Month 3, PHQ-9 response and remission rates were 89.1% and 60.0%, respectively; 87.7% of patients were either not depressed or only mildly depressed (PHQ-9 score  $\leq 9$ ). **Conclusion:** In this subgroup analysis of Malaysian patients with

**MDD, vortioxetine was effective and well-tolerated at reducing depressive symptoms, while significantly improving cognitive function and work productivity with high response and remission rates.**

**Keywords: Antidepressant, Major Depressive Disorder, Vortioxetine, Malaysia, Subgroup Analysis**

## Introduction

Major depressive disorder (MDD) is associated with deficits in cognitive function, alongside the more frequently mentioned symptoms of depressed mood, altered sleep, feelings of worthlessness, and suicidal thoughts [1]. Impairment in cognitive function is included as a criterion in the Diagnostic and Statistical Manual 5 as a diminished ability to think or concentrate, or indecisiveness, in the diagnosis of a major depressive episode [1]. While many treatments for depressive symptoms are available, many patients do not respond to treatment [2], and many of those who do may not achieve remission [3]. In patients who respond to treatment, and even in those who have a period of remission, residual symptoms such as cognitive impairment can still be present [4, 5]. Cognitive symptoms are present up to 94% of the time during depressive episodes and up to 44% of the time during periods of remission [6].

MDD is associated with significant impairments in work functioning including increased absenteeism and reduced work productivity compared with the general population [7, 8]. Despite an improvement in mood symptoms, persistent impairment in work performance can remain in patients who work or are studying, impeding full functional remission. Targeting cognitive function is therefore likely to improve workplace performance and enhance functional recovery [9], since perceived cognition dysfunction has been significantly

associated with functional disability independent of mood improvement [10].

Vortioxetine is an antidepressant with a distinct multimodal mechanism of action [11]. The efficacy of vortioxetine on depressive symptoms and cognitive functioning has been demonstrated in adults with MDD [12-14], and in elderly patients ( $\geq 65$  years) [15]. These studies demonstrated a clinical benefit of vortioxetine on cognitive function in patients with MDD, on neuropsychological tests of executive functioning, speed of processing, verbal learning, and memory. A post-hoc analysis investigating the effect of vortioxetine on cognitive functioning concluded that the beneficial effects of vortioxetine on objective and subjective measures of cognitive functioning were greater in working patients with MDD [16].

Here, we report the findings from a subgroup analysis of Malaysian patients from the primary REVIDA study (Real-world study on Vortioxetine In patients with major Depression in South East Asia) [17]. This subgroup analysis aimed to assess vortioxetine's effectiveness in routine clinical practice in Malaysia. In particular, we aimed to evaluate depressive symptom progression, cognitive function, and work productivity in Malaysian patients treated with vortioxetine over a 3-month treatment period.

## Methods

### ***Study design***

The REVIDA study was an open-label, observational study conducted between August 2016 and April 2017 at 18 sites across four South East Asian countries (Malaysia, Singapore, Thailand, and the Philippines). The full methodology for the study is described in the primary publication [17]. In Malaysia, seven sites mainly from private clinics or hospitals participated in the study.

Data were collected at four time points (baseline, Week 1, Month 1, and Month 3) over a 3-month treatment period. All treatments were prescribed according to the recommendations provided in the local summary of product characteristics.

The study protocol was reviewed and approved by the local Institutional Review Board/Ethics Committee for each site before study initiation. The sites in Malaysia received approval from the Medical Research and Ethics Committee, Ministry of Health Malaysia. Trial registration was not required for this observational real-world study. All patients provided written informed consent before study enrolment.

### ***Patients***

Patients were considered eligible based on the following inclusion and exclusion criteria. Inclusion criteria included: aged between 18–65 years (inclusive), clinically diagnosed with an active episode of major depression in the current visit, initiated vortioxetine treatment on the day of the visit, and provided signed written informed consent. Exclusion criteria included: concurrent diagnosis or past history of schizophrenia or other psychotic disorders, bipolar disorder, dementia or any other neurodegenerative disease, alcohol or

substance dependence, any psychiatric disorders due to a general medical condition or substances, a member of the study personnel or of their immediate families, or was a subordinate (or immediate family member of a subordinate) to any of the study personnel, previous enrolment in this study, participation in another clinical trial, deemed unlikely to comply with the protocol by the investigator, and contra-indicated for treatment based on the summary of product characteristics of vortioxetine.

