CLINICAL TRIAL

Vortioxetine for the treatment of post-COVID-19 condition: a randomized controlled trial

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Abstract

Hitherto no therapeutic has received regulatory approval for the treatment of Post-COVID-19 Condition (PCC). Cognitive deficits, mood symptoms, and significant reduction in health-related quality of life (HRQoL) are highly replicated and debilitating aspects of PCC. We sought to determine the impact of vortioxetine on the foregoing symptoms and HRQoL in persons living with PCC.

An 8-week randomized, double-blind, placebo-controlled study of adults ≥ 18 years of age residing in Canada and who are experiencing symptoms of World Health Organization (WHO)-defined PCC, with a history of confirmed SARS-CoV-2 infection, was conducted. Recruitment began November 2021 and ended January 2023. Of the 200 participants enrolled (487 invited: 121 ineligible and 59 eligible but declined participation; 307 cleared pre-screening stage), a total of 149 participants were randomized (1:1) to receive either vortioxetine (5-20 mg, n = 75) or placebo (n = 74) daily for 8 weeks of double-blind treatment (i.e., endpoint). The primary outcome was the change from baseline-to-endpoint in the Digit Symbol Substitution Test (DSST). Secondary outcomes included the effect on depressive symptoms and HRQoL, as measured by changes from baseline-to-endpoint on the Quick Inventory of Depressive Symptomatology-16-item (QIDS-SR16) and World Health Organization Wellbeing Scale-5-item (WHO-5), respectively.

A total of 68 (90.7%) participants randomized to vortioxetine and 73 (98.6%) participants randomized to placebo completed all 8 weeks. Between-group analysis did not show a significant difference in the overall change in cognitive function (p = 0.361, 95% CI [-0.179, 0.492]). However, in the fully adjusted model, a significant treatment-by-time interaction was

observed in favor of vortioxetine treatment with baseline c-reactive protein (CRP) as a moderator (p = 0.012). In addition, a significant improvement in DSST scores were observed in vortioxetine- versus placebo-treated participants in those whose baseline CRP was above the mean (p = 0.045). Moreover, significant improvement was obtained in measures of depressive symptoms ($p < 0.001$, 95% CI [-4.378, -2.323]) and HRQoL ($p < 0.001$, 95% CI [2.297, 4.647]) in vortioxetine-treated participants and between the treatment groups (depressive symptoms: $p = 0.026$, 95% CI [-2.847, -0.185]; HRQoL: $p = 0.004$, 95% CI [0.774, 3.938]).

Although vortioxetine did not improve cognitive function in the unadjusted model, when adjusting for CRP, a significant pro-cognitive effect was observed; antidepressant effects and improvement in HRQoL in this debilitating disorder were also noted.

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Introduction

According to the World Health Organization (WHO), more than 800 million cumulative cases of COVID-19 have been confirmed globally.[1] It is separately reported that a significant proportion of individuals who have recovered from acute SARS-CoV-2 infection manifest persistent, non-remitting, non-specific, distressing, and debilitating symptoms.[2] A large quantity of symptoms reflecting disturbances across multiple organs have been described, including cognitive function (e.g., *"brain fog"*) and mood.[3]

The WHO introduced and defined the moniker *"post COVID-19 condition"* (PCC) as the presence of non-remitting symptoms occurring three months after a confirmed COVID-19 infection that persists for at least two months and are distressing and/or impairing to the person living with the condition.[4] It is estimated that approximately 10-20% of persons infected with COVID-19 meet criteria for PCC.[5] Post COVID-19 Condition is associated with significant impairment in psychosocial function, workplace attendance and productivity, economic costs, and reduction in health-related quality of life (HRQoL).[6] It is hypothesized that disturbances in immune-inflammatory and vascular function contribute to PCC.[7] Notwithstanding many mechanistically dissimilar interventions for PCC, no therapeutic has established efficacy and tolerability in a large and rigorous randomized, double-blind, placebo-controlled trial and/or received United States Food and Drug Administration (FDA) and/or European Medicines Agency (EMA) approval (or clearance) for PCC.[7]

Replicated evidence indicates that along with cognitive impairment and disturbance in mood, reduced HRQoL significantly contributes to the illness burden attributable to PCC.[8] These observations provide the impetus to prioritize the development of therapeutics that can meaningfully improve the foregoing phenomenon. Mechanism-informed treatment development would suggest that an intervention with established efficacy in cognition and depression in other medical conditions as well as effects on neurobiological systems (e.g., immune-inflammation) implicated in PCC may be candidate treatments.[7]

Vortioxetine is a multimodal antidepressant with demonstrated improvement on

objective and subjective measures of cognition in adults with Major Depressive Disorder (MDD).[9] Vortioxetine exerts immunomodulatory and anti-oxidative effects, all of which are implicated in the neurobiology of PCC.[10] For example, it is documented that vortioxetine increases gene expression of Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) in resting monocytes and macrophages, and reduces the expression of tumor necrosis factor alpha (TNF-α).[10] Additionally, vortioxetine-challenged monocytes have been shown to express the anti-inflammatory M2 phenotype.[10] Vortioxetine is also a potent and efficacious COX-1 and COX-2 inhibitor with an inhibition constant (IC) 50 times lower than that of select NSAIDs (e.g., indomethacin).[11] It is acknowledged that the aforementioned research is largely conducted *in vitro*, and the immune-modulatory effects in human subjects with a diagnosable medical disorder are not fully ascertained. Finally, vortioxetine is also a serotonin modulator and reuptake inhibition; a working hypothesis is that, for some individuals with PCC, the symptomatic presentation is a consequence of diminished serotonin production, notably in the gastrointestinal tract.[12]

