Randomized, Double-Blinded, Placebo-Controlled Study Evaluating Vortioxetine for Cognitive Deficits in Persons with Post-COVID-19 Condition (Protocol Number: BCDF002)

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Background

Since the World Health Organization (WHO) declaration of COVID-19 as a global pandemic in March 2020, it is estimated that over 375 million people have tested positive for the virus globally

[1]. Consensus exists that the true infection rate is considerably higher, with estimates of approximately 5-10 fold greater, suggesting 1.9 to 3.75 billion persons have been infected with COVID-19. A significant percentage of individuals who have recovered from acute COVID-19 infection present with unabating, non-specific, distressing, and functionally impairing symptoms (i.e., post-COVID-19 condition) [1,23]. Commonly reported symptoms include, but are not limited to, cognitive impairment (e.g., "brain fog"), fatigue, apathy, depression, anxiety, insomnia, anergia, and loss of appetite [4,5]. Toward the aim of identifying a common nomenclature and case definition, the World Health Organization (WHO) has recently proposed the moniker 'post COVID-19 condition' [6]. It is estimated that approximately 10-30% of persons infected with COVID-19 experience characteristic symptoms persisting for more than 12 weeks following documentation of positive COVID-19 diagnosis [2,6].

Consensus exists that the phenomenology of post-COVID-19 condition is subserved by disturbance in immune-inflammatory systems [7]. Currently, no treatment is identified as safe and effective for post-COVID-19 condition [7,8]. A candidate treatment for post-COVID-19 condition should be capable of improving measures of cognitive function (i.e., objective and subjective), motivation and energy, as well as reducing fatigue [7–9]. The rationale for prioritizing cognition as a primary therapeutic target is based on a concatenation of study results reporting that cognitive complaints/deficits and fatigue are some of the most common and debilitating features of post-COVID-19 condition [10–12]. The candidate treatment would be preferred to target biological systems subserving circadian rhythms, as well as reward and reinforcement brain mechanisms. The profile of the candidate treatment should also have preliminary evidence documenting favourable modulatory effects on circulating pro-inflammatory cytokines, as well as immune cellular systems (e.g., macrophages). Preliminary evidence suggests that some antidepressants (e.g., SSRIs) are capable of reducing respiratory complications secondary to COVID-19 [13,14]. Putative mechanisms implicated include sigma-1 agonism and acid sphingomyelinase [13]. A limitation of SSRIs, however, for specifically targeting post-COVID-19 condition, is that they are not proven to be pro-cognitive and/or beneficial for reward systems and are, instead, reported to have, in some cases, dyscognitive and reward blunting effects (e.g., emotional blunting) [13,15–17].

Vortioxetine is established as pro-cognitive, as evidenced by significant improvement on both subjective and objective measures [1819,20]. Vortioxetine is also documented to improve anticipatory and consummatory measures of reward function/anhedonia as evaluated by validated reward paradigms, as well as the Snaith Hamilton Pleasure Scale (SHAPS) [21,22]. Vortioxetine also improves general functioning [18]. Furthermore, vortioxetine has demonstrated significant improvement on measures of motivation and energy [23,24]. Moreover, vortioxetine is not associated with emotional blunting and has preliminary evidence of improving sleep behaviour and circadian rhythms [23,25]. The candidacy of vortioxetine as an effective treatment for post-COVID-19 condition is also strengthened by evidence indicating that vortioxetine exerts modulatory effects on cellular and cytokine systems known to be activated in persons with post-COVID-19 condition [26,27].

Hypotheses

Herein, we hypothesize that vortioxetine (5-20 mg) will be more effective than placebo in the treatment of cognitive impairment in persons with post-COVID-19 condition.

Study Design

Eight-week, randomized, double-blinded, placebo-controlled clinical trial

- Eight-week intervention (i.e., weeks 0-8)
- Two-week drug discontinuation and safety follow-up period (i.e., weeks 8-10)

Primary Endpoint: Week 8

Outcomes

Primary Outcomes

- Baseline-to-endpoint (i.e., Week 8) change in Digit Symbol Substitution Test (DSST) (Pen/Paper Version and Online CogState Version as part of the CogState Online Cognitive Battery). Remote participants will not complete the pen/paper version of the DSST.

Secondary Outcomes

- Baseline-to-endpoint change in:
    - CogState Online Cognitive Battery
    - Trails Making Test (TMT)-A/B
    - Rey's auditory verbal learning test (RAVLT)
    - Perceived Deficits Questionnaire, 20-item (PDQ-20)
    - Fatigue Severity Scale (FSS)
    - Snaith Hamilton Pleasure Rating Scale (SHAPS)
    - Generalized Anxiety Scale, 7-item (GAD-7)
    - World Health Organization Wellbeing Scale, 5-item (WHO-5)
    - EuroQol, 5-dimension, 5-level (EQ-5D-5L)
    - Sheehan Disability Scale (SDS)
    - Post-Covid Functional Scale (PCFS)
    - fMRI and the Effort Expenditure for Rewards Task (EEfRT)
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    - Behavioural Activation Scale (BAS)
    - International Physical Activity Questionnaire (IPAQ)
    - Quick Inventory of Depressive Symptomatology (16-Item) (Self-Report) (QIDS-SR16)
- Safety outcomes
    - Spontaneously reported adverse events
    - Laboratory (including but not limited to CBC, TSH, electrolytes)

Study Population

Inclusion Criteria

- Age 18+
- Meets WHO-defined post-COVID-19 condition
    - WHO definition: ‘Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of

COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.' [6]

  - To ensure the above criteria is met, participants will only be included in the study if they meet all eligibility criteria more than 12 weeks from their confirmed and documented positive polymerase chain reaction (PCR) SARS-CoV-2 test, rapid antigen, or antibody test. In lieu of a prior positive test, a signed confirmation of a presumptive prior COVID-19 case from a healthcare provider, including the study physician, is acceptable.

- Documented history of SARS-CoV-2 infection with typical symptoms, and requiring positive SARS-CoV-2 test (PCR,antigen, or serology) at some point during the course of the acute course of illness. In lieu of a prior positive test, a confirmation of a presumptive prior COVID-19 case from a healthcare provider, including the study physician, is acceptable.
- Subjective cognitive complaints as detected by the Perceived Deficits Questionnaire (PDQ)-5.
- Ability to provide written informed consent.
- Resident of Canada.

Exclusion Criteria

- Current symptoms are fully explained by major depressive disorder or bipolar disorder.
- Pre-existing conditions that may cause cognitive impairment, or symptoms similar to those seen in post-COVID-19 condition (e.g., ADHD, major neurocognitive disorder, schizophrenia, chronic fatigue syndrome [CFS]/ encephalitis meningitis [EM]), as assessed by Mini International Neuropsychiatric Interview (MINI) 7.0.2.
- Inability to follow study procedures.
- Known intolerance to vortioxetine and/or prior trial of vortioxetine with demonstrated inefficacy.
- If participants are currently taking other antidepressants, they will be asked to discontinue the antidepressant for 2-4 weeks in order to participate in the study.
- Patients on other antidepressants are allowed to participate only if the antidepressant is prescribed at subtherapeutic doses for a primary indication other than mood disorders. Participants will be made aware in the consent form that the combination of the two antidepressants would be considered investigational and that the safety/efficacy profiles are unknown [28–30].
- Current alcohol or substance use disorder.
- Inability to provide consent.
- Current alcohol and/or substance use disorder as confirmed by the M.I.N.I 7.0.2.
- Presence of comorbid psychiatric disorder that is a primary focus of clinical concern as confirmed by the M.I.N.I. 7.0.2.
- Medications approved and/or employed off-label for cognitive dysfunction (e.g., psychostimulants).