### ***Study assessments***

#### *Treatment compliance*

Treatment compliance was assessed by the physician via patient interview, and was recorded as a percentage between 0% (no dose taken) and 100% (all doses taken as prescribed) depending on the proportion of prescribed dose taken since the last visit.

#### *Depression severity and improvement in illness*

Depression severity was assessed using the patient-completed Patient Health Questionnaire-9 (PHQ-9) [18], and by the physician using the Clinical Global Impression – Severity (CGI-S) scale. Improvement or worsening in the patient's condition was assessed by the physician using the Clinical Global Impression – Global Improvement (CGI-I) scale.

#### *Cognitive function and work productivity*

Cognitive function was assessed using the patient-completed Perceived Deficit Questionnaire – Depression (PDQ-D) [19]. Work productivity was assessed by the Work Productivity and Activity Impairment (WPAI) patient-completed questionnaire [20].

### *Safety*

Adverse drug reactions (ADRs) were defined as adverse effects considered by the physician as possibly related to vortioxetine treatment. All ADRs were spontaneously reported by the patient or observed by the physician and were collected using an ADR report form.

### *Statistical analyses*

The safety population consisted of all eligible patients who provided informed consent, and who received at least one dose of vortioxetine; the eligible population included patients in the Safety population who completed at least one post-baseline evaluation by the physician as captured in the case report form and at least one post-baseline patient-reported outcome questionnaire. Sociodemographic variables, baseline data, and safety data were analysed in the Safety population; PHQ-9, PDQ-D, CGI-S, CGI-I, WPAI outcome scores were analysed in the Eligible population.

Descriptive statistics were used to summarise all assessment data. Partially answered questionnaires were treated as missing and were not replaced. Continuous

variables were reported using summary statistics (mean, standard deviation [SD], median, minimum and maximum values). Categorical and binary variables were reported using counts and percentages.

## **Results**

### *Demographic and baseline characteristics*

Sociodemographic and baseline characteristics for the Malaysian subgroup and the primary study population are presented in Table 1. Of 138 patients recruited in the primary study, 76 were enrolled in Malaysia. The remaining patients were recruited from Thailand (35 patients), Singapore (20 patients) and the Philippines (7 patients). All patients took at least one dose of vortioxetine and were included in the Safety population. Of the 76 Malaysian patients, three did not complete at least one post-baseline patient-reported outcome questionnaire and were excluded from the efficacy analyses, leaving 73 patients in the Eligible population. Twelve patients withdrew from the study before the last visit (11 were lost to follow-up, and one due to other unspecified reasons).

**Table 1. Sociodemographic and baseline characteristics (Safety population)**

	Primary analysis		Malaysian subgroup analysis	
	n	Data	n	Data
Age (years), mean (SD)	137	39.7 (12.5, 18–64)	76	41.9 (11.9)
Gender, n (%)	138		76	
Male		47 (34.1)		30 (39.7)
Female		91 (65.9)		46 (60.53)
Marital status, n (%)	138		76	
Single		57 (41.3)		24 (31.6)
Married or living as a couple		71 (51.4)		47 (61.8)
Divorced/separated		10 (7.2)		5 (6.6)
Living area, n (%)	133		73	
City		103 (77.4)		51 (69.9)

Small town		27 (20.3)		20 (27.4)
Rural		3 (2.3)		2 (2.7)
Educational years (years), median (Min, Max)	129	15 (4, 22)	72	15 (6, 22)
Main work status, n (%)	137		76	
Paid work		65 (47.4)		34 (44.7)
Self-employed		28 (20.4)		17 (22.4)
Student		13 (9.5)		6 (7.9)
Homemaker		15 (10.9)		12 (15.8)
Retired		5 (3.6)		4 (5.3)
Unemployed (health reasons)		4 (2.9)		1 (1.3)
Unemployed (other reasons)		5 (3.6)		2 (2.6)
Duration of inability to work due to current Major depressive episode (weeks), median (Min, Max)	81	3 (0.0, 52.0)	48	4 (0.0, 52.0)
Length of current episode, n (%)	137		76	
<1 week		1 (0.7)		0 (0.0)
1 to 2 weeks		7 (5.1)		6 (7.9)
2 to 4 weeks		24 (17.5)		20 (26.3)
4 to 8 weeks		18 (13.1)		12 (15.8)
>8 weeks		87 (63.5)		38 (50.0)
Had a significant life event within the past 3 months, n (%)	137	76 (55.5)	76	46 (60.5)
Had suicidal ideation, n (%)	138	39 (28.3)	76	17 (22.4)
First depressive episode, n (%)	138	87 (63.0)	76	53 (69.7)
At least one concomitant clinical diagnosis with current MDD episode	137	58 (42.3)	76	40 (52.6)
Received treatment for current MDD episode prior to baseline visit, n (%)	137	58 (42.3)	76	21 (27.6)