Herein, we sought to determine the effect of vortioxetine on objective measures of cognition, self-reported mood-related symptoms, and HRQoL in adults ≥ 18 years of age meeting WHO criteria for PCC.[13]

Materials and methods

Study design and participants

This randomized, double-blind, flexible-dosed, placebo-controlled study comprised individuals residing in Canada. Recruitment began November 2021 and ended January 2023, and included media advertisements (e.g., Facebook, Instagram, Twitter, and posters) or referral by medical practitioners.

The first author (RSM) conceived and designed the study as well as created the protocol. The study was conducted in accordance with the principles of Good Clinical Practice (ICH, 1996) and the Declaration of Helsinki (WMA, 2008). A local research ethics board (REB) approved the trial design and all eligible participants provided written informed consent before enrollment. This study was registered on ClinicalTrials.gov (NCT05047952).

Randomization and masking

Persons expressing interest in the study were pre-screened by trained trial personnel and if no apparent exclusion criteria were met, they were subsequently screened for trial eligibility. Eligible participants were randomized (1:1) to receive either vortioxetine (5-20 mg/d) or placebo for 8 weeks of double-blind treatment. Both medication and placebo were provided by H. Lundbeck A/S, Copenhagen, Denmark. Randomization was completed internally by blinded staff members; sequentially enrolled participants were assigned the lowest randomization number available in blocks of 10. All investigators, research coordinators and participants were blinded to treatment assignment for the duration of the study, except for two designated, unblinded staff who were responsible for labeling and dispensing the investigational product, and had no interaction with participants. The randomization code was not broken for any participant during the study.

Procedures

Persons aged ≥ 18 years residing in Canada with a history of confirmed SARS-CoV-2 infection (i.e., positive SARS-CoV-2 PCR test, rapid antigen test, or serology test) or probable SARS-CoV-2 infection (i.e., signed confirmation of presumptive case from a healthcare provider or clinical diagnosis by the study physician) who met WHO-defined criteria for PCC occurring within 3 months after acute COVID-19 infection were included. All eligible participants were required to provide written informed consent at the screening visit or baseline stage to be enrolled in the study. Individuals were excluded if they met any of the pre-defined exclusion criteria **(Table S1)**.

Eligible participants aged 18-65 years randomized to the vortioxetine group received vortioxetine at 10 mg/d during weeks 1 and 2 and 20 mg/d from weeks 3-8. Participants aged 65+ years randomized to the vortioxetine group received vortioxetine at 5 mg/d during weeks 1 and 2 and 10mg/d from weeks 3-8. For participants unable to tolerate higher doses, down titration to the index dose was permitted. Participants were seen at baseline and weeks 2, 4, and 8. Participants who withdrew prior to study completion were evaluated at the earliest possible date following withdrawal.

Choice of primary measure

The effect of vortioxetine on cognitive function, as compared to placebo, was evaluated using the Digital Symbol Substitution Test (DSST) (Pen/Paper plus Online CogState Version as part of the CogState Online Cognitive Battery).

Secondary outcomes

Secondary outcome measures included baseline-to-endpoint changes in the CogState Online Cognitive Battery, Trails Making Test (TMT)-A/B, Rey's Auditory Verbal Learning Test (RAVLT), Perceived Deficits Questionnaire, 20-item (PDQ-20), World Health Organization Wellbeing Scale, 5-item (WHO-5), Sheehan Disability Scale (SDS), and Quick Inventory of Depressive Symptomatology, 16-Item (Self-Report) (QIDS-SR-16). The CogState Online Cognitive Battery, TMT-A/B, and RAVLT were measured at baseline and weeks 2 and 8. The PDQ-20, WHO-5, SDS, and QIDS-SR16 were measured at baseline and weeks 2, 4, and 8.

In light of public health measures implemented in Canada during the COVID-19 pandemic, participants were provided the opportunity to participate through remote study visits, which were conducted via online or telephone platforms (e.g., Zoom). Remote study visits with the study physician were conducted using the secure Ontario TeleNetwork (OTN) system or telephone. The REB and Health Canada approved the mailing of study medication to remote participants.

Herein, we include two secondary outcomes of interest (i.e., improvement in self-reported depressive symptoms and HRQoL). The rationale for focusing on these two secondary outcomes is due to their high prevalence among individuals with PCC, their significant impact on overall health, and previous research indicating improvements in these areas with vortioxetine in other medical populations.[14–21]

Statistical analysis

All statistical analyses were conducted via the IBM SPSS Statistics software, version 28.0.1.1 (15) with two-sided statistical significance set at $\alpha = 0.05$. An intent-to-treat analysis (i.e., all randomized participants) was used to assess baseline-to-endpoint changes in the DSST total

scores.