- Any medication for a general medical disorder that, in the opinion of the investigator, may affect cognitive function.
- Use of benzodiazepines within 12 hours of cognitive assessments.
- Consumption of alcohol within 8 hours of cognitive assessments.
- Physical, cognitive, or language impairments sufficient to adversely affect data derived from cognitive assessments.
- Diagnosed reading disability or dyslexia.
- Clinically significant learning disorder by history.
- Electroconvulsive therapy (ECT) in the last 6 months.
- History of moderate or severe head trauma (e.g., loss of consciousness for >1 hour), other neurological disorders, or unstable systemic medical diseases that in the opinion of the investigator are likely to affect the central nervous system.
- Pregnant and/or breastfeeding.
- Received investigational agents as part of a separate study within 30 days of the screening visit.
- Actively suicidal/presence of suicidal ideation or evaluated as being at suicide risk (as per clinical judgment).
- Currently receiving treatment with Monoamine Oxidase Inhibitors (MAOIs) antidepressants, antibiotics such as linezolid, or intravenous methylene blue.
- Previous hypersensitivity reaction to vortioxetine or any components of the formulation. Angioedema has been reported in patients treated with vortioxetine.
- Serotonin syndrome.
- Abnormal bleeding.
- Previous history of mania/hypomania.
- Angle closure glaucoma.
- Hyponatremia.
- Moderate hepatic impairment.
- Active seizure disorder/epilepsy, not controlled by medication (per study physician assessment).
- Presence of any unstable medical conditions.

Recruitment

Recruitment will take place via media announcements (e.g., print, social media, public broadcasting stations). Announcement of study recruitment will also be provided to primary health care providers in Canada.

Study Visits

Study visits may be conducted remotely (e.g. zoom), by telephone or in-person. Visits with the study physician will primarily occur via a secure online platform (e.g. OTN) or by telephone. If required/requested, in-person visits with the study physician may be scheduled.

Participants may be emailed a secure, unique and anonymized RedCap link to complete self-report questions at home within 24 hours of their scheduled visit (before or after visit). This is to reduce participant burden during the visit with research staff/study physicians. Participants will

be asked to complete self-report questionnaires at the same time block of the day during all study visits (i.e. all mornings, afternoons or evenings).

Pre-Screen

Participants will be pre-screened via telephone, email, or an online form to determine if they meet above noted inclusion and exclusion criteria.

Screening Visit (Visit 0)

Once participants provide written, informed consent, they will undergo a comprehensive assessment to determine eligibility during the screening visit. Details of assessments completed are included in Table 1.

Baseline (Visit 1)

Participants will undergo the various assessments listed in Table 1. In addition, participants will have their blood drawn and may be invited to participate in an optional fMRI scan (see details below). Participants will also be assessed by a study physician at one time point between the screening and baseline visits and be provided a prescription for vortioxetine. Research staff (i.e.research coordinators/research assistants) will dispense the medication to the participant based on the direction from the study physician/prescription from the study physician for the first two weeks of the study. For remote participants, research staff will mail medication for the first two weeks of the study with appropriate temperature monitoring.

Laboratory Assessment: Participants will be asked to fast for 8 hours prior to their baseline (visit 1) and week 8 (visit 4). Participants will have blood drawn for standard clinical parameters. These include glucose, insulin, electrolytes, liver and kidney function tests, lipids, CBC, inflammatory markers (e.g. CRP, ESR), albumin and protein. Participants may also have their blood drawn for various exploratory secondary analyses (e.g. cytokines). Approximately 20 mL of blood will be drawn in 4-5 blood tubes. Two of these tubes will include lavender tubes with EDTA for exploratory analyses. A urine or blood pregnancy test will be conducted for all female participants.

Remote participants will be provided a blood requisition form via email or mail to have clinical blood drawn and analyzed at the participant's local blood lab facility. Blood will not be collected for exploratory purposes from remote participants. Female participants may provide a blood or urine sample to the local blood lab to confirm non-pregnancy. Participants may also be mailed a home pregnancy test.

Exploratory Blood Analyses: For participants seen in-person, they will be able to volunteer to provide a blood sample for exploratory analyses. The sample will be collected at a local blood lab (e.g. Mount Sinai Hospital), followed by processing and storage of the sample at the Biospecimen Repository and Processing Lab (Lunenfeld-Tanenbaum Research Institute, Sinai Health). Participants may also have blood drawn at the same time for clinical purposes at Mount Sinai Hospital. The clinical blood tubes will be delivered to another local lab (e.g.Dynacare, LifeLabs) for analyses. Alternatively, participants may also have blood drawn separately for clinical analyses at a local blood lab near them - this will result in two separate blood draws.

fMRI: A subset of participants may be offered the opportunity to have an fMRI scan completed at baseline and endpoint for secondary, exploratory purposes. This is optional and not the primary focus of the study. Participants may still participate in the study and decide not to participate in this component. During the imaging, participants will be asked to complete a cognitive task (e.g. Effort Expenditure for Rewards Task, Trails Making Test A/B). Participants will be awarded the amount of money they earn during this task, on top of the standard compensation to all participants. Please see "Participant Compensation" for more details.

Week 2 (Visit 2): Participants will complete items listed in Table 1, Week 2 (Visit 2). The study physician will determine if the participant is eligible for a dose increase. Research staff (i.e.research coordinators/research assistants) will dispense medication to the participant based on the direction from the study physician/prescription from the study physician for the next six weeks of the study. For remote participants, medication for the remaining six weeks of the study will be mailed out as well as medication for discontinuation by research staff with appropriate temperature monitoring.
Week 4 (Visit 3): Participants will complete items listed in Table 1, Week 4 (Visit 3).

Week 8 (Visit 4): Participants will complete items listed in Week 8 (Visit 4). The study physician will also discuss transition of care (see below) and/or medication continuation. Participants will also have their blood drawn and may be asked to participate in the optional fMRI scan.

Optional Post-Study (Week 10): Clinical visit with physician if the participant is discontinuing the study medication and/or as needed. If a participant chooses to continue with the study medication, he/she will be asked to follow up with his/her most responsible physician (MRP) for ongoing care and this post-study visit would not be needed. Participants will be informed prior to signing the consent form that research staff/research physician will not be able to tell them if they received drug or placebo when they finish the study at week 8 and they will have to wait until the entire study is complete to find out.