Percentages are based on the number of patients with non-missing values in each specified category. MDD, major depressive disorder; n, number of patients with non-missing values in the specified category; SD, standard deviation.

The mean age of Malaysian patients was 41.9 years (SD 11.9 years, range 18–64 years) and 60.5% were female. The majority were doing paid work (44.7%). Slightly more than half of patients (52.6%) had at least one concomitant clinical diagnosis with the current MDD episode, the most common

of which were generalized anxiety disorder (25 patients; 33.8%), followed by panic disorder (18 patients; 25.4%), agoraphobia (10 patients; 14.3%), and obsessive-compulsive disorder (5 patients; 7.1%). At baseline, the eligible Malaysian population had a mean PHQ-9 score of 20.6

(SD 4.7; Figure 1A), which indicates severe depression, while that for the primary study population was 18.7 (SD 5.7; moderately severe). The mean CGI-S score of the eligible Malaysian population at baseline was 4.6 (SD 0.6; Figure 2A) and that for the primary study population was 4.4 (SD 0.7), indicating that patients from both study populations were moderately to markedly ill. The majority of patients (72.4%) had not received treatment for the current MDD episode prior to the baseline visit. For those who were treated prior to baseline (21 patients; 27.6%), most were treated with selective serotonin reuptake inhibitors (SSRI; 12 patients; 57.1%).

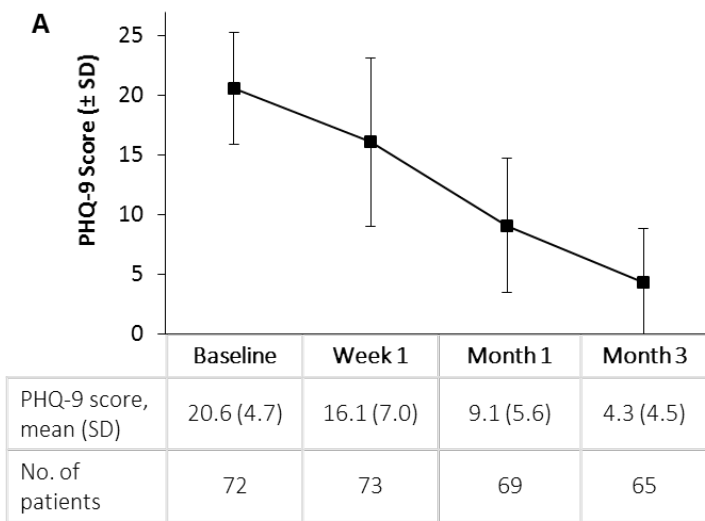
The median daily dose of vortioxetine prescribed was 10.0 mg (range 5.0–20.0 mg)

throughout the treatment period. The mean patient compliance was more than 95% at all study time points (Week 1: 97.8%, Month 1: 97.0%, Month 3: 95.1%). The proportion of patients using anxiolytics decreased from 89.5% at baseline to 38.2% at Month 3.

