The relationship among changes in Brain Network Activation, changes in core depressive and cognitive symptoms and safety and tolerability in adult outpatients with major depressive disorder treated with open-label, flexible-dose vortioxetine: A proof of concept study

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Study Synopsis

This study will include adult outpatients 18-65 years of age with major depressive disorder (MDD) with subjective reporting of cognitive dysfunction treated with flexible-dose vortioxetine (5-20 mg/day) for eight weeks. Following completion of the informed consent process, this study will consist of a screening period (visit 1) of 2-14 days to assess inclusion/exclusion criteria. Subjects who continue to meet inclusion criteria at baseline (visit 2) will begin the assessment and treatment phase of the study.

The first EEG/BNA (BNA) will be performed at the screen visit. Subsequent BNA will be at baseline, 2-weeks after the start of treatment, and at the end of 8 weeks of treatment (or early termination).

The Schedule of Events (Appendix I) shows detailed study procedures that will be performed at each visit. The table below clarifies the schedule of dosing and attendant BNA tests.

Quick Summary of Study Visits, Dosing and BNA

Visit #	Screen 1	Baseline 2	3	4	5	6	7	8	9	10 (or ET)
Day	-2 to -14	0	7	14	21	28	35	42	49	56
Treatment Week	-1	0	1	2	3	4	5	6	7	8
Dose mg/day		10	5-10	5-10	5-20	5-20	5-20	5-20*	5-20*	5-20
BNA test	BNA	BNA		BNA						BNA

*No dose changes allowed after visit 8

Subject Population:

Subjects aged 18 to 65 years old with acute single episode, acute recurrent MDD and acute recurrent MDD with incomplete inter-episode recovery who report subjective cognitive dysfunction (such as difficulty concentrating, slow thinking, and difficulty in learning new things or remembering things) that correlated with the timing of their current major depressive episode (MDE).

Number of Subjects:

40 subjects enrolled. For purposes of IRB reporting, an enrolled subject is one who signs informed consent. For purposes of data analysis and reporting to the funding organization, an enrolled subject is one who meets all inclusion criteria and no exclusion criteria and completes the baseline visit including the baseline BNA.

Number of Sites: (U.S. Study)

2: Chicago, IL and Skokie, IL

Dose Level(s):

5 mg/d, 10mg/d, 15 mg/d, 20mg/d. Route of Administration: Oral

Duration of Vortioxetine Treatment:

One dose daily for 8 weeks.

Period of Evaluation:

Screening phase 1-2 weeks; treatment phase 8 weeks.

Introduction:
Major depressive disorder (MDD) is the most common psychiatric disorder with a lifetime prevalence of 16.2% and a 12-month prevalence of 6.6% in developed countries [1]. It represents one of the most serious challenges faced by healthcare providers throughout the world, being a leading cause of disability globally [2] [3]. MDD is characterized by the presence of 1 or more MDEs that presents with depressed mood, loss of interest or pleasure, disturbed sleep or appetite, low energy, and feelings of guilt or low self-worth [4].

It is well established that mood disorders are also associated with cognitive dysfunction [5,6]. In fact, growing evidence from neuropsychological studies suggests that the majority of patients suffering from MDD present with some form of dysfunction in certain cognitive domains (such as executive function [7-10], visuospatial short-term memory and learning and on verbal learning [11]; psychomotor speed and in immediate and delayed free recall [12] and working memory [13]) before treatment and are among the most common residual symptom domains after apparent successful treatment of other core MDD symptoms. Patients with depression also seem to perform significantly worse than normal controls on effort-demanding tasks, while they did not differ on the effortless tasks [14,15]. A study by Burt [16] showed that patients with depression performed approximately one half of an standard deviation worse than healthy subjects on verbal learning and memory tests. Other studies, however, found non-significant or only minimal differences in neuropsychological tests among patients with MDD and normal controls [17-19].

Regarding prevalence of cognitive dysfunction in MDD patients, little is still known. Afridi et al. [20], assessed cognitive disturbances among newly diagnosed depressed (n=30) and healthy subjects (n=30). He found that 63.3% of the depressed patients had cognitive difficulties compared to 3.3% of healthy-controls, with attention/concentration being the most common domain of cognition affected, followed by memory disturbance. The presence or absence of cognitive dysfunction in MDD patients depends on a number of factors including symptom severity [21], presence of melancholic features [22], presence of recurrent episodes [23], presence of psychotic features [24], remitted versus acute states [25], age [26], and pharmacological and non-pharmacological interventions [27]. Regarding pharmacological interventions, some evidence shows that conventional antidepressants may worsen cognitive function (e.g., tricyclic antidepressants (TCAs) secondary to anticholinergic or antihistaminic effects; selective serotonin reuptake inhibitors (SSRIs) secondary to selective increase of serotonin (5-HT) resulting in diminished norepinephrine (NE) and dopamine (DA) output; mirtazapine secondary to antihistaminic effects [30].

Cognitive dysfunction in MDD may be a symptom of depressive illness and persist, as residual symptoms, despite otherwise effective antidepressant therapy [34]. As discussed above, they may also, however, emerge as adverse effects of some psychotropic medications, including antidepressants [26].

Various neurotransmitters are implicated in cognitive processes, including 5-HT, DA, NE, acetylcholine and histamine. Regarding 5-HT, it is known that 5-HT1A receptor agonists have shown differential effects on memory and executive function in healthy and psychiatrically ill populations [35]. In animal studies, 5-HT2A receptor agonists enhance
associative learning and certain antagonists impair associative learning [36]. In addition, depletion of 5-HT has been shown to impair discrimination reversal performance, a form of cognitive flexibility [37]. Dopamine is also involved in cognitive flexibility, with a role in attentional selection, reversal and extinction learning [38], [39]. Animal studies have shown that blockade of DA receptors in the prefrontal

cortex impairs spatial working memory [39]. Norepinephrine appears to play a role in spatial working memory formation [38] as well as attentional set-shifting [37,38]. Acetylcholine has been implicated in aspects of reversal learning in the orbitofrontal cortex [37]. Furthermore, behavioral studies in humans suggest that acetylcholine is responsible for maintenance of attention and increased levels of this neurotransmitter are related to attentional effort [40]. Finally, histamine seems to affect learning and memory, partly via modulating acetylcholine release [41]. In rats, blockade of 113 receptors improves social memory, enhances attention and improves cognitive performance. Cetirizine, an H1 receptor antagonist, impairs memory processing speed [42; data on file with Takeda].

Vortioxetine is a novel antidepressant with hypothetical multimodal mechanism of action. It is thought to work through a combination of multiple pharmacological modes of action: 5-HT reuptake inhibition, 5-HT_3 and 5-HT_7 receptor antagonism, 5-HT_{1A} receptor agonism, and 5-HT_{1B} receptor partial agonism [43]. In vivo nonclinical studies have demonstrated that vortioxetine enhances levels of the neurotransmitters 5-HT, NE, DA, acetylcholine and histamine in specific areas of the brain [43]. These affinities are all considered to be of clinical relevance and involved in the mechanism of action at therapeutic doses.