Table 1. Study schedule with assessments

Study Visit	**Screening (Visit 0)**	**Baseline (Visit 1)**	**Visit 2**	**Visit 3**	**End-of-study (Visit 4)**
Week	(-1 to -21 days from baseline)	**0**	**2** (+/- 2 days)	**4** (+/- 2 days)	**8** (+/- 2 days)
Consent	X				
Inclusion/Exclusion	X				
Demographics	X				
Past COVID-19 Infection Information	X				

M.I.N.I 7.0.2	X				
Psychiatric/Medical History	X				
Lifestyle Factors	X				
Current Medications	X	X	X	X	X
Medication Changes	X	X	X	X	X
Adverse Events		X	X	X	X
Anthropometrics		X	X		X
MoCA		X			
SETS		X			
DSST		X	X		X
TMT-A/B		X	X		X
RAVLT		X	X		X
CogState Online Cognitive Battery**		X	X		X
PDQ-20		X	X	X	X
GAD-7		X	X	X	X
SHAPS		X	X	X	X
FSS		X	X	X	X
WHO-5		X	X	X	X
SDS		X	X	X	X
BAS		X	X	X	X
EQ-5D-5L		X	X	X	X
QIDS-SR16		X	X	X	X
IPAQ		X		X	X
PCFS	X	X	X	X	X
EEfRT		X			X

Physician Assessment*	X		X	X	X
Laboratory assessments		X			X
fMRI + Cognitive Test		X			X

Abbreviations: [a]: BAS: Behavioural Activation Scale; DSST: Digit Symbol Substitution Test; EQ-5D-5L: 5-Level EQ-5D version; fMRI: functional magnetic resonance imaging; FSS: Fatigue Severity Scale; GAD-7: Generalized Anxiety Disorder, 7-item; IPAQ: International Physical Activity Questionnaire; EEfRT: Effort Expenditure for Rewards Task ; M.I.N.I: Mini-International Neuropsychiatric Interview; MoCA: Montreal Cognitive Assessment; PCFS: Post-Covid Functional Scale; PDQ-20: Perceived Deficits Questionnaire, 20-item; Quick Inventory of Depressive Symptomatology (16-Item) (Self-Report) (QIDS-SR16); RAVLT: Rey's auditory verbal learning test; RPE: Borg Rating of Perceived Exertion Scale; SDS: Sheehan Disability Scale; SETS: Stanford Expectations of Treatment Scale; SHAPS: Snaith-Hamilton Pleasure Scale; TMT-A/B: Trails Making Test-A/B; WHO-5: World Health Organization Well-Being Index, 5-item.
*One physician assessment will be conducted between the baseline and screening visit.
**May be conducted remotely.

Sample Size

- Total recruitment N=200 (i.e., 100 subjects allocated to vortioxetine [5-20 mg] and placebo each).
- The target sample size is based on effect sizes reported by previous clinical trials that evaluated the efficacy of antidepressants vs placebo and nutraceuticals in individuals with chronic fatigue syndrome [6,23–25].
- The effect size of vortioxetine on DSST-measured cognitive function is estimated at approximately 0.2-0.5 [2627]. Previous experience without patients enrolled in clinical trials (investigator-initiated trials) with vortioxetine as part of the THINC-it tool validation indicated that vortioxetine improves measures of processing speed (the prominent domain validated by the DSST) of significance with a sample size of 200.
- It is then estimated that a sample size of 100 per treatment arm would detect clinically relevant change with vortioxetine treatment on DSST as the dependent measure [27,31].

Feasibility

- It is estimated, based on prior general population research conducted by the BCDF, that recruitment will take approximately 12 months.
- Community research ethics board approval, 2-4 weeks (BCDF is an independent research center not requiring university- or hospital-based REB reviews).

Description of Study Procedures

Efficacy Assessments

Digit Symbol Substitution Test (DSST)
The DSST is a neuropsychological test sensitive to brain damage, dementia, age and depression.[32,33]. The DSST consists of digit-symbol pairs followed by a list of digits. The participant will select the corresponding symbol as fast as possible. The number of correct symbols within 90 seconds will be recorded. The test is administered by trained personnel. The DSST will be administered at baseline (visit 1), and weeks 2 and 8 visits.

Rey Auditory Verbal Learning Test (RAVLT)
The RAVLT is a neuropsychological assessment designed to evaluate verbal memory in patients aged 16 years and older [34]. It is presented as a list-learning paradigm wherein the participant is read a list of 15 nouns and is asked to recall as many words from the list as possible. After five repetitions of free-recall, a second "interference" list (List B) is presented in the same manner, and the participant is asked to recall as many words from List B as possible. After the interference trial, the participant is immediately asked to recall the words from List A, which they have heard five times previously. After a 20 min delay, the participant is asked to again recall the words from List A. This assessment directly tests recognition memory, as opposed to free-recall. The test is administered by trained personnel. The RAVLT will be administered at baseline (visit 1), and weeks 2 and 8 visits.

Trail Making Tests A/B (TMT-A/B)
The TMT-A/B are well established tests sensitive to impairment in multiple cognitive domains, including attention, visual memory and processing speed, executive functioning, and overall cognitive functioning. The tests are administered by a trained personnel. Participants are asked to connect circles in numerical sequence as part of TMT-A and in alternating numerical and alphabetical sequence as part of TMT-B (e.g., 1-A-2-B). If a participant makes a mistake, the administrator points out the error, and the participant must return to the last correct circle and continue the task. The tests are timed and participants are given five minutes to complete each test; a shorter time denotes higher performance [35]. The TMT- A/B will be administered at baseline (visit 1), and weeks 2 and 8 visits.

CogState Online Cognitive Battery
The CogState Online Cognitive Battery (https://www.cogstate.com/) employed in the present trial will consist of four tests:

Domain: Executive Function

1. Operation: Digit Symbol substitution test
   Cognitive Test: CogState DSST – Symbols - "In this test, subjects are presented with a legend that defines nine symbols, with each symbol corresponding to a digit from 1 to 9. The subject is then presented with a conveyor belt in the middle of the screen that displays a series of empty boxes labelled with a number. The subject must select the symbol that corresponds to the number of a given highlighted box from symbol options presented at the bottom of the screen. The subject must try to place as many correct symbols in the boxes as possible over the duration of the test." [36]

Time: 3 min

Domain: Attention

2. Operation: Choice Reaction Time
   Cognitive Test: CogState Detection Test - “The Detection test measures processing speed using a simple reaction time paradigm. The on-screen instructions ask: “Has the card turned over?”. A playing card is presented face down in the center of the screen. The card flips over so it is face up. As soon as the card flips over the participant must press “Yes”. The participant is encouraged to work as quickly as they can and be as accurate as possible.” [36]
   Time: 3 min
3. Operation: Choice Reaction Time
   Cognitive Test: CogState Identification Test - “The Identification test measures attention using a choice reaction time paradigm. The on-screen instructions ask: “Is the card red?”. A playing card is presented face down in the center of the screen. The card flips over so it is face up. As soon as it flips over the participant must decide whether the card is red or not. If it is red the participant should press “Yes”, and if it is not red the participant should press “No”. The participant is encouraged to work as quickly as they can and be as accurate as possible.” [36]
   Time: 3 min

Domain: Memory

4. Operation: Visual Learning
   Cognitive Test: CogState One Card Learning Test - “The One Card Learning test measures visual memory using a pattern separation paradigm. The on-screen instructions ask: “Have you seen this card before in this test?”. A playing card is presented face up in the center of the screen and the participant must decide whether they have seen the card before in this test. The participant is encouraged to work as quickly as they can and be as accurate as possible.” [36]
   Time: 6 min

Each participant will be completing the battery twice on the same day to assess test reliability and as an objective measure of fatigue.The CogState Online Cognitive Battery will be administered at baseline (visit 1), and weeks 2 and 8 visits.

Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR-16)
The QIDS-SR-16 [37] is a 16-item self-rated scale designed to assess the severity of depressive symptoms in the nine diagnostic symptom domains of a major depressive episode, exclusive of atypical or melancholic symptoms, over the past 7 days. The QIDS-SR-16 is sensitive to change with various treatments, demonstrating its utility in research settings. The total score ranges from 0 to 27 with 0 representing no depression and 27 representing severe depression. The total score is the sum of the 9 symptom domains. The QIDS-SR-16 will be administered at baseline, and weeks 2, 4, and 8 visits.

Patient Health Questionnaire, 9-item (PHQ-9)

The PHQ-9 is a self-rated measure of depressive symptom severity in the past two weeks. Each of the nine items is rated on a Likert scale, ranging from 0 (not at all) to 3 (nearly every day), and summed for a total score between 0 (no symptoms) to 27 (most severe) [38]. The standardized cut-off scores are ≥5, 10, 15, and 20 for mild, moderate, moderate-severe, and severe symptoms, respectively. The PHQ-9 will be administered at baseline, and weeks 2, 4, and 8 visits.

Perceived Deficits Questionnaire, 20-item (PDQ-20)

The PDQ-20 is a self-report measure originally developed for the assessment of cognitive impairment in the past two weeks for multiple sclerosis [39]. It is a 20-item questionnaire that generates 4 subscale scores (attention/concentration, retrospective memory, prospective memory, and planning/organization), and a total score which is the sum of the scores for the 20 items. Each item is rated on a 5-point scale ranging from 0 (never) to 5 (almost always). The combined subscales yield a total score ranging from 0 to 80, with a higher score indicating greater perceived cognitive impairment. The PDQ-20 will be administered at baseline, and weeks 2, 4, and 8 visits.

Snaith-Hamilton Pleasure Scale (SHAPS)

The SHAPS is a self-report measure designed to assess the degree to which a person is able to experience pleasure or the anticipation of a pleasurable experience [40]. It includes 14 items involving four domains of hedonic experience: interest/pastimes, social interaction, sensory experience, and food/drink. Each item has four possible responses: strongly disagree, disagree, agree, or strongly agree. For each item, a score of 2 or less constitutes a “normal” score, while an “abnormal” score is defined as 3 or more, and the final score ranges from 0 to 14 [41]. The SHAPS will be administered at baseline, and weeks 2, 4, and 8 visits.

Generalized Anxiety Disorder Scale, 7-item (GAD-7)

The GAD-7 is useful in primary care and mental health settings as a screening tool and symptom severity measure for the seven most common anxiety disorders [42]. Participants choose one of 4 severity scores (i.e., 0: not at all, 1: several days, 2: more than half the days, 3: nearly every day) associated with problems related to the common anxiety disorders and then indicate the degree to which these problems caused functional and/or social difficulties over the past two weeks. Scores are determined by calculating the values for each column. The minimum score is 0 and the maximum score is 32, where higher scores indicate worse anxiety. The GAD-7 will be administered at baseline, and weeks 2, 4, and 8 visits.

EQ-5D, 5-level (EQ-5D-5L)

The EQ-5D is a standardized measure of health status for clinical and economic appraisal that was developed by the EuroQol Group. The 5-level version of the EQ-5D (i.e., EQ-5D-5L) consists of a descriptive system and a visual analogue scale and has been validated in 34 countries, including Canada [43,44]. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five

response levels: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems, and the participant is asked to rate their present health (i.e., “your health today”). Responses are coded as single-digit numbers expressing the severity level selected in each dimension, ranging from 1 (no problems) to 5 (extreme problems). A participant’s self-rated health is recorded on a vertical visual analogue scale (range 100 to 0), where the endpoints are labelled ‘The best health you can imagine’ (100) and ‘The worst health you can imagine’ (0). EQ-5D-5L health states can be summarized to derive how good or bad a health state is according to the preferences of the general population of a country/region. The EQ-5D-5L will be administered at baseline, and weeks 2, 4, and 8 visits.

World Health Organization Well-Being Index, 5-item (WHO-5)
The WHO-5 is a measure of overall well-being, rated on a scale of 0 to 25, with higher scores denoting higher quality of life in the past two weeks [45]. There are five items, each rated on a five-point Likert scale (5-All the time to 0-At no time). A score below 13 denotes poor wellbeing. A ≥10% difference denotes a significant change. The WHO-5 will be administered at baseline, and weeks 2, 4, and 8 visits.

Fatigue Severity Scale (FSS)
The Fatigue Severity Scale (FSS) is a self-rated 9-item measure used to evaluate the impact of fatigue within the last week [46]. Responses to the FSS are based on the past week and each statement may be rated from a scale of 1 to 7 where 1 represents “disagree” and 7 represents “agree”. The minimum score that can be achieved from this scale is 9, and the maximum is 63. A total score of 36 or more suggests the presence of fatigue.The FSS will be administered at baseline, and weeks 2, 4, and 8 visits.

Behaviour Inhibition System/Behavioural Activation System (BIS/BAS)
The behaviour inhibition system (BIS)/ behavioural activation system (BAS) is a 24-item self-report questionnaire [47]This questionnaire assesses aversion to threat as well as reward-seeking behaviour. Items are based on a 4-point Likert scale ranging from 1 (i.e, very true for me) to 4 (very false for me). Items 1, 6, 10, 13, 15, 18 and 20 represent BIS (i.e., punishment sensitivity scale). Items 3, 5, 11, 14 and 19 represent the BAS Reward Responsiveness. Items 2, 7, 9 and 17 represent BAS drive (i.e., motivation and pursuit to achieve goals). Items 4, 8, 12 and 16 represent BAS Fun Seeking (i.e., to seek new reward as well as obtain it spontaneously). BIS/BAS scores may be calculated based on the sum of each subsection.The BIS/BAS will be administered at baseline, and weeks 2, 4, and 8 visits.

International Physical Activity Questionnaire (IPAQ)
The International Physical Activity Questionnaire (IPAQ) is a 7-item scale that measures various intensities of physical activity as well as sitting time based on the past 7 days [48]. The minimum number of days is 0 and the maximum number of days is 7. The IPAQ is administered by research staff at baseline, week 4 and week8 visits.