The primary efficacy analysis was conducted using the generalized estimating equation (GEE) model to examine the baseline-to-endpoint change in the composite z-score, the equally-weighted sum of the z-scores of the Pen/Paper plus Online CogState Versions. Of the 149 enrolled participants, 11 (7.4%) completed the Pen/Paper version, 78 (52.3%) completed the Online CogState Version, and 60 (40.3%) completed both. For participants that completed both, performance in the Pen/Paper and Online CogState Version were strongly correlated (r = 0.588, $p < 0.001$). The Online CogState Version scores were primarily used for participants who had it available. The secondary efficacy analyses were also examined using the GEE model to examine the baseline-to-endpoint changes in mood symptoms and HRQoL, as measured by QIDS-SR16 and WHO-5.

The sample size calculation was based on effect sizes reported with vortioxetine on DSST-measured cognitive function in MDD, which has been estimated at approximately 0.2-0.5.[22–24] Therefore, it was estimated that a sample size of 100 participants per treatment arm would detect clinically relevant change with vortioxetine treatment on DSST-measured cognitive function as the dependent measure using a mixed models for repeated measures with a 1-sided significance level of $p < 0.05$.[22]

Safety and tolerability assessments

All adverse events observed by the investigator or reported spontaneously by the participant were recorded with vital signs.

Role of the funding source

The funder of the study had no role in the study design; collection, analysis, and/or interpretation of the results; or manuscript writing and journal selection for publication.

Results

Participant characteristics

Baseline sociodemographic and clinical characteristics of the intent-to-treat (ITT) population

are described in **Table 1**. There were no statistically significant differences observed between the treatment groups. Four participants were excluded due to non-adherence to the study medication regimen.

Of the 200 participants enrolled, 149 were randomized to receive vortioxetine (n = 75) or placebo (n = 74). Of the foregoing sample, 68 (90.7%) participants randomized to vortioxetine and 73 (98.6%) participants randomized to placebo completed all 8 weeks of the double-blind treatment period. There were no significant differences between groups in the study completion rates (p = 0.089). The complete recruitment and enrollment summary is shown in **Figure 1**.

Efficacy

Primary endpoint

ITT GEE analysis was conducted on 149 participants with PCC administered vortioxetine (n = 75) or placebo (n = 74). After adjustment for the type of cognitive test (Pen/Paper vs. Online CogState Version), there were no significant group (χ^2 = 0.999, p = 0.317) and treatment by time interaction (χ^2 = 0.658, p = 0.720) effects observed in endpoint results. However, there were time effects (χ^2 = 38.779, $p < 0.001$), indicating that participants' DSST scores improved over time but at similar rates within each treatment group **(Figure 2)**. The baseline-to-endpoint change for DSST-measured cognitive function ($N_{combinedDSST}$ = 149, $n_{Pen/PaperDSST}$ = 72, $n_{OnlineCogStateDSST}$ = 137) was 0.31 (SEM = 0.08) at week 8 (p < 0.001) for vortioxetine and 0.33 (SEM = 0.08) at week 8 (p < 0.001) for placebo **(Table 2)**.

Similar results were observed when adjusting for age, sex, education, QIDS-SR-16 scores, and baseline DSST scores (treatment by time interaction: χ^2 = 1.317, p = 0.518) or when considering only the computerized tests (treatment by time interaction: χ^2 = 0.695, p = 0.707). Moreover, in the adjusted model (including sociodemographics), a significant between-group difference (p = 0.028, 95% CI [0.029, 0.492]) was observed **(Table 2)**. In addition, a significant treatment by time interaction (χ^2 =10.914, p = 0.012) on cognitive function was observed using baseline CRP as a moderator in favor of vortioxetine. A significant improvement in DSST scores were also observed in vortioxetine- versus placebo-treated participants in those whose baseline CRP was above the mean (χ^2 = 8.072, p = 0.045).

Secondary endpoint

For QIDS-SR-16-measured depressive symptoms, a significant treatment by time interaction (χ^2 = 4.837, p = 0.028) was observed after adjusting for age, sex, education, and baseline QIDS-SR-16 total score. A significant group (χ^2 = 4.653, p = 0.031) and time (χ^2 = 49.184, p < 0.001) effects were also observed. This indicates that participants' QIDS-SR-16 scores improved over time and at significantly different rates within each treatment group (**Figure 3**). Furthermore, a significant between-group mean difference was observed (mean difference = -1.516, SEM = 0.679, 95% CI [-2.847, -0.185], p = 0.026) (**Table 2**).

For WHO-5-measured HRQoL, there was a significant treatment by time interaction (χ^2 = 7.893, p = 0.005) after adjusting for age, sex, education, and baseline WHO-5 total score. Significant time (χ^2 = 29.69, p < 0.001) and group (χ^2 = 8.675, p = 0.003) effects were also observed, indicating that participants' WHO-5 scores significantly improved over time and at significantly different rates within each treatment group **(Figure 4)**. Furthermore, a significant between-group difference was observed (mean difference = 2.356, SEM = 0.807, 95% CI [0.774, 3.938], p = 0.004) **(Table 2)**. Moderators were also analyzed (treatment × time × QIDS-SR-16 total score interaction effects: χ^2 = 90.205, p < 0.001) in a separate model (group effects: χ^2 = 9.928, p = 0.002; time effects: χ^2 = 29.034, p < 0.001) (**Table 2**).