Vortioxetine showed antidepressant activity in completed MDD studies in which primary endpoints were change in depressive symptoms. Currently, three placebo-controlled clinical trials demonstrate vortioxetine's efficacy on cognitive performance in adult outpatients with MDD (Katona, et al., 2012; McIntyre, et al., 2013; data on file with Takeda). Two of the above studies (Katona, McIntyre) included duloxetine as a comparator antidepressant; both active antidepressants demonstrated antidepressant efficacy compared to placebo. Vortioxetine, not duloxetine, showed improvement compared to placebo on the Digit Symbol Substitution Test (DSST). Results of these two studies also suggested that the improvement with vortioxetine (and not duloxetine) was a result of direct effects versus indirect (via mood) improvement in cognition. Correlating the clinical changes in mood and cognition with translational imaging data could provide insight to diagnose and manage cognitive changes associated with MDD.

Vortioxetine improved cognition sub-items in the Montgomery-Åsberg Depression Rating Scale (MADRS) [44] (Item 6 — concentration difficulties) [45] and Hamilton Anxiety Scale (HAM-A) [46] (Item 5 - concentration and memory) [47] when compared to placebo (in the trials in which the primary endpoint was also positive). In addition, exploratory cognitive tests for verbal learning (RAVLT — Rey Auditory Verbal Learning Test) [48] and executive function, working memory, processing speed and visuospatial attention DSST [49]) were included in a vortioxetine conducted study in elderly patients [50] with MDD (primary endpoint was change in depressive symptoms). In this study, vortioxetine 5 mg/day improved cognitive dysfunction in both tests whereas duloxetine (active reference) improved cognitive dysfunction in the RAVLT but not in the DSST. This finding is consistent with the literature as shown by a study in which elderly patients receiving duloxetine demonstrated significantly greater improvement in a composite cognitive score mainly driven by improved verbal learning and memory [51].

Brain Network Activation:
Appropriate diagnosis and differential diagnosis is critical to finding a treatment that will provide optimal efficacy. Currently, diagnosis depends on an assumption that historical and current clinical information is accurate and reliable. The need to find biomarkers to improve current diagnosis and differential diagnosis, and the potential to predict treatment outcome, remains a significant unmet need in the optimal management of MDD.

In recent years more attention has been devoted to the use of functional magnetic resonance imaging (fMRI) to assess the state of the frontolimbic circuit to diagnose depression and monitor response to treatment. In particular the activity of the rostral anterior cingulated cortex (rACC) measured both on fMRI and EEG has been demonstrated to be a reliable biomarker of depression and its response to antidepressant therapy.

Sensory evoked potentials (SEPs) are electrical potentials, recorded from the central nervous system of humans or animals (usually via EEG) while stimulating sense organs. They are distinct from spontaneous potentials (background EEG), which are recorded without stimulation. Contrary to spontaneous potentials, SEPs are phase-locked to the stimulus.

Event Related Potentials (ERPs) are msec by msec reflections of the direct macroscopic neural mass electrical activity of cell assemblies located in specific regions of the brain, during sensory, motor, and cognitive tasks. They are extracted from the background electroencephalogram (EEG) through a process of time-locked averaging process of many trials of the same type to the onset of a sensory stimulus or a motor response. As such, they offer a powerful technique for the noninvasive characterization of human brain function by means of identifying the timing, order of activation, and dynamic orchestration of brain regions during the unfolding of cognitive tasks.

Although Positron Emission Tomography (PET) and fMRI allow for precise localization of functional activations during cognitive tasks, their temporal resolution is limited by the slow time course of the hemodynamic response that they are reflecting (peaking 5 sec after an event and subsiding after 12-15 sec, and affecting both blocked and event-related fMRI designs). Because of the slowness of the hemodynamic response PET and conventional fMRI have limited temporal resolution, while ERPs allow selective averaging of different stimulus types within the same experimental block, thus allowing mixed-trial analysis (such as Successful and Failed inhibitions in the Go/NoGo signal). Moreover, ERPs can provide unique temporal information concerning the timing and order of activations of normal and abnormal neural activity within the block during the unfolding of cognitive tasks which can be the only significant information that differentiate between those activities. Finally EEG methodology is less invasive, less costly, and cumbersome than PET and fMRI methodology.

ERPs consist of an ordered sequence of waveforms such as P100, N100, P200, N200, P300, N400 depending on their latency and their polarity. Early components (P100 and N100 etc.) are called exogenous, because they require a stimulus, and reflect activity in primary or secondary sensory areas. However, such early ERP waves can be modulated by sustained attention and top-down cognitive control processes. Longer latency components (P300, N400 etc.) are called endogenous, because they can be present even in response to an expected missing stimulus. P300 is elicited in visual or auditory oddball tasks in response to task-relevant, salient infrequent targets, with greater amplitude over the posterior (parietal) scalp. Another waveform of interest is the N200, a prominent N200 with a frontal distribution is observed in response to NoGo stimuli in Go/NoGo tasks, and it is thought to reflect response inhibition processes. In contrast, Go stimuli elicit the parietally distributed P300.

Although spatial resolution of the ERP method is coarse, it is improved by the use of high-density and new active amplifiers sensor arrays.

Brain Network Activation (BNA) technology uses high density EEG to collect ERP data for generation of a reference brain network model (RBNM) based on common neural activations, or event-pairs, defined as any two salient electrophysiological events, each at a given scalp location, frequency band and time range, with a specific temporal relationship. The algorithm produces a visual display of BNA network patterns that is simpler to interpret than traditional EEG output, while providing information on cortical connectivity. In addition, a RBNM similarity index (BNA score) is calculated for the EEG components of time (relative and absolute), amplitude, and overall pattern (connectivity) providing objective and easily interpretable results.

The present study aims at clarifying dynamic spatio-temporal aspects of brain functional organization (e.g. inhibitory control, working memory) in MDD and cognitive dysfunction associated with MDD using BNA during the performance of the different tasks.

Recent studies have validated the use of brain network activation (BNA) analysis using ERPs to diagnose and predict treatment response in attention deficit hyperactivity disorder (ADHD), models of schizophrenia and Alzheimer's disease, concussion, pain and fibromyalgia (data on file, ElMindA).

We hypothesize that the application of BNA using ERPs may be used as a non-invasive tool to improve diagnosis, differential diagnosis, target-specific depression symptom domains such as cognition and monitoring treatment response in MDD with cognitive dysfunction.

Considering the compromised course of untreated depression and its well-known robust responsiveness to treatment, the development of an objective diagnostic tool to help diagnose individuals with MDD and predict treatment response can have a significant clinical and public health impact.

Rationale for the Proposed Study:
Vortioxetine has been shown to improve core depressive symptoms and improve cognitive function in adult outpatients with MDD and subjective complaints of cognitive function. This pilot study is intended to evaluate the extent to which BNA technology can provide clinically valuable information and provide information toward designing a subsequent confirmatory study that will further elucidate the effect of vortioxetine on MDD and cognitive function in this population. This exploratory study will ascertain the acute changes in core depression symptoms, cognitive function, tolerability, and safety using flexible-dose vortioxetine in adult outpatients with MDD with subjective complaints of cognitive functioning, as measured by BNA changes and standard outcome measures for depression and cognition.

Data suggest that the impact of vortioxetine on cognition in MDD may be independent of the antidepressant effect, perhaps through a centrally-mediated pathway different from that involved in the antidepressant effects. This study will investigate the effect of vortioxetine on cognitive dysfunction more broadly covering specific measures of attention, executive functioning and psychomotor speed, as well as assess its effect on core depressive symptoms, function and global change. The number of subjects treated in this study is generally accepted for exploratory studies and intended to demonstrate 1) improvement in cognition and efficacy in conventional MDD symptom domains, 2) improvement in cognition but no antidepressant efficacy in conventional MDD symptom domains, and, 3) no improvement of cognition and no antidepressant efficacy in conventional MDD symptom domains. We predict distinct patterns in brain network activity among these subgroups. This preliminary data is expected to provide greater insight into understanding the direct versus indirect antidepressant effects

of acute treatment with vortioxetine on cognition in MDD, and provide a basis for future clinical trials and applications.