Post-COVID-19 Functional Status Scale (PCFS)

The Post-COVID-19 Functional Status (PCFS) scale assesses present functional ability (i.e., "in your current daily life") as it relates to daily activities (including work and/or school) [49]. The PCFS is based on a grading system wherein the lowest grade 0 indicates no limitations/symptoms and the highest grade 4 represents the most limitations. The PCFS will be administered at baseline, and weeks 2, 4, and 8 visits.

Effort-Expenditure for Rewards Task (EEfRT)

The Effort-Expenditure for Rewards Task (EEfRT) is a multi-trial task that measures reward and motivation [50]. Participants are given an opportunity to earn a monetary reward based on successful completion of a task under various reward probabilities. In each trial, participants may choose to complete either the "easy task" or "hard task". To complete the "easy task", the participant must use their dominant index finger and press the space bar 30 times within 7 seconds. To complete the "hard task", the participant must use their non-dominant little fingers and press the bar 100 times within 21 seconds. The value associated with the "easy task" is $1 while the value associated with the "hard task" may vary from $1.24-$4.30. However, successful completion of the task does not guarantee delivery of the monetary reward. More specifically, a probability is applied to the each trial and the probability varies from trial to trial. . This probability and the monetary value associated with a particular trial's "easy" and "hard" tasks is presented to the participant so they may make an informed decision as to which task they would like to complete. The EEfRT will be administered at baseline and week 8 visit. Participants are notified before they start the EEfRT task that they will be awarded the entire monetary value they earn from completing this task.

fMRI

Individuals who participate in the fMRI will complete a cognitive task (e.g., EEfRT, TMT A/B) to obtain various functional, physiological and anatomical measurements. This is a secondary measure in this study and the data will be used for various exploratory analyses. Analyses may include standard anatomical examination, magnetic resonance spectroscopy (MRS) to measure brain chemistry; diffusion tensor imaging (DTI) to measure the electrical connections between neurons and arterial spin labelling (ASL) to measure blood flow in the small vessels of the brain.

Exploratory Blood Analyses

Plasma samples will be collected and stored for exploratory analyses. Please see above "Baseline (Visit 1)" for further description of the procedure.

Safety Assessments

Clinical Laboratory Tests

Blood samples will be obtained at baseline for routine laboratory test:

- Haematology: complete blood count (CBC)
- Biochemistry: hemoglobin A1c (HbA1C), Sodium, Potassium, Lipid Assessment (includes cholesterol, HDL-C, Triglycerides, calculated LDL-C & Chol/HDL-C ratio)
- Other tests: Chloride, Bicarbonate, C-reactive peptide (CRP), erythrocyte sedimentation rate (ESR), estimated glomerular filtration rate (EGFR)

- hCG pregnancy screen (as applicable)

A urine pregnancy test will be administered if no hCG pregnancy screen has been conducted.

In the event of an unexplained clinically significant abnormal laboratory test value, the test should be repeated and will be followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

Adverse Events
All AEs occurring after the participant signs the ICF and up to the last study event will be recorded. Any unresolved AEs that are ongoing at the end of the study will be followed until resolution or no longer considered clinically significant by the investigator.

Other Assessment Instruments

Mini International Neuropsychiatric Interview Version 7.0.2 (M.I.N.I. Version 7.0.2)
The MINI was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-5 and International Classification of Diseases-10. Validation and reliability studies have been done comparing the MINI to the Structured Clinical Interview for DSM-5 Patient Edition and the Composite International Diagnostic Interview (a structured interview developed by the World Health Organization). Version 7.0.2 of the MINI will be used for this study. The results of these studies show that the MINI has similar reliability and validity properties, but can be administered in a much shorter period (mean 18.7 ± 11.6 min, median 15 min) than the above referenced instruments. It can be used by clinicians after a brief training session. At screening, participants will be assessed for MDD and BD, as documented by DSM-5 criteria, and the lack of other psychiatric diagnoses will be confirmed by use of the MINI.

Montreal Cognitive Assessment (MoCA)
The MoCA is a 10-minute cognitive screening tool designed to detect mild cognitive impairment [51]. The MoCA evaluates short-term memory recall, visuospatial abilities, executive functioning, attention, concentration, and working memory, language, and orientation to time and place. It is a one-page 30-point test. In clinical practice, patients screened and found to have a MoCA score over 26 would be extremely unlikely to meet clinical and neuropsychological criteria for MCI even after extensive evaluation. The MoCA demonstrates high test-retest reliability, and good internal consistency, and there is a close correlation between MoCA and MMSE scores. Version November 7, 2004 will be administered by clinicians who have completed the official MoCA training and certification (https://www.mocatest.org/training-certification/). At baseline in-person visits, participants will be assessed for mild cognitive impairment (operationalized as a MoCA score <26).

Stanford Expectations of Treatment Scale (SETS)
The SETS is a self-report tool designed to measure patient outcome expectancy in clinical trials [52]. The six-item SETS contains two subscales: positive expectancy (α = 0.81–0.88) and negative expectancy (α = 0.81–0.86). Each of the six items includes 7 selection options: strongly disagree, moderately disagree, slightly disagree, neither agree nor disagree, slightly

agree, moderately agree, strongly agree. The positive and negative subscales demonstrate strong internal reliability and are able to predict post treatment response. Most participants are able to complete the SETS in approximately 1 min. The SETS will be administered at baseline visits.

Study Site

The study will be conducted at the Brain and Cognition Foundation (BCDF) main site in Toronto (77 Bloor St. West, Toronto, ON, M5S 1M2). BCDF is a non-profit organization engaged in research and educational activities as it relates to brain health and disease, including but not limited to studies in persons with mood disorders, as well as persons who are at-risk for mood disorders. BCDF conducts both proof-of-mechanism, as well as phase 1-3 clinical trials and is one of the most active clinical research organizations in the world based on bibliometrics. Study medication and placebo will be stored in a secured/locked cabinet and office at BCDF and medication will be dispensed by research staff per instruction/prescription of the study physician.

The study physician will be based out of the medical clinic at CRTCE/KJK HealthPlex in Mississauga. As part of participants' ongoing clinical monitoring and care, all participants will have a medical file opened for them at CRTCE/KJK HealthPlex. The study physician evaluating the participant will be documenting the visits in the participant's medical chart at CRTCE/KJK HealthPlex. The majority of the study visits with the study physician will be conducted remotely. However, in-person visits with the study physician may be scheduled at CRTCE/KJK HealthPlex upon the request of the participant or the study physician.

Participants will complete blood draws for clinical and exploratory blood analyses at a local laboratory near the BCDF office in Toronto. Exploratory blood samples will be stored at the Biospecimen Repository and Processing Lab (Lunenfeld-Tanenbaum Research Institute, Sinai Health). Please see "Baseline (Visit 1)" for more details.

fMRI scans are completed at an external institution (e.g. Sunnybrook Health Sciences Centre, University of Toronto). The research staff will inform participants where these scans will be taking place.