Safety

The overall percent of individuals experiencing a treatment-emergent adverse event was 26.8% (n = 40 of 149) and 22.1% (n = 33 of 149) for vortioxetine and placebo, respectively. There were no adverse events affecting ≥ 5% of the within group sample and twice the rate of placebo. The percentage of persons who discontinued treatment were 3% (n = 4) and 0% (n = 0) for the vortioxetine and placebo group, respectively.

Discussion

Herein, we did not observe a significant between-group difference in the objective measure of cognitive function in persons living with PCC. However, in the adjusted model, there was a significant between-group difference and an improvement in cognitive function with vortioxetine treatment over time using baseline CRP as a moderator. The latter finding is in

keeping with the hypothesized pathogenetic model of cognitive function in PCC (i.e., immune inflammatory dysregulation) and putative mechanism of vortioxetine. Additionally, vortioxetine treatment significantly improved depressive symptoms and HRQoL when compared to the placebo group. This is clinically meaningful from the point of view of lived experience given the impact that these aspects have on the overall burden of illness due to PCC.

The non-significance of vortioxetine on objective cognitive function in the unadjusted model has multiple potential explanations. In addition to the possibility that vortioxetine is inefficacious for cognitive function in PCC, it is also possible that the heterogeneity of cognition deficits as well as its neurobiologic substrates in PCC results in multiple biotypes, reducing assay sensitivity. This is not dissimilar to MDD where vortioxetine has been shown to be effective for cognition in subpopulations of persons with MDD.[25] It is noteworthy that the within-group effect size of vortioxetine treatment on DSST is similar to what has been observed with vortioxetine treatment in adults with MDD, suggesting that the study herein was underpowered to detect a between-group separation from placebo at week 8 using the DSST.[22]

We also did not stratify participants as part of eligibility on the basis of having a predetermined threshold of objective cognitive impairment (i.e., $\geq$ 1.0 standard deviation below the norm on a cognitive measure) prior to enrolment. Consensus exists amongst researchers that stratifying participants on the basis of a pre-existing cognitive deficit is preferred when evaluating a putative procognitive agent.[26] Moreover, a comprehensive review by our group of 81 studies, of which 43 studies were subject to meta-analysis, concluded that the proportion of individuals exhibiting cognitive impairment was 0.22 (95% CI, 0.17, 0.28; $p < 0.001$; n = 13,232; I_2 = 98.0).[8] The foregoing results indicate that a significant proportion of persons with PCC do not have cognitive impairment but other aspects of the syndrome are instead mediating impairment in patient reported outcomes (PROs).

An additional factor for consideration is the use of DSST as the primary cognitive measure in our study.[26] Multiple domains of cognitive functions are adversely affected in persons living with PCC.[8] It is well established that the DSST is a multifaceted cognitive measure that is subject to extensive validation across cultures, age groups, and medical populations. Notwithstanding the ability of the DSST to proxy deficits across multiple domains of cognitive function, the DSST is principally a measure of processing speed.[27] It is

possible that a separate cognitive measure that is less dependent on processing speed may have resulted in a different outcome. Also, the study was conducted during the global pandemic, of which most persons had completed a virtual version of the DSST; this aspect along with the fact that we combined results from virtual and pen-paper DSST version—although done herein for public health reasons and restrictions on participant contact—may have influenced the sensitivity of the scale.

It was noteworthy that in the adjusted model with baseline CRP included, a significant effect of vortioxetine on cognitive function was observed. Previous studies provide replicated evidence that CRP—a non-specific marker of immune-inflammatory activation—is associated with cognitive impairment.[28] It is separately reported that vortioxetine indirectly targets immune-inflammatory effectors, suggesting that benefits of vortioxetine in cognitive functions are more likely to be observed in persons with PCC and immune-inflammatory activation.

Similar to depressive symptoms, we observed improvements in HRQoL. Several lines of research indicate that vortioxetine improves measures of HRQoL in MDD populations.[29] It can be hypothesized that vortioxetine improvement in HRQoL may be mediated in part by improvement in depression as well as other aspects not measured in our study. For example, it is possible that vortioxetine may have improved measures of resiliency and/or motivation that were not fully captured in our study.[30] For many affected persons, rather than improving the symptoms of PCC, the Centers for Disease Control and Prevention (CDC) recommends a comprehensive management plan that focuses on improving physical, mental, and social well-being in affected persons.[31]

There are additional methodological limitations that affect inferences and interpretations of our data. Participants in our study were primarily recruited via media announcements including presentations at PCC online groups. Our sample was not recruited from a medical clinic including *"Post COVID-19 Condition clinics."* Consequently, our results may not extend to persons with PCC without access to digital sources. A further limitation is that the majority of participants were Caucasian; it is recognized that our results may not generalize to people of different race, ethnicity, ancestry, and/or social determinants of health. An additional limitation is that we did not look at all secondary outcomes and instead delimited our evaluating to two secondary outcomes guided by clinical and pharmacological rationale.