STUDY OBJECTIVES AND OUTCOMES

OBJECTIVES

Primary Objective:

- To explore BNA changes from baseline to endpoint on 1) efficacy of core MDD symptoms and, 2) improvement of cognitive dysfunction with acute treatment of flexible dose vortioxetine in adult outpatients with MDD and subjective complaints of cognitive dysfunction.

Secondary Objectives:

- To evaluate the efficacy over eight weeks of treatment of flexible-dose vortioxetine (5-20 mg/day) on standard outcome measures for core depression symptoms
- To evaluate the changes in cognitive function from baseline to endpoint with flexible-dose vortioxetine (5-20 mg/day)
- To evaluate the changes in functionality over eight weeks of treatment with flexible-dose vortioxetine (5-20 mg/day)
- To explore baseline BNA patterns and clinical baseline features of:
  - core MDD symptoms (including severity)
  - cognitive dysfunction
  - functionality
- To explore change in BNA patterns and clinical changes on:
  - core MDD symptoms
  - cognitive function
  - functionality
  - adverse events attributed to vortioxetine (per investigator opinion)
- To explore correlations between patterns of BNA changes and evaluated changes in RDOC (Research Domain Criteria) domains and structures
- To explore differences in BNA patterns and identify potential neural pathways that may impact core depressive symptoms different from cognitive function
- To explore change in BNA patterns from baseline to after 2 weeks of treatment with vortioxetine with efficacy, using standard outcome measures of core depression symptoms at the end of acute treatment
- To strengthen the level of confidence with BNA patterns observed during the course of treatment that may allow identification of potential trends observed as a result of treatment, by having a screen and baseline BNA done prior to receiving treatment
- To obtain baseline BNA data in adult outpatients with MDD and subjective cognitive dysfunction prior to treatment that can be utilized for identification of BNA patterns associated with MDD
- To confirm the safety and tolerability of vortioxetine (5-20mg/day).

OUTCOMES

Primary Outcome:
The primary outcome of this study is to explore changes in BNA patterns from baseline to endpoint with 1) antidepressant response status; response defined as $\geq$ 50 % change in total MADRS score from baseline to endpoint and, 2) change in cognitive function defined as change from baseline to endpoint on change in total number of correct symbols on the DSST .

Secondary Outcomes:

1. Explore effect of core MDD symptoms, cognitive function, and functionality from baseline through eight weeks of treatment with vortioxetine:
    a. Depressive symptoms
        i. HDRS-17 total score
        ii. QIDS-SR-16 total score
        iii. HDRS-28 total score
        iv. Response defined as ≥50% decrease in MADRS total score
        v. Remission defined as <11 MADRS total score at endpoint
        vi. Asymptomatic remission defined as MADRS total score <4
        vii. Cognition and functionality
        viii. MGH-CPFQ total score
        ix. PDQ
        x. TMT-A/B
        xi. Stroop Test
        xii. UPSA
        xiii. WLQ
    b. Global clinical status
        i. CGI-Severity
        ii. CGI-Improvement
2. Explore effect of core MDD symptoms, cognitive function, and functionality from baseline to endpoint following treatment with vortioxetine and the relationship between changes in BNA patterns from baseline to endpoint on:
    a. Depressive symptoms (change from baseline to endpoint)
        i. HDRS-17 total score
        ii. QIDS-SR-16 total score
        iii. HDRS-28 total score
        iv. Response defined as ≥50% decrease in MADRS total score
        v. Remission defined as <11 MADRS total score at endpoint
        vi. Asymptomatic remission defined as MADRS total score <4
    b. Cognition and functionality (change from baseline to endpoint)
        i. MGH-CPFQ total score
        ii. PDQ
        iii. TMT-A/B
        iv. Stroop Test
        v. UPSA
        vi. WLQ
    c. Global clinical status (change from baseline to endpoint)
        i. CGI-Severity

ii. CGI-Improvement

3. To explore changes in BNA patterns from baseline in predicting clinical outcome at endpoint on:
    a. Depressive symptoms (change from baseline, 2 week, 8 week)
        i. MADRS total score
        ii. HDRS-17 total score
        iii. HDRS-28 total score
        iv. QIDS-SR-16 total score
    b. Cognitive function and functionality (change form baseline, 2 week , 8 week)
        i. MGH-CPFQ total
        ii. PDQ
        iii. WLQ
    c. Clinical global status (change from baseline, 2 week, 8 week)
        i. CGI-Severity
        ii. CGI-Improvement
4. To explore differences in BNA patterns and identify potential neural pathways that may impact core depressive symptoms different from cognitive function:
    a. Explore differences in patterns of BNA changes from baseline to endpoint between:
        i. Subjects meeting antidepressant efficacy criteria (based on response and remission criteria for MADRS, HRSD, QIDS) and improvement in cognition (based DSST).
        ii. Subjects failing to meet antidepressant efficacy criteria (based on response criteria for MADRS, HRSD, QIDS) but show improvement in cognition (based on DSST).
        iii. Subjects failing to meet antidepressant efficacy criteria (based on response criteria for MADRS, HRSD, QIDS) and failing to show improvement in cognition (based on DSST).
        iv.
        v.
5. To explore changes in BNA patterns in MDD with cognitive dysfunction prior to receiving treatment with vortioxetine and:
    a. Severity of MDD as measured by baseline MADRS total score, QIDS-SR-16 total score, HDRS-28 item total score and CGI-Severity.
    b. Severity of cognition dysfunction and functionality as measured by baseline DSST, TMT-A/B, TMT-B, Stroop, MGH-CPFQ total score, UPSA, WLQ.
    c. Prediction of achieving symptomatic remission of MDD as measured by remission status on MADRS total score, HDRS-17 total score and CGI-Improvement (1 or 2)
    d. Prediction of cognitive improvement measured by DSST score; cutoff 70% improvement from baseline.
6. Explore relationship with changes in BNA patterns in remitted vs. non-remitted subjects after 8 weeks of treatment with vortioxetine as measured by MADRS total score, HDRS-17 total score, QIDS total score,, and CGI-Improvement.
7. Assess safety and tolerability of 8 weeks open-label, flexible-dose vortioxetine in all subjects for:
    a. Spontaneously reported adverse events
    b. Clinical safety laboratory tests (when indicated, vital signs, weight, EKGs and physical exam)

c. Evaluate relationship between adverse events after 2 and 8 weeks of treatment with changes in BNA patterns for nausea, worsening of baseline suicidal ideation (as measured by MADRS item 10, HDRS-17 item 2 and C-SSRS)

Informed Consent:
The informed consent document, in conjunction with verbal discussion of the protocol, will be used to explain the study, including the risks and benefits, to the subject in simple terms before the subject is entered into the study. The investigator is responsible to see that informed consent is obtained from each subject and to obtain the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to any changes made to a subject's medical treatment plan for the purpose of study participation. The original signed consent form will be retained by the investigator.

All subjects will take part in the informed consent process prior to participating in any study specific assessments or procedures, including assessment of study specific inclusion and exclusion criteria. The principal investigator and his designee will conduct the informed consent process in compliance with Good Clinical Practice Guidelines. Subjects will then be eligible for Screening Visit.