Remote Visits

Due to the ongoing COVID-19 pandemic, participants may choose to participate in the study completely remotely. Study visits will be conducted over online (e.g. Zoom) and telephone platforms. Visits with the study physician may be done over the secure Ontario TeleNetwork (OTN) or telephone. Participants will be mailed the study medication. Anthropometrics (e.g. height and weight) will be self-reported by participants. Participants will be mailed or emailed a lab requisition form to complete standard clinical blood tests at their local blood lab. Female participants will be asked to provide a urine or blood sample to confirm non-pregnancy. Female participants may also be mailed a home pregnancy test.

Study Flow

Study Flow

Vortioxetine Dose
18-64 years: Start at 10mg once daily (OD) for the first two weeks, then dosed up 20mg OD thereafter.

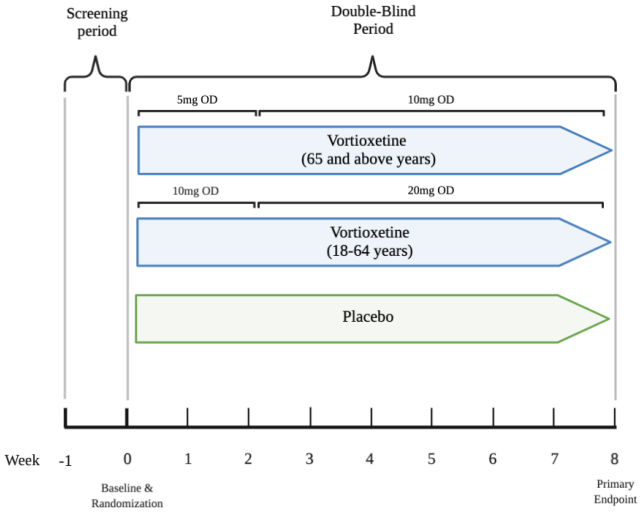
65 and above years: Administered 5mg OD for the first two weeks, then dosed up 10mg OD thereafter.

Primary Outcome
Digital Symbol Substitution Test (DSST) and CogState Online Cognitive Battery assessed at weeks 0, 2 and 8.

Secondary Outcome
fMRI and Effort-Expenditure for Rewards Task (EEfRT) assessed at weeks 0 and 8.

Trails Making Test-A and B (TMT-A/B) and Rey's Auditory Verbal Learning Test (RAVLT) assessed at weeks 0, 2 and 8.

Perceived Deficits Questionnaire-20 (PDQ-20), Generalized Anxiety Disorder-7 (GAD-7), Snaith-Hamilton Pleasure Scale (SHAPS), Fatigue Severity Scale (FSS), Post-Covid Functional Scale (PCFS), World Health Organization-5 (WHO-5), Sheehan Disability Scale (SDS), Behavioural Activation Scale (BAS), 5-Level EQ-5D version (EQ-5D-5L), Quick Inventory of Depressive Symptoms (16-Item) (Self-Report) (QIDS-SR16) and International Physical Activity Questionnaire (IPAQ) assessed at weeks 0, 2, 4 and 8.



Conditions for Withdrawal From the Study

Premature Discontinuation

If participation in the study is terminated prematurely for any reason, the reason for such early termination should be documented. The reason for any early termination should be recorded, providing as much information as possible.

The reason for early termination can be selected from as follows:

- Screen Failure: Participant does not qualify to participate in the study.
- Lack of efficacy (e.g., increased suicidality).
- Adverse Event: Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the participant, are grounds for discontinuation. This includes serious and non-serious AEs regardless of relation to study medication.
- Death: The participant died.
- Withdrawal of Consent: The participant desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the participant gave a reason for withdrawing, it should be recorded in the eCRF.
- Protocol Violation: The participant's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., drug non-compliance, failure to return for a defined number of visits, becoming pregnant during trial). The violation necessitated early discontinuation from the study.
- Lost to Follow-Up: The participant stopped coming for visits and study personnel were unable to contact the participant.

- Non-compliance: The participant was non-compliant with study visits or procedures.
- Other: The participant was discontinued for a reason other than those listed above.

Withdrawal Procedures and Next Steps

All data outlined in Table 1 will be collected for all participants up until and including the time of withdrawal from the study. Recruitment will occur for this study on an ongoing basis until 200 participants are recruited and have completed the study. Participants withdrawn from the study will follow the outlined "Transition to Standard Care" and "Medication Discontinuation Process" outlined below.

Participant Compensation

Compensation for In-Person Participants

Participants will receive $125 CAD at week 2 visits, $125 at week 4 visits and $250 at week 8 visit. Participants may also choose to receive the full $500 at the end of the study (week 8). Participants who complete the EEfRT task will be awarded their earnings from this task in addition to the $500. The EEfRT may also be administered as a stand alone assessment (i.e., outside of fMRI) or as part of the fMRI assessment. Participants who complete the EEfRT will be compensated with what they earn from this task in addition to the $500. Participants that complete exploratory blood work will also be compensated $50.

Compensation for Remote Participants

Participants will receive $31.25 CAD at week 2 visits, $31.25 at week 4 visits and $62.50 CAD at week 8 visit. Participants may also choose to receive the full $250 at the end of the study (week 8).

Study Medication: Vortioxetine

AGE: 18-64

Participants receiving vortioxetine will be provided 10 mg/day on days 1–14 of the treatment period, and will be titrated to 20 mg/day at the start of week 3 (day 15) based on study clinician judgment. For the remaining 6 weeks, the dose of vortioxetine will be 20 mg/day, unless adjudicated otherwise by a study clinician.

AGE: >65

Per product monograph, participants 65+ receiving vortioxetine will be provided 5 mg/day on days 1–14 of the treatment period, and will be titrated to 10 mg/day at the start of week 3 (day 15) based on study clinician judgment. For the remaining 6 weeks, the dose of vortioxetine will be 10 mg/day, unless adjudicated otherwise by a study clinician.

Age: 65

Individuals aged 65 may start at 5mg or 10mg on days 1-14, and this dose may be titrated to 10mg or 20mg, respectively, at the start of week 3 based on the recommendation of the study physician.

Vortioxetine will be encapsulated in a capsule shell made of Capsugel® empty hard gelatin capsule (non-porcine / pure-bovine origin). Colorant: Swedish Orange OpC307. Size: AA.

Excipients: Gelatin, Red Iron Oxide, Titanium Dioxide. The filler used for both the active capsule with vortioxetine and the entire placebo capsule is Capsulac® 60 Lactose Monohydrate (Ph.Eur/USP-NF/JP).

Individuals aged 65 may start at 5mg or 10mg on days 1-14, and this dose may be titrated to 10mg or 20mg, respectively, at the start of week 3 based on the recommendation of the study physician.