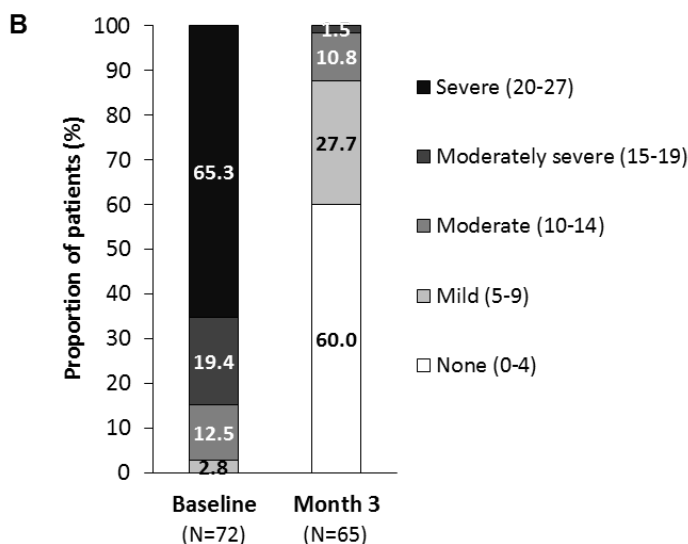
**Depression severity**

*Patient-assessed depressive symptom severity*

The mean PHQ-9 score decreased at each visit from 20.6 (SD 4.7) at baseline to 4.3 (SD 4.5) at Month 3 (Figure 1A). The proportion of patients who had severe depressive symptoms based on their PHQ-9 scores reduced from 65.3% at baseline to 0.0% at Month 3 (Figure 1B). By Month 3, most patients significantly improved in depression severity, having mild or no depressive symptoms (27.7% and 60.0%, respectively; Figure 1B).



**Figure 1. Patient-assessed depression severity as measured with the PHQ-9 (Eligible population). (A) PHQ-9 scores over the 3-month treatment period. (B) Levels of depression based on PHQ-9 scores at Baseline and Month 3.**

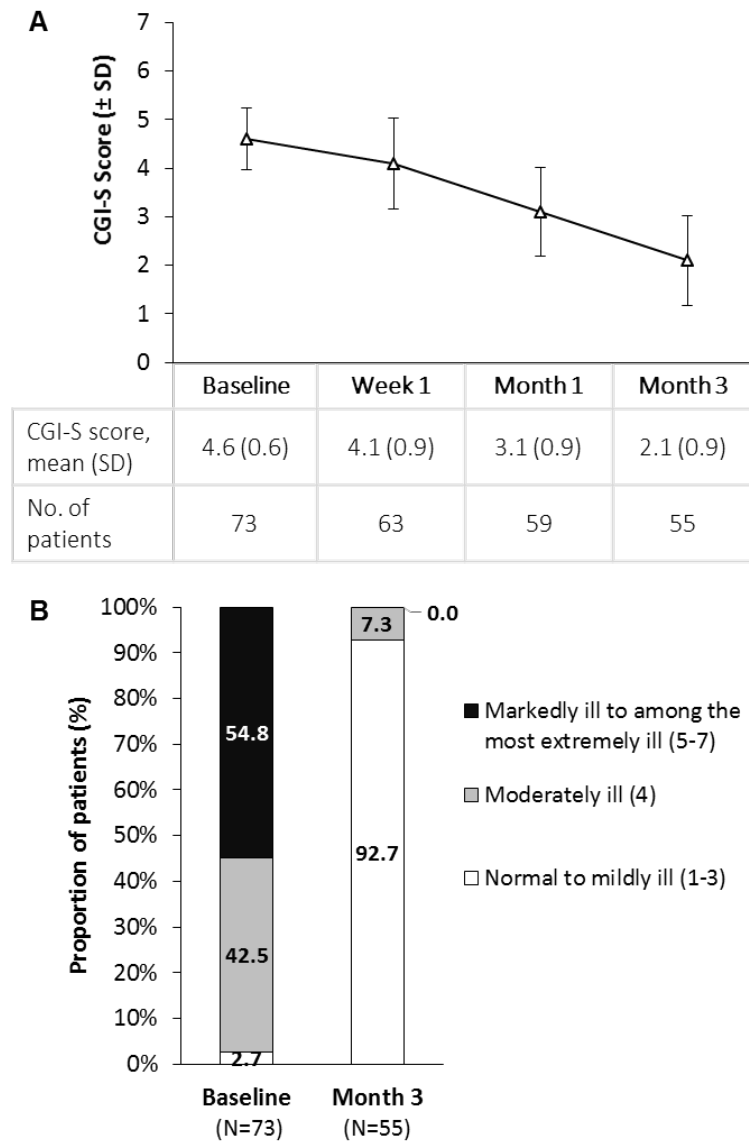


*Physician-assessed depressive symptom severity*

The mean CGI-S score decreased at each visit from 4.6 (SD 0.6; moderately to markedly ill) at baseline to 2.1 (SD 0.9; borderline mentally ill) by Month 3 (Figure

2A). The proportion of patients who were moderately to markedly ill based on their CGI-S scores decreased from 97.3% at baseline to 7.3% at Month 3 (Figure 2B). By Month 3, 92.7% were assessed to be normal to mildly ill (Figure 2B) based on their CGI-S scores.