Subject Selection:
Subjects will be screened for study inclusion and exclusion criteria, and the case report form (CRF) will be reviewed by the principal investigator prior to Baseline Visit (Visit 2).

Main Criteria for Inclusion:

- The subject has single episode or recurrent MDD (acute onset of recurrence of recurrent MDD with poor inter-episode recovery) (inter-episode periods cannot meet full MDD criteria) as the primary diagnosis according to DSM-IV-TR criteria. The current MDE will be confirmed using the Mini International Neuropsychiatric Interview (MINI V6.0.0).
- The subject has a MADRS total score ≥26.
- Subject reports subjective cognitive dysfunction (such as difficulty concentrating, slow thinking, and difficulty in learning new things or remembering things).
- The reported duration of the current MDE is at least 3 months and no longer than 24 months.
- The subject is a man or woman between 18 and 65 years old, inclusive.
- Right-handed, normal (corrected) vision, and normal hearing.

Main Criteria for Exclusion:

- The subject has a score of ≥70 on the DSST at the Baseline Visit.
- Failure to respond to or inability to tolerate an adequate trial of vortioxetine in the past.
- Exposure to an investigational compound 30 days prior to enrollment
- Exposure to any psychoactive or otherwise excluded medication within five half-lives of the baseline visit or during the study. Excluded medications include: antidepressants, anxiolytics, anticonvulsants, barbiturates, chloral hydrate, lithium, antipsychotics, benzodiazepines, hypnotics, MAO-Inhibitors, muscle relaxers, triptans, centrally-acting antihistamines, central alpha-2 agonists, decongestants, psychostimulants, dopamine agonists, opioid pain medications, oral corticosteroids, L-methylfolate, SAMe, 5-HTP, St. John's Wort.
- The subject has 1 or more of the following:
    - Primary psychiatric disorder other than MDD as defined in the DSM-IV-TR (as assessed by the MINI, Version 6.0.0).

    - Current or history of attention deficit hyperactivity disorder (ADHD), pervasive developmental disorder, manic or hypomanic episode, schizophrenia, or any other psychotic disorder, including major depression with psychotic features, mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in the DSM-IV-TR.
    - Current diagnosis of alcohol or other substance abuse or dependence (excluding nicotine or caffeine) as defined in the DSM-TV-TR that has not been in sustained full remission for at least 6 months (for abuse) and 12 months (for dependence) prior to Screening.
    - Positive urine drug screen prior to Baseline.
    - Presence or history of a clinically significant neurological disorder (including epilepsy) or severe head injury, or any condition that has caused an abnormal EEG or that may interfere with an EEG recording in the opinion of the investigator.
    - Neurodegenerative disorder (Alzheimer Disease, Parkinson Disease, multiple sclerosis, Huntington Disease, etc).
    - Any unstable medical condition as determined by the principal investigator (PI).
    - Any DSM-IV Axis II disorder that might compromise the study as determined by the PI.
- The subject has any other disorder for which the treatment takes priority over treatment of MDD or is likely to interfere with study treatment or impair treatment compliance.
- The subject has physical, cognitive, or language impairment of such severity as to adversely affect the validity of the data derived from the neuropsychological tests.
- The subject has a significant risk of suicide according to the PI's clinical judgment.
- The subject, in the opinion of the PI, poses a risk of harm to others.
- The subject has initiated formal cognitive or behavioral therapy, systemic psychotherapy within less than 6 months of study screening, or has plans to initiate such therapy during the study.
- The subject has received electroconvulsive therapy, vagus nerve stimulation, or repetitive transcranial magnetic stimulation within 12 months prior to Screening.
- The current MDE is considered by the PI to have been resistant to 2 adequate antidepressant treatments of at least 6 weeks duration each at the recommended dose.
- The subject is pregnant or breastfeeding, or is intending to become pregnant before, during, or within 30 days after participating in this study.
- Hair or scalp conditions that may significantly compromise the quality of an EEG with 64 scalp electrodes, including but not limited to braids or significant alopecia, in the opinion of the investigator (collaboration with ElMindA will be sought if unclear).

Contraception

From signing of the informed consent through the duration of the study (and for no less than 30 days after last dose of study medication), female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (e.g., defined as at least 1 year since last regular menses with an FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year post-vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate.

In this study, the only acceptable methods of contraception are:

- Barrier methods (male condom PLUS spermicide; cap (plus spermicidal cream or jelly) PLUS male condom and spermicide; diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide
- Intrauterine devices (IUDs) (copper T PLUS condom or spermicide; progesterone T PLUS condom or spermicide
- Hormonal contraceptives (implants; hormone shot/injection; combined pill; minipill; patch; vaginal ring PLUS male condom and spermicide)

Female subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova during the course of the study and within 30 days following the study completion.

A urine pregnancy test will be performed at the screening visit for women of childbearing potential and may be repeated at the investigator's discretion.

Pregnancy

If any subject is found to be pregnant or breastfeeding during the study, she will be withdrawn and any sponsor-supplied drug will be immediately discontinued.

If the pregnancy occurs during administration of active study medication (e.g., after Visit 2 or within 30 days of the last dose of active study medication), the pregnancy will be reported immediately to the IRB using standard procedures per the sponsor and PI.

If the female subject agrees to her primary care physician being informed, the investigator will notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide adequate details of treatment the subject received.

All pregnancies discovered post-baseline will be referred to the subject's primary care physician, obstetrician or other designated medical care provider and followed via regular communication for 30 days (including any premature termination).

STUDY PROCEDURES

See Schedule of Events (Appendix I) for complete list of study procedures performed at each visit.

All BNA procedures will be done as early in the visit as possible to avoid any confounding factors that may impact the outcome, except during the screen visit (at this visit, the BNA will occur after the subject completes the informed consent process and clinician-assessed inclusion/exclusion criteria are assessed). The screening visit can be split into 2 visits, as long as the screening period does not exceed the 14-day screen period.

Visit 1 (Screen)

- Following the informed consent process, subjects will begin the Screening Visit (Visit 1), which will include a psychiatric/medical history, vital signs, urinalysis, urine drug screen, urine pregnancy test (females), EEG/BNA, blood drawn for laboratory tests (CMP, CBC w/diff, TSH), ECG, and clinician- and patient-rated scales.

Visits 2-10

All Subjects

- Subjects who meet all inclusion criteria and no exclusion criteria following the screening visit will enter the study. Weekly study visits will be conducted for efficacy, safety, and tolerability. No dose changes will be allowed after Visit 8.
- A baseline EEG/BNA will be taken before the subject begins taking vortioxetine and follow-up EEG/BNA readings will be taken at Visit 4, and Visit 10 (or last study visit if a subject is withdrawn early).
- Vital signs, review of adverse events, study drug accountability and clinician- and patient-rated scales will be conducted at specific study visits.

Description of BNA

BNA is a method of analyzing electrophysiological and neuropsychological brain network activity using multichannel signals acquired by EEG/ERP non-invasive system hardware. The following sections describe the EEG methodology and the neurocognitive tasks.

EEG Procedures

Subjects will be fitted with a net containing 64 EEG electrodes. While wearing the net, subjects will complete a series of cognitive tasks during which time data will be collected.
Standard EEG recording will be performed using the FDA system manufactured by Electrical Geodesics, Inc (EGI) from 64 locations by using Ag-AgCl electrodes mounted in an elastic net, referenced to electrode Cz. Channels will be sampled at 250 Hz.