Side effects

- Serotonin Syndrome has been reported with serotonergic antidepressants (SSRIs, SNRIs, and others), including with vortioxetine both when taken alone, but especially when coadministered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort).
- Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase the risk of abnormal bleeding. Patients should be cautioned about the increased risk of bleeding when Vortioxetine is coadministered with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation.
- Activation of Mania/Hypomania can occur with antidepressant treatment.
- Angle Closure Glaucoma: Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants.
- Hyponatremia can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Most Common

- Gastrointestinal adverse events; including nausea, vomiting, constipation/diarrhea. Highest incidence occurs during the first week of treatment: 21-32%
- Sexual dysfunction: 14-34%

Less Common: 1-10%

- Dry mouth
- Dyspepsia (discomfort of the abdomen)
- Dizziness
- Somnolence/sedation
- Fatigue
- Insomnia
- Abnormal dreams
- Hyperhidrosis (increase sweating)
- Arthralgia (joint pain)
- Decreased appetite
- Itchy skin
- Nasopharyngitis

Rare: Less than 1%

- Nervous system disorders
- Skin and subcutaneous tissue disorders
- Psychiatric disorders
- Abnormal bleeding

- Clinical worsening or suicide risk

Post-Market Adverse Reactions

The following adverse events have been identified during post-approval use of Vortioxetine. These events are reported voluntarily from a population of uncertain size, and it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hyperprolactinaemia
- Acute pancreatitis
- Anaphylactic reaction
- Serotonin syndrome, headache
- Agitation, aggression
- Angioedema
- Hemorrhage (including contusion, ecchymosis, epistaxis, gastrointestinal or vaginal hemorrhage)

Please see product monograph for full details.

Contraindications

Hypersensitivity to vortioxetine or any components of the formulation. Angioedema has been reported in patients treated with vortioxetine. The use of monoamine oxidase inhibitors (MAOI) intended to treat psychiatric disorders with vortioxetine or within 21 days of stopping treatment with vortioxetine is contraindicated because of an increased risk of serotonin syndrome. The use of vortioxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated.

Starting vortioxetine in a patient who is being treated with MAOIs or antibiotics such as linezolid or
intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome.

Storage

Medication will be stored at room temperature in a locked cabinet and office space at BCDF (77 Bloor Street West, Suite 600, Toronto, ON, M5S 1M2).

Transition to Standard of Care

Patients will be informed of the transition to standard of care procedures (outlined here) post study prior to providing consent to participate in the study. These procedures will also be outlined in writing in the patient consent form itself.

Upon completing the 8-week course of vortioxetine, if patients benefit from this drug, they will be encouraged to continue the treatment with their most responsible physician (MRP). Patients will be notified prior to study consent that not all drug plans will cover the cost of vortioxetine. Should patients wish to continue to use this drug post-study when they do not have coverage, they will be personally responsible for the costs.

If patients do experience side effects during the study, the study physician will make a recommendation regarding the discontinuation or dose reduction of the medication for the

remainder of the study. If participants do not experience any improvement upon study completion in mood or cognition, the medication will be gradually discontinued over a two-week period upon study completion (end of week 8). Participants will take half of their final dose of vortioxetine during the first week post-study and no medication during the second week of discontinuation. Participants will be provided with one week worth of medication for this discontinuation process but will not be provided any further supply thereafter.

Vortioxetine discontinuation process

At the end of week 8, patients will be seen by the study physician and provided with half of current vortioxetine dosage for a period of 1 week. This is in keeping with the product insert, although vortioxetine does not cause discontinuation syndrome. During the second week, patients will not be on medication and will be seen by the study physician at the end of two weeks, to ensure that there are no risks or adverse events during this time period. This visit with the clinician is post-study, and not part of the study visits. Patients are encouraged to contact the study team in the event that they would like to be scheduled with the physician earlier.

Data Handling

Personal Data Protection

All data collection material will be de-identified. Participant records will be distinguished using participant identification (PID) numbers.

Data Collection and Retention

The majority of data will be collected electronically through the secure RedCap platform. Participants will also sign the consent form via the RedCap platform after a thorough discussion with research staff during the in-person screening visit. Participants will receive an electronic copy of their consent form via email. Participants may also receive a printed copy of the consent form if this is preferred. Records and documents pertaining to the conduct of the study as well as all data collected as part of the study will be retained in a secure place for 25 years in accordance with Health Canada regulations. All data collected throughout the study will be kept with membership of the BCDF for 25 years. Data collected as hard copies (e.g. paper format) may be digitized and stored electronically, after which the hard copies will be destroyed (even before the 25 years).

Participants' de-identified plasma samples (labelled with participant ID) will be stored in a -80 degrees Celsius freezer for a maximum of 15 years from the time of collection. Participants may choose to withdraw their samples at any time.

Participant Protection

Participants will not be placed at any risk as a result of the study. Information obtained will be maintained in a secure and confidential fashion. No participant will be coerced and/or placed under duress to complete study procedures.

Adverse Events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a

pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Follow-up of adverse events should be based upon the clinical judgement of the investigator.

Assessment of Intensity

Each AE will be classified according to the following criteria:

- Mild: The AE does not interfere in a significant manner with the participant's normal level of functioning.
- Moderate: The AE produces some impairment of functioning, but is not hazardous to the participant's health.
- Severe: The AE produces significant impairment of functioning or incapacitation and is a definite hazard to the participant's health.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over several days, those changes should be recorded separately (with distinct onset dates).

Severity versus Seriousness

It is important to distinguish between serious and severe AEs. Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on participant/event outcome at the time of the event. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE. Symptoms associated with overdose should be reported as AEs. For further information regarding overdose, see section.

Recordings of Adverse Events

Adverse events will be collected from baseline to endpoint. At each visit, subjects will be asked if they have experienced any health problems or side effects since the previous visit. All AEs will be recorded appropriately, whether or not considered related to the investigational product. This will include AEs spontaneously reported by the patient and/or observed by members of the research team as well as AEs reported in response to a direct question (e.g., "Have you experienced any health problems or side-effects since your last visit?").

For each AE, the following parameters will be described:

- Discovery (i.e., spontaneous or solicited)

- Start date
- Stop date or ongoing
- Action taken with regards to investigational product
- Outcome if the AE caused the patient to discontinue the investigational product
- A statement if the AE fulfills the criteria for a SAE or not
- The investigator's assessment of the causal relationship between the event and the investigational product
- Intensity of the AE
    - Mild (awareness of sign or symptom, but easily tolerated)
    - Moderate (discomfort sufficient to cause interference with normal activities)
    - Severe (incapacitating, with inability to perform normal activities)
- Resolution

Assessment of Causality

Each AE will be assessed as to its relationship to the IP, based on the following criteria. Although the attribution by the investigator will be collected for reported events, for analytic purposes a temporal association with the use of the IP will be assumed sufficient for at least plausible association.

- Not related: No causal relationship exists between the IP and the AE, but an obvious alternative cause exists, eg, the participant's underlying medical condition or concomitant therapy.
- Possibly related: A connection with the administration of the IP appears unlikely, but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the IP; (2) it could not readily have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant; or (3) it follows a known pattern of response to the IP.
- Related: There is a reasonable/plausible possibility that the AE may have been caused by the IP.

When assessing the relationship to the IP, the following criteria will be considered:

- Known class effect
- Biological plausibility
- Lack of alternative explanation—concomitant drug or disease

Action Taken Regarding Investigational Product

Dose modifications of IP (ie, dose not changed, drug withdrawn, drug interrupted, or dose increased).

- Not Applicable: Participant died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment.