**Figure 2. Physician-assessed depression severity as measured with the CGI-S (Eligible population). (A) CGI-S scores over the 3-month treatment period. (B) Severity of illness based on CGI-S scores at Baseline and Month 3.**



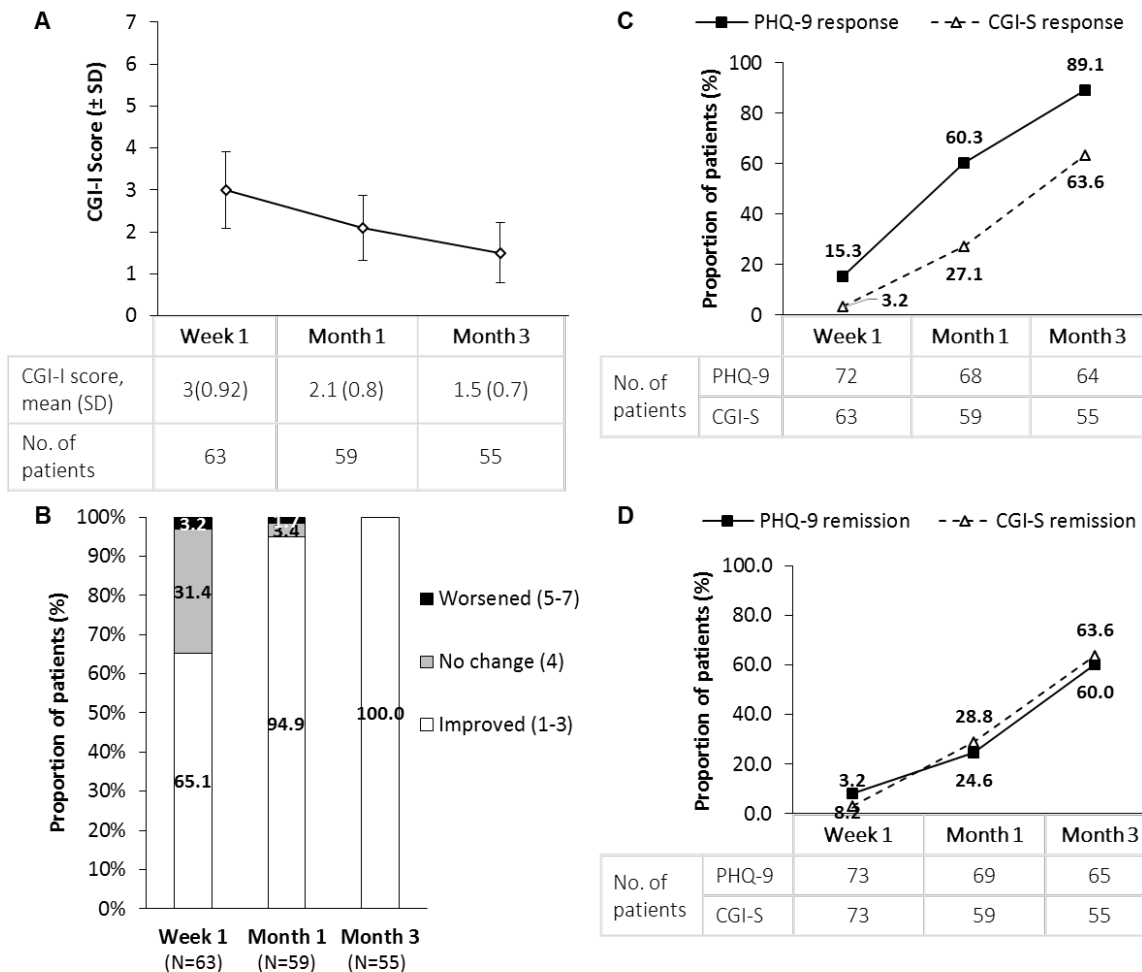
*Improvement, response, and remission*

The mean CGI-I score decreased from 3.0 (SD 0.9; minimally improved) at Week 1 to 1.5 (SD 0.7; much to very much improved) at Month 3 (Figure 3A). At Week 1, 65.1% of Malaysian patients showed improvement (CGI-I score 1–3; minimally to very much improved); this percentage increased to 94.9% at Month 1 and 100.0% at Month 3 (Figure 3B).