The EEG system complies with the standard electrical safety (EN 60601-1) and EMC compatibility. During the recording of ERPs, triggers sent by the test presentation script to mark the onset of the stimuli and the subject response are recorded concurrently with EEG signals.

Neurocognitive tests (ERPs)

The following battery of tasks will be performed by subjects during the EEG. If total recording time reaches 60 minutes, the Delayed match-to-sample task below may be excluded.

Eyes Open/Eyes Closed tasks: EEG will be recorded at rest (no cognitive task), 2 minutes with eyes open and 2 minutes with eyes closed. The aim of the resting EEG recording is to extract patterns of the default mode network (DMN). The DMN is a network comprising many brain regions which show in fMRI studies reduced activation during task execution. Recently, the DMN has been studied also in EEG signals (Laufs et al. 2003). There is evidence that the DMN is impaired during emotional processing in MDD patients (for example see Grimm et al. 2009).

Auditory oddball task: The oddball task is a classic EEG paradigm that has been extensively used for many years, in numerous studies and in many neurological patient populations. It is considered to

involve executive functions, attention and memory processes. During the task, sounds will be presented, at an average rate of 1 every 1.5 sec. A total of 80% of the sounds ("standard') will be tones of repeating frequency and intensity. A total of 10% of the sounds ("target") will be tones of another frequency to which participants will respond by pressing a button. The remaining 10% of sounds ("novel") will be multi-frequency sounds, different for each trial). Segments of 1200 ms will be averaged separately for "standard", "target," and "novel" sounds. The task duration is approximately 12 minutes.

Visual Go-Nogo: The Go stimuli consist of white color English alphabetic letters the NoGo stimuli consist of white colored X symbol. The NoGo appears 20% of the time and the Go stimuli appears 80%. The stimuli are presented in the center of a black background computer screen for 150 ms, and are located between two vertical white lines which remain constant on the screen. Subjects are instructed to press a key as quickly as they can when presented with the Go stimulus and withhold pressing the key when the NoGo stimulus appears. The task duration is approximately 14 minutes.

Delayed match-to-sample: Memory and emotional processing related evoked potentials will be measured by presenting pairs of fearful or neutral faces with a delay of 1.8 sec. Subjects will judge whether the second face stimulus matches or not the first one. The task duration is approximately 13 minutes.

Optional tasks:
If recording time allows, additional, optional tasks may be completed which will be chosen from the following list, for a total EEG recording time of approximately 45-60 minutes.

Inter hemispheric transfer time (IHTT): In this task the subject needs to count red dots that appear in the middle of the screen while white squares flashes either in the left or right visual fields. At the end of each block the subject reports the number of red dots. The inter-hemispheric transfer time is calculated from the evoked response to the peripheral stimuli. The task duration is approximately 12 minutes.

Auditory Go/No Go test: The Go/NoGo paradigm is among the most well-characterized assays of response inhibition to perceptual stimuli. Go/NoGo tasks involve the presentation of a continuous series of “Go” or “target” cues to which subjects are asked to respond as quickly as possible, and “NoGo” or “distractor” cues that require subjects to inhibit motor responses. ERP studies reliably identify a negative-going component occurring 200 – 400 ms following NoGo stimuli known as the “NoGo N2”, which occurs maximally at fronto-central scalp locations. On NoGo trials, the N2 is followed by a positive-going shift. This positive complex, termed the “NoGo P3”, also occurs maximally at fronto-central scalp sites and is typically seen 300 – 700 ms following the NoGo stimulus. There is evidence showing a specific deficit in response inhibition in depressed patients, which requires executive control.

Both ERP source localization and fMRI data have demonstrated that the right ventral lateral prefrontal cortex (PFC), particularly the inferior frontal gyrus (IFG), is consistently activated with successful motor control on Go/NoGo tasks, and lesions to the IFG impair such inhibitory control. The IFG has been showing abnormal activity and connectivity in MDD. Based on these observations, the Go/NoGo may be a useful tool for assessing well-defined neural pathways in major depression. The task duration is approximately 18 minutes.

LDAEP: Subjects are seated with open eyes and are asked to look at a fixation cross in front of them. Tones (1000 Hz, 40 ms duration with 10 ms rise and 10 ms fall time, ISI randomized between 1800 and

2200 ms) of five intensities (54, 64, 74, 84, 94 dB sound pressure level) are presented binaurally in a pseudorandomized form by earphones. Before the study, the sound pressure level of the headphones should be calibrated with a sound level. The task duration is approximately 13 minutes.

INITIAL ASSESSMENT:

Mini International Neuropsychiatric Interview Version 6.0.0 (MINI or eMINI)
The MINI is a short structured diagnostic interview developed jointly by psychiatrists and clinicians in the United States and Europe for DSM-IV and International Classification of Diseases 10th Revision psychiatric disorders. With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology studies. It is to be used as a first step in outcome tracking in non-research clinical settings. Validation and reliability studies have been done comparing the MINI to the Structured Clinical Interview for DSM-IV, Patient Edition and the Composite International Diagnostic Interview. The results of these studies showed that the MINI has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7±11.6 minutes, median 15 minutes) than the above referenced instruments.

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist
The ASRS is a tool to help screen for ADHD in adult patients. Insights gained through this screening may suggest the need for a more in-depth clinician interview. The questions in the ASRS are consistent with DSM-IV criteria and address the manifestations of ADHD symptoms in adults. The checklist takes less than 5 minutes to perform.

DESCRIPTION OF CLINICAL OUTCOME MEASURES

DEPRESSION:

Montgomery and Åsberg Depression Scale (MADRS)
The MADRS is a 10-item rating scale designed to assess the severity of the symptoms in depressive illness that was shown to be sensitive to treatment effects. Items in the scale assess apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts. Symptoms are rated on a 7-point scale from 0 (no symptom) to 6 (severe symptom). Definitions of severity are provided at 2-point intervals. The total score of the 10 items ranges from 0 to 60. An experienced clinician can use the MADRS after a training session. It takes approximately 15 to 20 minutes to administer and rate the MADRS. All efforts will be made to keep the rater consistent.

Hamilton Depression Rating Scale (HDRS)
The HDRS is a clinician-rated used to rate the patient's depressive state based on feelings of depression, guilt, suicidality, anxiety, agitation, level of insight, patterns of insomnia, loss of interest in work and other activities, weight loss, hypochondriasis, and degree of psychomotor retardation. It also can be used to identify genital and somatic symptoms. This instrument will be administered by an experienced rater meeting the training requirements and qualifications set by the rater training vendor. All efforts will be made to keep the rater consistent.

Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-16-SR)
The QIDS-16-SR is a 16-item self-rated assessment of the severity of depressive symptoms. The QIDS assesses all the criterion symptom domains designated by the American Psychiatry Association Diagnostic and Statistical Manual of Mental Disorders - 4th edition, text revised (DSM-IV-TR) (APA 1994) to diagnose a major depressive episode. These assessments can be used to screen for depression, although they have been used predominantly as measures of symptom severity. The seven day period prior to assessment is the usual time frame for assessing symptom severity.

COGNITION AND FUNCTIONALITY:
Digit Symbol Substitution Test (DSST)
The DSST is a cognitive test designed to assess psychomotor speed of performance requiring visual perception, spatial decision-making and motor skills. The DSST consists of 133 digits and requires the subject to substitute each digit with a simple symbol in a 90-second period. The number of correct symbols within the allowed time (eg, 90 sec) is measured. It takes approximately 5 minutes to complete and score the DSST.