Moreover, a large quantity of symptoms has been attributed to PCC and as such we cannot assume that our results would extend to all persons living with PCC. Also, eligibility required laboratory confirmation of COVID-19 infection and if unavailable, clinician determination that COVID-19 infection was present was used. It is recognized that concordance between healthcare provider clinical diagnosis of COVID-19 and laboratory confirmation is not ideal, but was pragmatic due to insufficient capability of testing at the public health level.[32]

Our results provide the basis to hypothesize that vortioxetine treatment may improve cognitive functions in subpopulations of persons living in PCC. We also observed significant benefits on other highly debilitating aspects of PCC (i.e., mood symptoms and HRQoL). The complex pathoetiology and symptom presentation indicates that multiple mechanistic approaches will need to be considered. Future interventional studies should include larger well-characterized samples of persons with PCC and seek to replicate our findings as well as ascertain the potential role of other agents that may benefit measures of cognition, mood, and HRQoL in persons with PCC.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary material. Upon reasonable request, raw data that support the findings of this study are available from the corresponding author.

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Competing interests

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Supplementary material

Supplementary material is available at *Brain* online.

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Figure legends

Figure 1 CONSORT flow diagram of the participant disposition (enrollment, randomization, and follow-up) in a phase 2 trial of vortioxetine for Post-COVID-19 Condition. [a]The safety population—also known as the all-patients-treated set (APTS)—included all randomized participants who received at least 1 dose of vortioxetine or placebo. [b]The modified intent-to-treat population included all randomized participants who received at least 1 dose of vortioxetine or placebo and had four post-baseline assessments of the primary or secondary efficacy variables. [*]The modified intent-to-treat population of the DSST sample included $n = 68$ for the vortioxetine group [7 total drop-outs due to side effects ($n = 4$) and personal issues ($n = 3$) and $n = 73$ (1 drop-out due to personal issues) [**]The modified intent-to-treat population of the QIDS-SR16 and WHO-5 sample included individuals who had completed assessments for both QIDS-SR16 and WHO-5 measures. [***]Participant excluded from the study due to a one-month gap between baseline and week 2 assessments.

Figure 2 Intention-to-treat GEE analysis of the effects of vortioxetine on cognitive function. There was a significant effect of time with both groups (vortioxetine, $n = 75$; placebo, $n = 74$), exhibiting significant improvement in DSST z-scores across treatment weeks ($p < 0.001$); but no treatment by time interaction effect ($p = 0.720$). Depicted is the least square (LS) mean (standard error of mean [SEM]) change in DSST z-scores from baseline to the indicated week using an independent covariance matrix with time as a categorical variable, adjusted for the type of cognitive test (Pen/Paper vs. Online CogState Version).

Figure 3 Intention-to-treat GEE analysis of the effects of vortioxetine on depressive symptoms. There was a significant effect of time with both groups (vortioxetine, $n = 67$; placebo, $n = 73$), exhibiting significant improvement in QIDS-SR16 across treatment weeks ($p < 0.001$) and treatment by time interaction effect ($p = 0.030$). Depicted is the least square (LS) mean (standard error of mean [SEM]) change in QIDS-SR16 from baseline to the indicated week using an independent covariance matrix with time as a categorical variable.

Figure 4 Intention-to-treat GEE analysis of the effects of vortioxetine on health-related quality of life. There was a significant effect of time with both groups (vortioxetine, $n = 67$; placebo, $n = 73$), exhibiting significant improvement in WHO-5 across treatment weeks ($p < 0.001$) and treatment by time interaction effect ($p = 0.003$). Depicted is the least square (LS) mean (standard error of mean [SEM]) change in WHO-5 from baseline to the indicated week using an independent covariance matrix with time as a categorical variable.

Table 1 Baseline characteristics of the intent-to-treat population (N = 149)

Characteristic	Placebo (*n* = 74)	Vortioxetine (*n* = 75)	p-value
Age (years), Mean (SD)	44.94 (12.03)	43.65 (12.26)	0.519[a]
Sex (female), n (%)	47 (63.5)	51 (68.0)	0.564[b]
Confirmed COVID Diagnosis, n (%)	59 (79.7)	59 (78.7)	0.873[b]
Lifetime MDD Diagnosis, n (%)	25 (33.8)	32 (42.7)	0.265[b]
Antidepressant Usage, n (%)	9 (12.16)	12 (0.16)	0.459[b]
Ethnicity (Caucasian), n (%)	55 (74.3)	58 (77.3)	0.668[b]
Education, n (%)			0.217[b]
High School	14 (18.9)	18 (24.0)	
Overweight	42 (56.8)	47 (62.7)	
Obese	18 (24.3)	10 (13.3)	
Baseline CRP, Mean (SD)	3.17 (3.42)	2.45 (2.91)	0.215[a]
Combined DSST (z-score), Mean (SD)	-0.21 (0.96)	-0.02 (0.91)	0.253[a]
Computerized DSST (Total Number of Symbols), Mean (SD)	46.35 (10.75)	48.40 (10.11)	0.217[a]
Remote Assessment, n (%)	40 (54.1)	38 (50.7)	0.679[b]
QIDS-SR16 (Total Score), Mean (SD)	10.28 (4.54)	10.32 (4.36)	0.956[a]
WHO-5 (Total Score), Mean (SD)	9.757 (3.948)	9.808 (4.579)	0.942[a]

DSST = Digit Symbol Substitution Test; MDD = Major Depressive Disorder; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self-Report, 16-iterm; SD = Standard Deviation; WHO-5 = The World Health Organisation-Five Well-Being Index, 5-item.