Treatment response based on patient-assessment (PHQ-9 response:  $\geq 50\%$  reduction in total score) was attained by 15.3% of patients at Week 1, 60.3% at

Month 1, and 89.1% at Month 3 (Figure 3C). Treatment response based on physician-assessment (CGI-S response:  $\geq 50\%$  reduction in CGI-S score) was attained by 3.2% of patients at Week 1, 27.1% at Month 1, and 63.6% at Month 3 (Figure 3C). Remission based on patient-assessment (PHQ-9 remission: total score  $\leq 4$ ) was attained by 8.2% of patients at Week 1, 24.6% at Week 2, and 60.0% at Month 3 (Figure 3D). Remission based on physician-assessment (CGI-S remission: CGI-S score  $\leq 2$ ) was attained by 3.2% of patients at Week 1, 28.8% of patients at Month 1, and 63.6% of patients at Month 3.

**Figure 3. Improvement, response, and remission over the 3-month treatment period (Eligible population). (A) CGI-I scores and (B) improvement in illness based on CGI-I scores. (C) Patient-assessed response (PHQ-9 response:  $\geq 50\%$  reduction in PHQ-9 score) and physician-assessed response (CGI-S response:  $\geq 50\%$  reduction in CGI-S score). (D) Patient-assessed remission (PHQ-9 remission: PHQ-9 score  $\leq 4$ ) and physician-assessed remission (CGI-S remission: CGI-S score  $\leq 2$ ).**