University of San Diego Performance-based Skill Assessment and UPSA-Brief
The UPSA was designed to evaluate the abilities of individuals to perform everyday tasks that are considered necessary for independent functioning in the community. The UPSA uses role-playing situations to evaluate skills in 5 areas: household chores (eg, preparing a shopping list for a specific cooking task and shopping for items in a mock grocery store); communication (eg, emergency call, dialing a number from memory, calling to reschedule a doctor's appointment); finance (eg, counting change, reading a utility bill, and write and record a check for the bill); transportation (eg, planning the use of a public bus system); planning recreational activities (eg, preparing for an outing to the beach or zoo).

Subscale scores for these scales range from 0 to 20 points, and total scores range from 0 to 100 points; higher scores reflect better performance. Administration of the UPSA requires about 30 minutes to be completed.

Stroop Test
The STROOP test [61] is a cognitive test designed to assess the ability to inhibit a prepotent response to reading words while performing a task that requires attention control. The STROOP test comprises 2 sheets with 50 words on each, and each word is the name of a color. On the first sheet, the Congruent STROOP Sheet, the word and ink color match; on the Incongruent STROOP Sheet, the word and ink color do not match. For each sheet, the subject has 4 minutes to name the ink color of each word. When the subject finishes the sheet, or once 4 minutes is up, the clinician notes the time taken and counts the number of correct and incorrect responses. It takes approximately 10 minutes to administer and score the STROOP test.

Trail Making Test – Part A and Part B (TMT-A AND TMT-B)
The TMT is a cognitive test designed to assess scanning, visuomotor tracking, executive function, and cognitive flexibility. Both parts of the TMT consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1–25, and the subject should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1–13) and letters (A–L); as in Part A, the subject draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (ie, 1-A-2-B-3-C, etc.). The subject should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. The subject is timed as he or she connects the "trail." If the subject makes an error, it is pointed out immediately and the subject is

allowed to correct it. Errors affect the subject's score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the subject has not completed both parts after 4 minutes have elapsed. It takes approximately 10 minutes to complete the TMT.

Cognitive and Physical Functioning Questionnaire (MGH-CPFQ)
The Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire is a brief scale used to measure cognitive and executive dysfunction in mood and anxiety disorders. It is a self-report unifactorial scale consisting of 7 items assessing aspects of cognitive and physical functioning, rated on a scale from 1 (greater than normal) to 6 (absent). The reliability and validity of this scale has been evaluated and results have shown it to have strong internal consistency, temporal stability and sensitivity to change with treatment.

Perceived Deficits Questionnaire (PDQ)
The PDQ is a subject-rated scale designed to assess cognitive function. The PDQ consists of four 5-item subscales: Attention/Concentration, Retrospective memory, Prospective memory and Planning/Organization. Each item is rated on a scale from 0 (never) to 4 (almost always). The total score of the 20 items ranges from 0 to 80 with higher scores reflecting greater subjective cognitive dysfunction. It takes approximately 15 minutes to complete the PDQ.

Working Limitation Questionnaire (WLQ)
The WLQ has 25 items summarized as 4 scales that represent the percentage of time that a person was limited in particular job demands: time and scheduling demands such as working without stopping or taking breaks and getting going easily at the beginning of the workday (WLQ Time); physical work demands such as sitting, standing or staying in 1 position for longer than 15 min while working and using hand-held equipment (eg, phone) (WLQ Physical); mental-interpersonal work demands such as thinking clearly when working and speaking with people in-person, in meetings or on the phone (WLQ Mental); and output demands, such as working fast enough and doing work without making mistakes (WLQ Output). Scales are scored from 0, limited none of the time, to 100, limited 100 percent of the time. Scores are weighted and aggregated to generate a productivity loss index score. The index is a weighted sum of scale scores that indicates reduction in output per hour compared with the output of a healthy (not limited) employee. This questionnaire will only be administered to subjects who have been employed at least 14 days before baseline.

GLOBAL:
Clinical Global Impression Scales (CGI-S and CGI-I)
The CGI consist of 2 subscales: CGI-S and the CGI-I. The CGI-S assesses the clinician's impression of the subject's current mental illness state. The clinician should use his/her total clinical experience with this subject population and rate the current severity of the subject's mental illness on a 7-point scale. The CGI-I assesses the subject's improvement (or worsening). The clinician is required to assess the subject's condition relative to Baseline on a 7-point scale. In all cases, the assessment should be made independent of whether the rater believes the improvement is drug-related or not.

Assessment of Suicidal Ideation and Behavior
Columbia-Suicide Severity Rating Scale ("Lifetime Recent – Clinical" and "Since Last Visit – Clinical"
The C-SSRS was developed by Kelly Posner, PhD and researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in subjects during participation in a clinical trial. The C-SSRS is comprised of 23 questions divided among four domains addressing suicidal behavior and

suicidal ideation, with sub-questions assessing severity. The scale is administered via clinician interview with the subject.

During the study, the EEG and neuropsychological tests are to be performed preferably at the same time of the day for an individual subject.

STATISTICAL ANALYSES

Primary Efficacy Analysis
The primary endpoint is the change from Baseline in the MADRS and DSST score. The primary endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment and center as fixed factors, and baseline score as covariate. The p-values, least squares (LS) treatment means, difference between the LS treatment means, and 95% CIs for the treatment differences will be displayed.

This is a pilot study that is intended to evaluate the extent of to which BNA technology can provide clinically valuable information, and to provide data that will help design a future confirmatory study. Because this is an exploratory study, no formal sample size calculation was performed; rather, sample size has been based on that which is generally accepted by the medical community for a study of this nature. In order to strengthen the level of confidence of the results, the BNA test is performed twice before the subject is given medication to provide repeatability and two additional times during the course of treatment to allow the identification of any potential trend that may occur as a result of treatment.

The relationship between changes in BNA and BNA total mean change from baseline and endpoint will be analyzed. Changes in BNA from baseline will also be analyzed by groups defined on endpoint status (e.g. response to MADRS, remission, change in DSST).

Statistical analysis should also consider the fact that changes in brain networks may be independent of symptoms or neurocognitive scores; thus, the analysis of BNA changes across treatment duration should be also performed independently. In other words, it is possible that BNA conveys information that is not found in other methods; trying to find correlations may limit the correct interpretation. Therefore, robust trends found in BNA scores should be further researched, regardless of finding correlations to symptoms or neurocognitive tests. For example, it could be that a change in BNA, without a significant change in symptoms, means that if the treatment will be continued for a few more weeks, a delayed improvement will be found; etc.

Secondary Efficacy Analyses
Change from Baseline in TMT A, TMT B, , PDQ, MGH-CPFQ, UPSA, percentage of productivity loss (WLQ), MADRS, CGI-S, and CGI-I will be analyzed at all time points (where rated) using ANCOVA model similar to the one described above for the primary endpoints.

MADRS responders (defined as a >50% decrease from Baseline), MADRS remission (defined as a MADRS total score <10). CGI-S remission (CGT-S2), and CGI-I response (CGI-I2) will be analyzed at all time points by logistic regression, adjusting for baseline score and treatment.

Proportion of cognitive dysfunction improvement that is not due to an improvement in depressive symptoms will be analyzed using a path analysis with change from Baseline in DSST score and change from Baseline in MADRS total score as endogenous variables.

C-SSRS will be summarized at all time points using descriptive techniques.

All statistical tests will be 2-sided and at the 5% level of significance. Ninety-five percent confidence limits will be presented together with the p-values.