[a]T-test

[b]Chi-square test

Table 2 Pairwise comparisons for the primary and secondary efficacy endpoints of the intent-to-treat population

(I) Treatment Allocation *x* Week	(J) Treatment Allocation *x* Week	Mean Difference (I – J)	Standard Error	95% Wald Confidence Interval			
				Lower	Upper	df	*P*-value
Combined DSST[b]							
Treatment Allocation (Placebo) x Week 8	Treatment Allocation (Placebo) x Week 0	0.332[a]	0.0752	0.185	0.479	1	<0.001
Treatment Allocation (Vortioxetine) x Week 8	Treatment Allocation (Vortioxetine) x Week 0	0.305[a]	0.0803	0.148	0.462	1	<0.001
	Treatment Allocation (Placebo) x Week 0	0.488[a]	0.161	0.173	0.804	1	0.002
Treatment Allocation (Vortioxetine) x Week 8	Treatment Allocation (Placebo) x Week 8	0.157	0.171	−0.179	0.492	1	0.361
Combined DSST[c]							
Treatment Allocation (Placebo) x Week 8	Treatment Allocation (Placebo) x Week 0	0.184[a]	0.0934	0.00122	0.368	1	0.048
Treatment Allocation (Vortioxetine) x Week 8	Treatment Allocation (Vortioxetine) x Week 0	0.448[a]	0.098	0.256	0.640	1	<0.001
	Treatment Allocation (Placebo) x Week 0	0.444[a]	0.098	0.252	0.637	1	<0.001
Treatment Allocation (Vortioxetine) x Week 8	Treatment Allocation (Placebo) x Week 8	0.260[a]	0.118	0.029	0.492	1	0.028
QIDS-SR16[b]							
Treatment Allocation (Placebo) x Week 8	Treatment Allocation (Placebo) x Week 0	−1.756[a]	0.503	−2.742	−0.769	1	<0.001
Treatment Allocation (Vortioxetine) x Week 8	Treatment Allocation (Vortioxetine) x Week 0	−3.351[a]	0.524	−4.378	−2.323	1	<0.001
	Treatment Allocation (Placebo) x Week 0	−3.272[a]	0.491	−4.234	−2.309	1	<0.001
Treatment Allocation (Vortioxetine) x Week 8	Treatment Allocation (Placebo) x Week 8	−1.516[a]	0.679	−2.847	−0.185	1	0.026
WHO-5[b]							
Treatment Allocation (Placebo) x Week 8	Treatment Allocation (Placebo) x Week 0	1.107	0.590	−0.0497	2.263	1	0.061
Treatment Allocation (Vortioxetine) x Week 8	Treatment Allocation (Vortioxetine) x Week 0	3.472[a]	0.600	2.297	4.647	1	<0.001
	Treatment Allocation (Placebo) x Week 0	3.463[a]	0.589	2.308	4.618	1	<0.001
Treatment Allocation (Vortioxetine) x Week 8	Treatment Allocation (Placebo) x Week 8	2.356[a]	0.807	0.774	3.938	1	0.004
Treatment Allocation (Placebo) x Week 8[d]	Treatment Allocation (Placebo) x Week 0	0.664	0.528	−0.370	1.698	1	0.208
Treatment Allocation (Vortioxetine) x Week 8[d]	Treatment Allocation (Vortioxetine) x Week 0	1.759	0.489	0.802	2.717	1	<0.001
	Treatment Allocation (Placebo) x Week 0	1.902	0.430	1.059	2.744	1	<0.001
Treatment Allocation (Vortioxetine) x Week 8[d]	Treatment Allocation (Placebo) x Week 8	1.238	0.599	0.0647	2.412	1	0.039

Pairwise comparisons of estimated marginal means based on the original scale of dependent variables: combined DSST (composite z-score of the combined Pen/Paper & Online CogState Versions; if participants completed both test versions, the Online CogState Version was used), total QIDS-SR16, and total WHO-5.

[a]The mean difference is significant at the 0.05 level.

[b]Unadjusted model.

[c]Adjusted model.

[d]Represents the effects of vortioxetine on WHO-5 total score, moderated by QIDS-SR-16 total score.