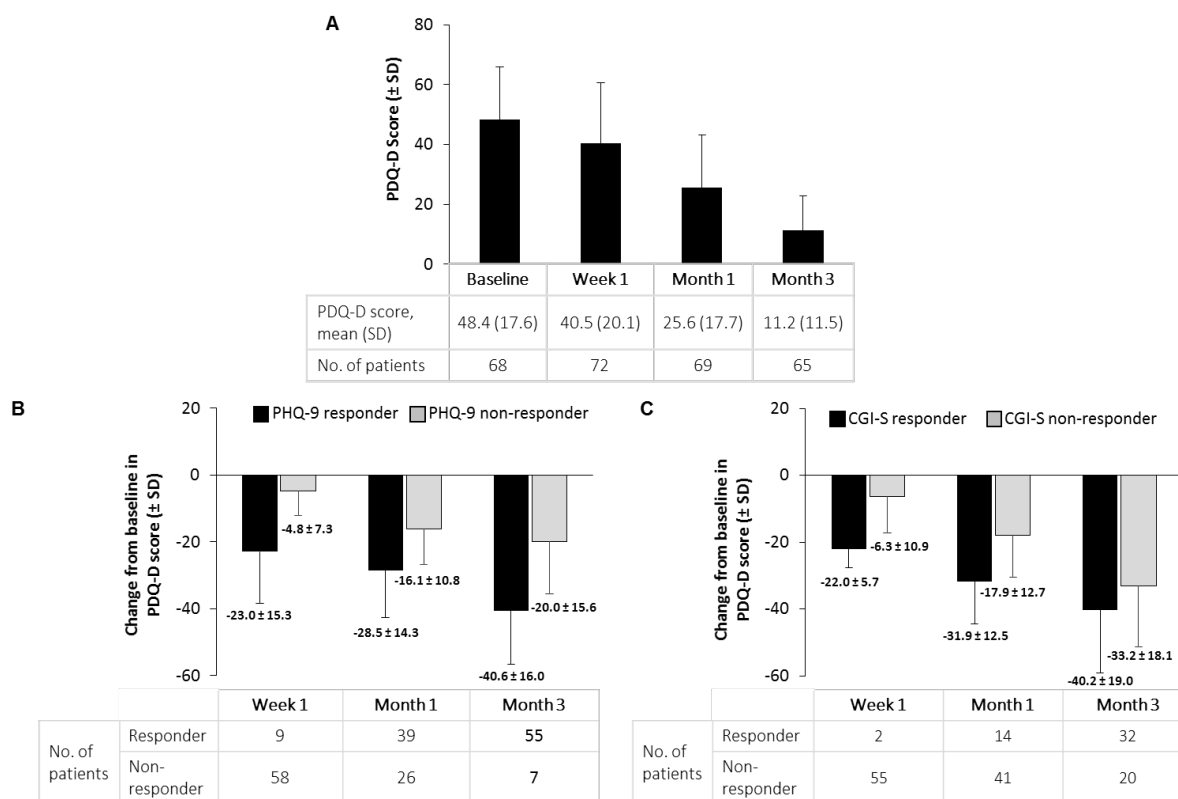


**Patient-reported cognitive deficit**

The mean PDQ-D score decreased from 48.4 (SD 17.6) at baseline to 11.2 (SD 11.5) at Month 3 (Figure 4A), indicating an improvement in cognitive function. A score of 20 and above indicates clinically significant cognitive impairment [21]. Both

patient-assessed response (PHQ-9 responders/non-responders; Figure 4B) and physician-assessed response (CGI-S responders/non-responders; Figure 4C) showed that non-responders had less improvements in cognitive function than responders at each study visit.

**Figure 4. Cognitive function measured with the PDQ-D (Eligible population). (A) PDQ-D scores over the 3-month treatment period. Change from baseline in PDQ-D score by (B) patient-assessed responder status (PHQ-9 responder:  $\geq 50\%$  reduction in PHQ-9 score) and (C) physician-assessed responder status (CGI-S responder:  $\geq 50\%$  reduction in CGI-S score).**



**3.4 Work productivity and activity impairment**

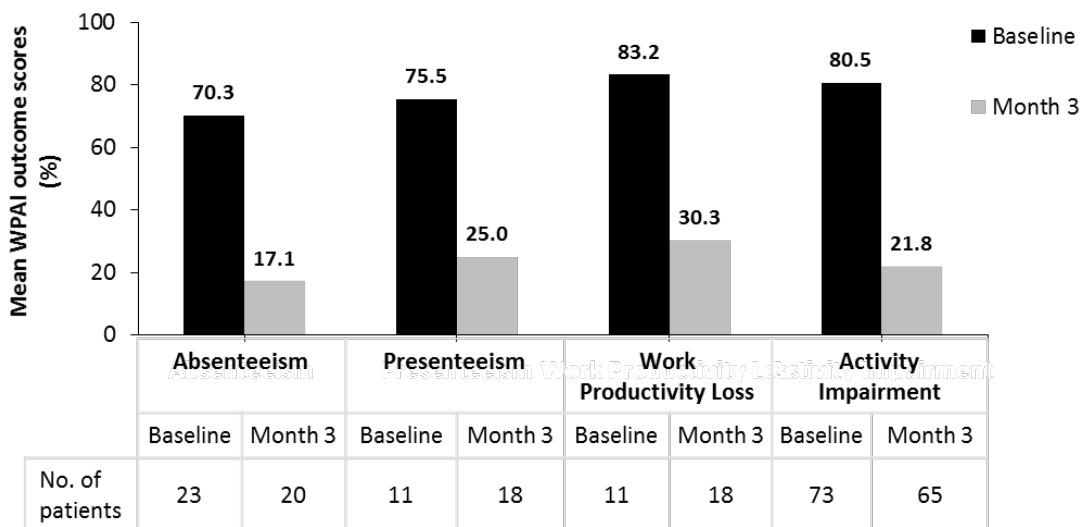
Employed workers (67.1%) and students (7.9%) made up the majority of the Malaysian subgroup (Table 1). The mean WPAI outcome scores at baseline and

Month 3 are presented in Figure 5. Over the 3-month treatment period, the mean percent absenteeism per patient decreased from 70.3% to 17.1%, presenteeism improved from 75.5% to 25.0%, work productivity loss decreased from 83.2% to 30.3%, and activity impairment decreased from 80.5%

to 21.8%. Overall, all four outcome scores improved by at least 50% reduction by the

end of the study.

**Figure 5. Mean WPAI outcome scores at Baseline and Month 3 (Eligible population)**



**Safety**

A total of 20 ADRs were reported by 13 patients in the primary study population; however, no ADRs were reported for any of the Malaysian patients.

**Discussion**

This subgroup analysis sought to evaluate depressive symptom progression, cognitive function, and work productivity in Malaysian patients treated with vortioxetine over a three months. Results from this subgroup analysis reflected those reported in the primary REVIDA study population. Vortioxetine was effective at reducing depressive symptoms, from both patient-reported and physician-reported outcomes. In addition, we observed significant improvements in cognitive function and work productivity, which are important determinants of functional recovery from an MDD episode. Vortioxetine was also well-

tolerated by these patients, as shown by the lack of adverse events in this subgroup analysis.