Other Action Taken for Event

- 1 = None (ie, no treatment was required)
- 2 = Medication required (ie, prescription and/or OTC medication was required to treat the AE)
- 3 = Hospitalisation or prolongation of hospitalisation required (ie, hospitalisation was required or prolonged because of the AE, whether medication was required)
- 4 = Other

Adverse Event Outcome

- 1 = Recovered/Resolved (ie, the participant fully recovered from the AE with no residual effect observed)
- 2 = Recovering/Resolving (ie, the AE improved but has not fully resolved)
- 3 = Not Recovered/Not Resolved (ie, the AE itself is still present and observable)
- 4 = Recovered/Resolved with Sequelae (ie, the residual effects of the AE are still present and observable, including sequelae/residual effects)
- 5 = Fatal (ie, 'fatal' should be used when death is a direct outcome of the AE)
- 6 = Unknown

Clinical Laboratory Changes

Any abnormality in a laboratory value that is new in onset or which has worsened in severity or frequency from the baseline condition and meets 1 of the following criteria will be recorded on the AE pages of the eCRF:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of IP
- Has accompanying or inducing symptoms or signs
- Is judged by the investigator as clinically significant

Combined elevations of aminotransferases and bilirubin, either serious or nonserious, and whether causally related, meeting the criteria of a potential Hy's Law case (total bilirubin level ≥ 2 × upper limit of normal [ULN] with simultaneous ALT or AST ≥ 3 × ULN) should always be reported to the sponsor as soon as possible following the procedures outlined in Section 10.2 for SAE reporting, with the investigator's assessment of seriousness, causality, and a detailed narrative.

Overdose

Any instance of overdose (suspected or confirmed) must be fully documented as an AE or SAE if it meets the SAE criteria. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

Adverse Event Follow-up

All AEs will be followed until resolved or stable and the outcome documented on the eCRF. If the investigator detects an AE in a study participant after the last scheduled follow-up visit and

considers the event possibly related or related to prior study treatment, the investigator will document it.

Serious Adverse Events (SAE)/Serious Adverse Drug Reaction (SADR)

Definition: A serious adverse event (SAE)/Serious Adverse Drug Reaction (SADR) is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any procedure, that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapability
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Any serious, untoward event that may occur subsequent to the reporting period that the investigator assessed as related to IP should also be reported and managed as an SAE. The investigator should follow participants with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal clinical laboratory values at the end of study assessment, these events will be followed until resolution or until they become clinically not relevant. Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the participant's ability to carry out normal life functions.

The causality of SAEs/SADRs (i.e., their relationship to study treatment) will be assessed by the investigator(s). Note that SAEs/SADRs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as “yes”.

Serious unexpected adverse drug reaction (SUADR) Definition: means a serious adverse drug reaction (SADR) that is not identified in nature, severity or frequency in the risk information set out in the investigator's brochure or on the label of the drug.

Reporting of SAEs/SADRs/SUADRs

All SAEs/SADRs/SUADRs should be reported to the sponsor immediately. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses.

The QI should comply with the applicable regulatory requirement(s) related to the reporting of serious unexpected adverse drug reactions to the regulatory authority(ies) and the REB.

SAEs/SADRs: The sponsor-investigator will comply with any and all national rules and regulations concerning safety reporting (SADRs or SAEs as required). All SAEs/SADRs (according to the definition in ICH GCP) will be done by the investigator in accordance with local regulations and reported to the appropriate regulatory bodies.

SUADRs: In accordance with section C.05.014 of the Regulations, it is the responsibility of a sponsor to inform Health Canada, in an expedited manner, of all **SUADRs** in respect of a drug during the course of a Phase I-III clinical trial, whether or not the event occurred inside or outside of Canada:

a. this information must be submitted **within 15 calendar days** after becoming aware of the event if it is neither fatal nor life threatening
b. if the event is **fatal or life threatening**, Health Canada must be advised of the event **within 7 calendar days** after the sponsor first became aware of it.

In cases where the event is **fatal or life threatening**, the sponsor must submit a **complete report** to Health Canada **within 8 calendar days** after the first notification (initial report) to Health Canada of the event. Follow-up reports of fatal or life threatening reactions must include an assessment of the importance of the event and the implication of any findings, including relevant previous experience with the same or similar drugs.

In addition, in keeping with ICH GCP, the sponsor should expedite reporting of all SUADRs to all concerned QI(s)/institution(s), the REB(s) where required (ICH E6, 5.17.1).

Statistical analysis plan

Data will be analyzed for a modified intent-to-treat set: the full analysis set (FAS) will comprise all patients who received at least one dose of study medication and had at least one valid post-baseline assessment of the primary outcome.

- The MMRM model will use study visit as a fixed factor and the interaction between treatment and visit to allow for estimation of treatment effect at specific time points. Additionally, the interaction term of visit and baseline to allow for time dependent adjustment of baseline. An unstructured covariance matrix will be used.

To control for type I error, the following sequence of hierarchically ordered primary and key secondary end points will be used at a significance level of 0.05 1-sided for the primary outcome:

- Primary endpoint: Change from baseline to week 8 between vortioxetine and placebo in DSST performance score
- Secondary endpoint: Change from baseline to week 2 between vortioxetine and placebo in DSST performance score

The change from baseline in DSST performance score after 8 weeks of treatment will be analyzed with a one-sided mixed model for repeated measures (MMRM) with treatment and study visits as fixed factors and baseline DSST performance as covariate. For secondary analyses, the change from baseline in DSST, CogState Online Cognitive Battery, PDQ-20, TMT-A/B, SHAPS, FSS, GAD-7, WHO-5, EQ-5D-5L, BAS, RPE, RAVLT, PCFS, EEfRT, SETS, QIDS-SR16, IPAQ and SDS will also be analyzed using a mixed model for repeated measures (MMRM) using all available data. Withdrawal rates will be compared between placebo- and vortioxetine-randomized participants at week 8.

A power calculation was obtained via computer simulations on the primary outcome of difference in the change from baseline in DSST performance score between vortioxetine and placebo. Assuming an SD of 8.0 for the change from baseline in the DSST performance score

at week 1 and a 15% dropout rate, based on previous randomized, placebo-controlled trials with vortioxetine, it was calculated that 100 subjects (modified per treatment group) are required to achieve 80% power to detect a difference of 3.1 in the change from baseline in DSST performance score between vortioxetine and placebo (i.e., Cohen's d=0.38) by an MMRM with a 1-sided significance level of $p<0.05$ [26,53].

The magnitude of fMRI-determined ventral striatal (including nucleus accumbens) activation during anticipation of gain versus no-incentive trials, as well as loss versus no-incentive trials, in the EEfRT task. Mean and maximum fMRI ventral striatal activation will be assessed.

Publication Plan

Manuscript will be prepared within two weeks of the last subject's last visit. Manuscript will be submitted to a high-impact peer-reviewed journal. Data from the study will also be presented at national and international meetings.

Documentation

We will be documenting the findings in the form of peer-reviewed manuscripts as well as posters at international meetings.

Contract Details

Brain and Cognition Discovery Foundation

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