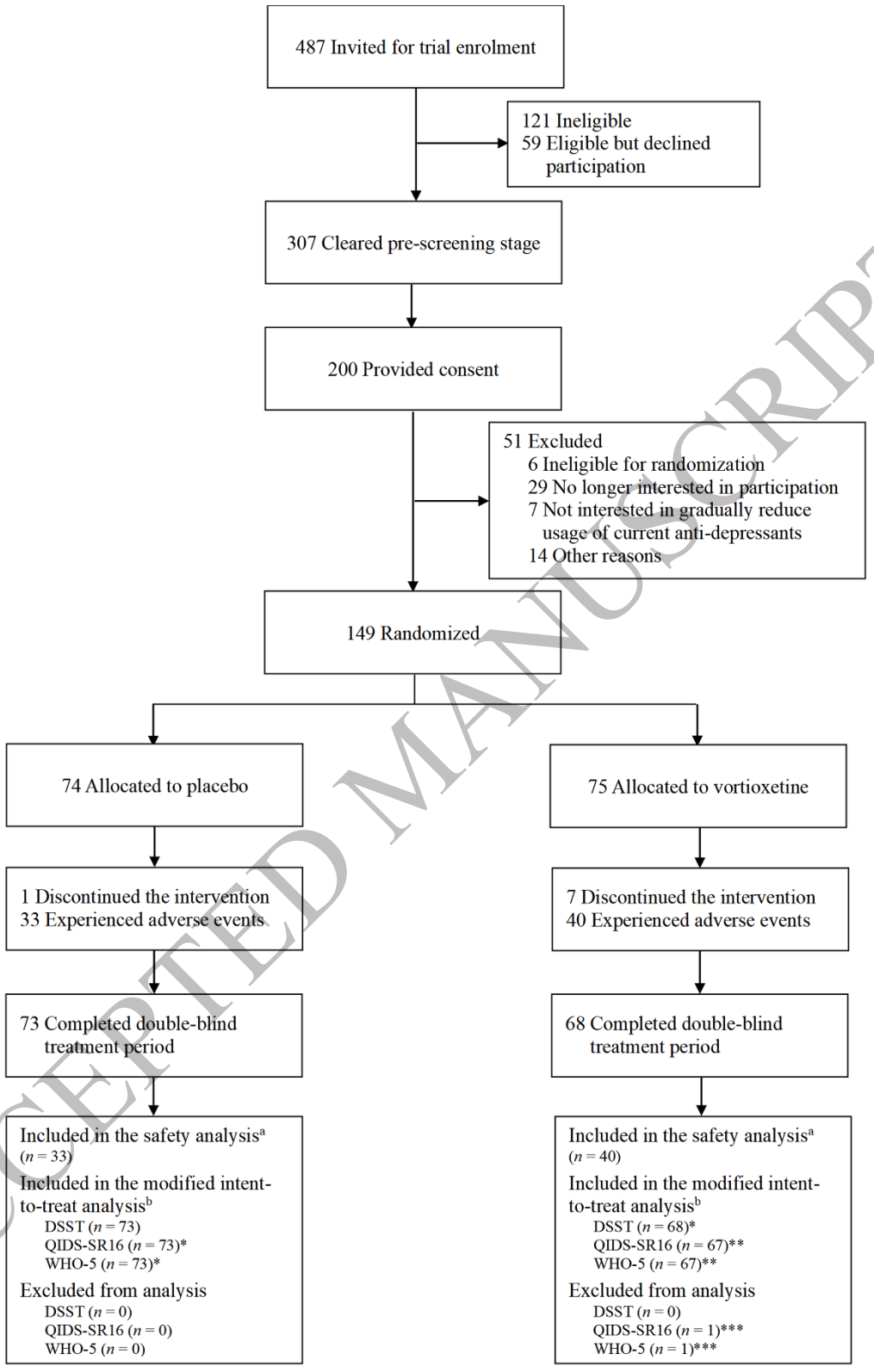

Figure 1
179x280 mm (x DPI)