Vortioxetine has demonstrated a clear effect on improving cognition in depressed patients [22, 23] and is the only antidepressant with an approved cognition claim. In support of this claim, results from this subgroup analysis and the REVIDA study demonstrated improvements in depressive mood and cognition. Cognitive impairment has been examined in cross-sectional studies in Asia, including Malaysia. Self-perceived cognitive dysfunction in Asian patients with MDD has been reported in the CogDAD study (mean PDQ-D score: 22.6) [10]. Compared to that of the CogDAD study, the higher level of cognitive impairment observed in the present analysis (mean PDQ-D score: 48.4) may be due to patients presenting with more severe depression at baseline (REVIDA Malaysia: mean CGI-S score: 4.6, mean

PHQ-9 score: 20.6; CogDAD: mean CGI-S score: 3.3, mean PHQ-9 score: 11.3). In another study that reported the symptom profile of depressive illness in Asian countries (China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Singapore, Taiwan, and Thailand) [24], patients from upper and lower middle-income countries such as Malaysia who had depressive symptoms also experienced more cognitive symptoms.

In the present study, PHQ-9 remission and response rates were 89.1% and 60.0% at Month 3, respectively. Response and remission rates were much higher in the present analysis than those reported in the STAR\*D study [25], which is the largest and longest real-world study of 2876 patients with MDD over a 14-week treatment period conducted to date. In the STAR\*D study [25], response and remission rates after the first round of treatment with an SSRI were 47% and 33%, respectively, based on the Quick Inventory of Depressive Symptomatology – Self Report. The recovery rates in the present study were also higher than previously reported response and remission rates of 69.8% and 55.2%, respectively, in vortioxetine-treated patients who had partial response to previous treatment with an SSRI or serotonin and norepinephrine reuptake inhibitor (SNRI) [26]; a possible explanation for this observation may be the inclusion of first-episode patients in our study. Taken together, our results provided promising evidence of vortioxetine in improving remission and response rates for MDD patients.

In the present analysis, three-quarters of patients (75.0%) were either employed or studying. In an Asian study of clinical features of depression – of which 16.5% of patients were from Malaysia – the “work/school” item of the Sheehan

Disability Scale had the highest mean score (6.5, SD 2.9) amongst other items such as “social life/leisure” and “family/home life” [27]. This finding suggests that Asian patients with depression consider their depressive symptoms to be most disruptive to their work/school lives, compared to their family or social lives. In our study, all four WPAI outcome scores improved over the study period, with a decrease of at least 50% on each score by the end of the study. Consequently, this knowledge is crucial when evaluating true functional response or remission in all areas relevant to the patient, including those outside of the core depressive symptoms.

As this was a subgroup analysis, limitations of the primary study would apply to the present analysis. These limitations include the open-label study design with lack of a placebo or comparator group; relatively short length of patient’s current MDD episode; pre-treatment with other antidepressants or anxiolytics that may confound interpretations; and possible under-reporting of ADRs. Additional limitations of this subgroup analysis include its post-hoc nature, and the inability to generalise findings to the MDD patient population in Malaysia since the participating study sites were private clinics and hospitals. No ADRs were reported by Malaysian patients suggesting that under-reporting could have been an issue in Malaysia.

## Conclusion

Results from this subgroup analysis were comparable with those from the primary study, indicating that vortioxetine was equally effective across different patient populations and healthcare settings. In this subgroup analysis of Malaysian patients with MDD, vortioxetine was well-tolerated

and effective at reducing depressive symptoms, while improving cognitive function and work productivity with high rates of response and remission.

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### Disclosures

Azhar Zain has received speaker honorarium from Lundbeck Malaysia Sdn Bhd. Marvin Swee Woon Chong has received a research grant from Lundbeck. Chin Hong Yap has received speaker honoraria from Lundbeck Malaysia Sdn Bhd and Laboratories Torrent (Malaysia) Sdn Bhd. Keira Joann Herr is an employee of Lundbeck Singapore Pte. Ltd. All other authors have no relevant relationships to disclose.

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The sponsor was involved in the study conception and the decision to submit the article for publication. The sponsor had no further role in data interpretation or in manuscript preparation.

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