Outcome Definitions

- Remission (Primary Remission Criteria)
  - MADRS total score $\leq$ 10; CGI-I < 2
- Remission (Secondary Remission Criteria)
  - Score $\leq$ 7 of first 17 items of the HDRS (28-item)
  - QIDS-SR16 total score < 5
- Asymptomatic Remission
  - MADRS total score $\leq$ 4
- Response (Primary Response Criteria)
  - ≥50% decrease in MADRS total score from baseline
- Response (Secondary Response Criteria)
  - ≥50% decrease from baseline of first 17 items of the HDRS (28-item)
  - ≥50% decrease from baseline in total score of HDRS (28-item)
  - ≥50% decrease from baseline in total score of QIDS-SR 16
  - ≥50% decrease from baseline in total score of MGH-CPFQ
- Non-Remitted (Primary)
  - MADRS total score > 10
- Non-response
  - Change in MADRS total score from baseline < 25%, and MADRS total score > 10
- Inadequate response
  - Change in MADRS total score from baseline 25-49%, and MADRS total score > 10

BNA Analysis

All BNA recordings will be transmitted to ElMindA for analysis.

We will use a receiver operating characteristic (ROC) curve to assess the ability of each EEG BNA group pattern to discriminate MDD cases from controls using individual BNA similarity indices. The ROC analysis uses each value across the entire range of the EEG BNA pattern as the cut-off for defining a case and compares this classification to the "true" diagnosis, as defined by the structured diagnostic interview. The ROC curve plots the sensitivity versus the false positive rate (1-specificity) across the entire range of cut-offs. This analysis generates a statistic called the area under the curve (AUC), which is proportional to the overall ability of the scale across its range of cut-offs to correctly identify both cases and non-cases.

Secondly, we will analyze the results of EEG measurement during the test within patients to identify possible predictors of treatment response. Those analyses are exploratory in nature, and they could potentially lead to develop an EEG biomarker to predict antidepressant response.

In the first stage EEG signals are pre-processed using standard methods of blind source separation followed by band pass filtering into overlapping physiological frequency bands, epoched and averaged to result with ERPs. For each band, the data is reduced into a set of discrete points that denote local extrema, the latencies and (z-score normalized) amplitudes of which are inputted to the algorithm. These activity peaks naturally contain the major conventional ERP components, but all other associated and induced peaks as well, which fully represent the significant information in the measured data. For each experimental state (i.e. pre- and post-treatment, monotherapy vs. adjunctive therapy, healthy control vs. MDD), the algorithm then searches for peaks that have latencies synchronous across subjects. Next, peak-pair patterns are identified, whether within a single electrode or between any two, such that the inter-peak intervals were also synchronous across subjects. More complicated patterns of 3 or more peaks are sought in a similar manner, until a state-unique multi-sited spatio-temporal pattern or several distinct patterns emerge – the BNA group network.

In addition, BNA change analysis will be performed. Each subject participating in the drug treatment arm of the study is assigned similarity indices that quantify the degree to which his/her individual BNA repertoire match that of each group BNA. The score is computed twice for each subject – once for pre-treatment, and once for post-treatment, the difference between them being termed 'BNA change'.

Safety Analyses

Adverse Events

- Spontaneously reported AEs will be investigator-evaluated and documented throughout the study.
- The definition of treatment-emergent adverse events (TEAEs) will be provided in the statistical analysis plan (SAP).
- AEs that were reported more than once by a subject during the same period will be counted only once for that subject and period at the maximum severity.

Clinical Evaluations

- Absolute values and changes from screening/Baseline in clinical safety laboratory tests, vital signs, ECG parameters, and weight will be summarized for each treatment group using descriptive techniques. Values outside normal ranges and potentially clinically significant values will be flagged and tabulated.
- Physical examination findings will also be summarized for each treatment group.

RISK/SAFETY INFORMATION

EEG recording is a safe and non-invasive diagnostic procedure with no significant risk for the health of subjects. The EEG system complies with the standard electrical safety (EN 60601-1) and electromagnetic (EMC) compatibility and has received FDA clearance. Staff will be trained to minimize the discomfort associated with electrodes placement. Subjects will be able to communicate with staff throughout the procedure. The recording will be discontinued if the subject will indicate that she has become uncomfortable.

Memory and thinking tests can sometimes make subjects tired or uncomfortable. The study staff will try to make all subjects as comfortable as possible. Subjects will be informed that they do not have to answer any questions they choose not to answer.

Antidepressant medication (vortioxetine)
At the time of informed consent, the subject will be instructed about the risks and benefits of the vortioxetine that will be used throughout the study.

The potential risks of the medication will be based upon the FDA-approved package insert labeling for vortioxetine and will include, but not limited to, spontaneous reported adverse events and potential serious adverse events. Source documents will contain documentation that the subject was informed of risks of treatment and that there was adequate time to read and discuss this information with the clinician during the informed consent process.

The FDA-approved package insert for vortioxetine recommends a starting dose of 10 mg/day, increased to 20 mg/day as tolerated. The maximum dose is 20 mg/day, and the minimum dose is 5 mg/day if a higher dose is not tolerated. This allows for individualized "flexible" dosing for efficacy and tolerability.

In order to standardize this flexible dosing, all subjects will be started at 10 mg/day following visit 2 (baseline). The dose will be increased to a maximum of 20 mg/day after visit 4 (2 weeks of treatment) if tolerated by the subject. Dose decreases may occur at any time until Visit 8 for tolerability issues, to a minimum dose of 5 mg/day, and the dose may be re-increased if the tolerability issue resolves.

No dose adjustments may take place after visit 8 through the end of treatment (Visit 10).

Safety, tolerability, and depressive symptoms/function assessments will occur at baseline and each subsequent visit through the end of the study. While this is an exploratory analysis, the impact of treatment at various points in the study will be analyzed. Baseline assessments will occur prior to the subject receiving medication.

Drug accountability will be recorded at all visits. Subjects failing to meet at least 80% adherence to study medication between study visits will be discontinued from the study.

Other Risks
Whenever a subject is determined to be at risk for suicide during a clinical visit by the examining clinician, she or he will be escorted to the nearest emergency room.

We will not share information about subjects' participation in this study with others to minimize risks relative to subjects' privacy. Every effort will be made to keep participation confidential. These issues will be clearly stated in consent forms and discussed with participants during the informed consent procedure.

Consistent with good clinical practice, safety will be monitored by each subject's assigned clinician at each study visit. This clinician will be available 24 hours a day by page. The PI will supervise all study activities including ratings, reported adverse events, laboratory tests, and vital signs. Subjects will be monitored for adverse events at each visit and during phone communications with the clinician. All adverse events will be recorded.

All procedures will aim to minimize subject discomfort, and no subject will be asked to engage in research procedures not outlined in the consent form. All adverse events will be reported to the PHRC according to PHRC guidelines.

Subjects who are judged to experience a worsening of depressive symptoms as manifested by a CGI-Improvement rating of 6 or more (1=Very much improved, 2=Much improved, 3=Minimally improved, 4=No change, 5=Minimally worse, 6=Much worse, 7=Very much worse) or per the investigator's opinion for 2 consecutive visits the subject may be removed from the study and provided referrals as appropriate.

Subjects with MDD will be offered three months of follow-up care at the completion of the study (or if they are required to discontinue for any reason) in which they will be seen by study staff for routine outpatient management of their MDD. Subjects will receive referrals to clinicians in their communities, either at the end of the 3 month period, or sooner upon their request or circumstances require such a referral as determined by the investigator.