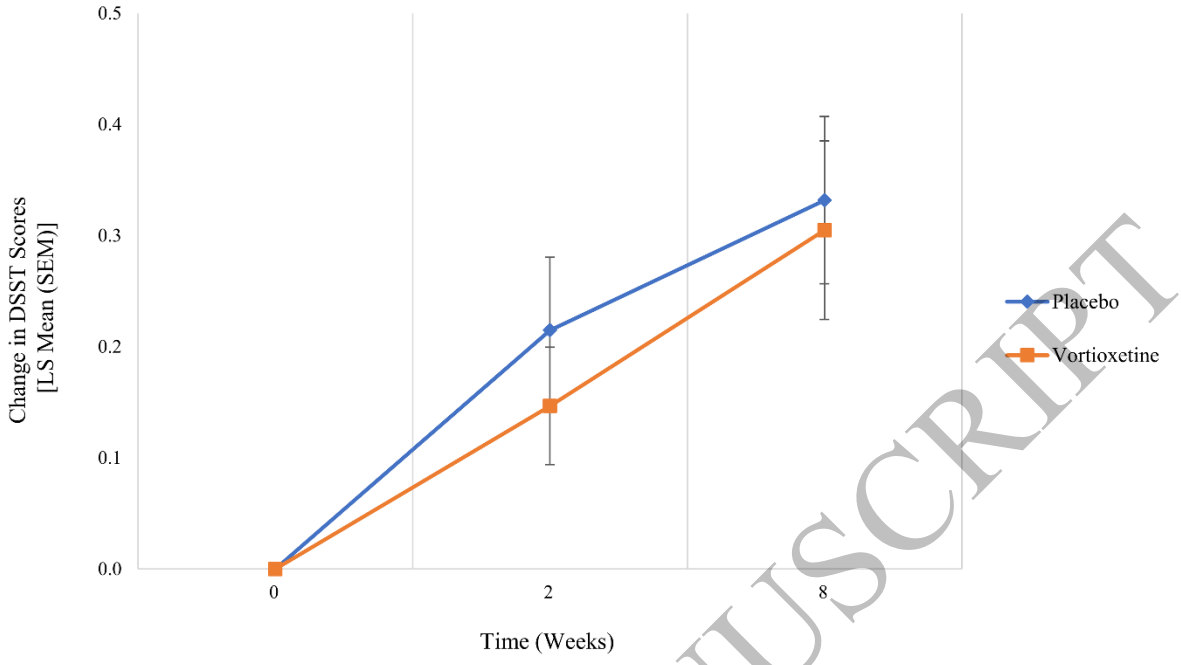

Figure 2
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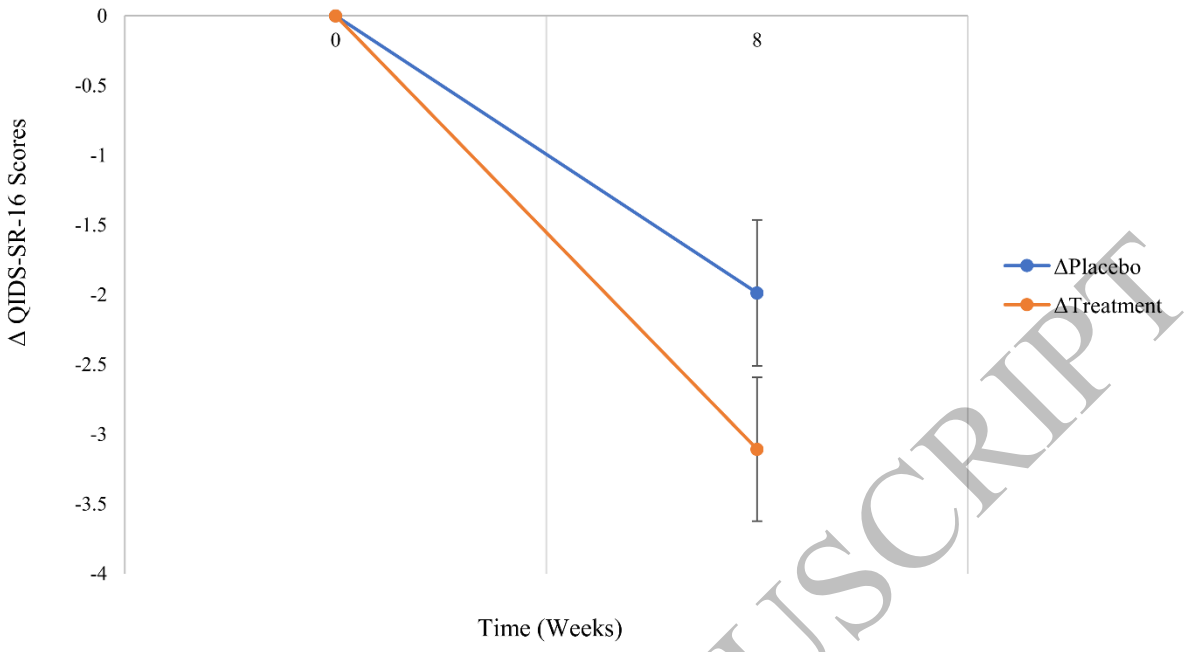

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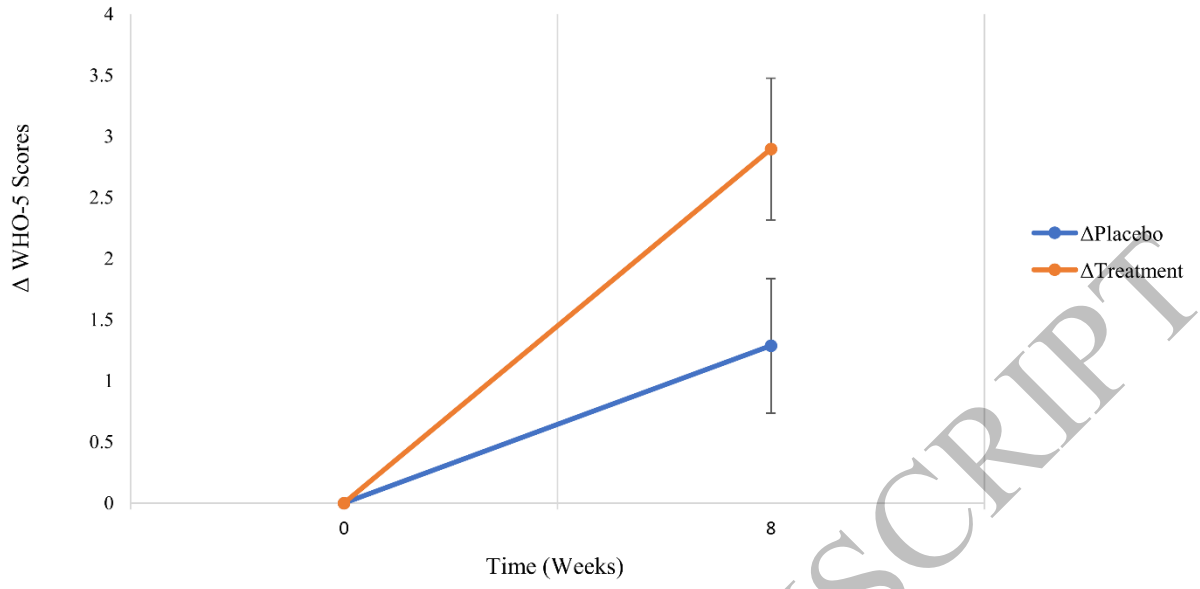
2 *Figure 3*

3 *185x105 mm (x DPI)*

4



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2 *Figure 4*
3 *185x94 mm (x DPI)*