If a subject becomes pregnant or is found to be abusing substances during the study, he or she will be discontinued from the study and given referrals.

If a subject would like to have their clinical history forwarded to his/her primary care physician, or a new clinician, we will forward any pertinent information upon completing release forms in compliance with Good Clinical Practice Guidelines. If a subject was referred from a health care provider that is appropriate for follow-up care, the investigator may offer this among other possible referrals after the last study visit.

EXPECTED BENEFITS

Potential benefits to the participants include a thorough assessment by an expert clinician, education about the disorder, a treatment for MDD that could be continued after the study, and the opportunity to contribute to medical science and thus help others with the disorder.

MONITORING/REPORTING OF AE/SAE *COLLECTION AND RECORDING:*

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or *life-threatening suspected adverse reaction*. An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or *serious suspected adverse reaction*. An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered

serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. *Suspected adverse reaction* means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or *unexpected suspected adverse reaction*. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

While reports of pregnancy and overdose are not adverse experiences as defined above, notifications of these events will be made per procedure defined by IRB requirements and in accordance with further practice as designated by the PI.

Any adverse event that is ongoing when a subject completes his/her participation in the study must be followed until any of the following occurs:

a. The event resolves or stabilizes;
b. The event returns to baseline condition or value (if a baseline value is available); or
c. The event can be attributed to agent(s) other than the study product, or to factors unrelated to study conduct.

REPORTING TO IRBs AND REGULATORY AUTHORITIES:

The sponsor must notify FDA in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv). The sponsor must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. See §312.32 of the CFR for guidance.

STUDY OVERSIGHT

The Principal Investigator will be responsible for monitoring and assuring the validity and integrity of all data and adherence to the IRB-approved protocol. The study staff will monitor source data and case report forms by routine internal monitoring. BNA data will be monitored and interpreted by ElMindA in collaboration with the principal investigator, sub-investigator and study staff to assure BNA data is accurately collected.

The principal investigator and sub-investigators are responsible for monitoring the safety of the subjects who have entered this study and for alerting the IRB of any event that meets IRB reporting criteria. The investigator is also responsible to follow, through an appropriate health care option, adverse events that are serious or that caused the subject to discontinue before completing the study. The subject should

be followed until the event resolves or is explained. Frequency of follow-up is left to the discretion of the investigator.

Data and Safety Monitoring

The principal investigator will be responsible for monitoring the safety of all subjects. In the event the principal investigator is unavailable, a sub-investigator will be available to monitor the safety of all subjects. Subjects will be evaluated throughout the study to assess comfort and safety. The principal investigator will be responsible for determining if a subject should be removed from the study. Subjects will be removed from the study if they decide to withdraw consent or are unable to tolerate the procedures due to anxiety and discomfort or if they develop a medical condition incompatible with their participation. The principal investigator will also terminate a subject's participation if they will determine that it is not in the subject's best interest.

IRB REVIEW/ETHICS/INFORMED CONSENT

IRB Review

Prior to enrolling any subjects, documentation will be obtained that the study protocol and informed consent form have been approved by the Schulman Associates Institutional Review Board. Any change in the protocol or informed consent form will require prior written approval except to prevent injury or risk to a subject.

Regulatory Considerations

This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represents the greater protection of the individual.

Recruitment

The study population will be recruited from the greater Chicago metropolitan area. Subjects will be recruited from several sources, including referrals, responders to our general depression recruitment (advertisements on craigslist, newspapers, radio, the PMA website, private practice settings and community health centers). Subjects will also be recruited from ongoing clinical trials at Psychiatric Medicine Associates, LLC (PMA). Subjects may also be recruited from other trials only if considered appropriate for an open label treatment study with vortioxetine and do not meet other exclusion criteria. This is a study of depression in adults and therefore children will be excluded.

Subjects will be reimbursed for appropriate travel expenses during participation in the study.

GENERAL STUDY PROCEDURES

All study personnel will have completed training for Good Clinical Practice guidelines prior to study initiation. There will be a start-up meeting on site for all study personnel prior to initiating the trial, including protocol review, study procedures, delegation of responsibility, recruitment, inter-rater reliability (for those who are involved in clinical ratings), and to review general study issues. Updates of the study will occur at weekly staff meetings, including internal monitoring of study-related documentation, enrollment updates, and to review amendments and/or serious adverse events.

All subject source documents and case report forms will be in written form and contained in a subject binder. Data for clinical patient/clinician assessments/outcomes will be entered into an electronic

database after review by the investigator/subinvestigator and internal monitor. Subjects will be assessed at each visit by investigator/subinvestigator to assure criteria are met to remain in the study. All study documents will be kept in a secure location and in compliance with GCP guidelines. Medication dispensing and recording of accountability will be done only by personnel who have authority (e.g., MD, PA). All medication will be kept in a double-locked, secure location in accordance with GCP guidelines and DEA requirements (for the investigational product). Temperature logs will be maintained daily and kept at a temperature recommended for the investigational drug.

CONFIDENTIALITY

All information collected about subjects for the purposes of this study will be treated as confidential to the extent allowed by law. The information obtained while subjects are enrolled in this study, including all study-related hospital and office records, will be made available to the study doctor, the study sponsor (Takeda), the Institutional Review Board and other regulatory agencies, including the United States Food and Drug Administration (U.S. FDA).

Sending Specimens/Data to Research Collaborators Outside of PMA:

EEG recordings, neurocognitive tests, depression outcomes and demographic data will also be sent to ElMindA Ltd headquarters in 16 Haminhara St. Beit Bachar, Herzliya 46586, Israel for analysis. Any personal information and/or identifier will be removed to protect participants' identity and privacy.

ElMindA Ltd will have access to EEG data, study-related case report forms and questionnaires, and neurocognitive test results to perform BNA analysis (including electronic database information). Study documents and data will also be accessible by the study sponsor, Takeda.

INTENDED USE OF THE DATA

The results of this research project may be presented at meetings or in publications, but the identity of subjects will not be disclosed in such presentations.

REFERENCES

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APPENDIX I - SCHEDULE OF EVENTS

Visit #	Screen 1	Baseline 2	3	4	5	6	7	8	9	10 (or ET)
Day	**-2 to -14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**
Week	**-1 to-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Informed Consent	X									
Incl/Excl Criteria	X	X								
MINI	X									
ASRS	X									
Medical and Psychiatric History	X									
Demographics	X									
Physical Exam	X									
Laboratory tests, urinalysis, urine pregnancy test and urine drug screen[1]	X									
Vital signs and weight[2]	X	X	X	X	X	X	X	X	X	X
Height		X								
12-Lead ECG	X									
HDRS (28-item)	X	X	X	X	X	X	X	X	X	X
QIDS-SR-16	X	X	X	X	X	X	X	X	X	X
MADRS	X	X	X	X	X	X	X	X	X	X
DSST	X									X
UPSA	X									X
TMT-A AND TMT-B	X									X
Stroop Test	X									X
MGH-CPFQ	X	X	X	X	X	X	X	X	X	X
PDQ	X	X	X	X	X	X	X	X	X	X
CGI-S	X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X
WLQ	X	X	X	X	X	X	X	X	X	X
C-SSRS[3]	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X
Study drug dispensed		X	X	X	X	X	X	X	X	
Study drug accountability			X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
EEG (BNA reading)	X	X		X						X

[1]may be repeated at investigator's discretion
[2]including body temperature (oral), blood pressure and pulse.
[3]C-SSRS lifetime version at screen only; Since Last Visit version at V2-10