Remediation of Age-related Cognitive Decline: Vortioxetine and Cognitive Training

NCT03272711

Study Protocol & Statistical Analytic Plan

September 23, 2016

IISR GUIDE: STUDY INFORMATION **Date: (*09/23/2016)*** **Protocol Version: Sixth**	
Country(s) the study will be conducted in:	USA
Compound/Product: (Generic Drug Name)	Vortioxetine
Study Type (ie, clinical, non-clinical):	Clinical
Study Title:	"Remediation of age-related cognitive decline: vortioxetine and cognitive training" (IISR-2014-100821; PI: Eric Lenze, M.D.).
Indication *(List Area of Focus: Gastroenterology, Diabetes/Metabolism, Hypertension, Central Nervous System, Respiratory, Nephrology, Other):*	Age Related Cognitive Decline (Central Nervous System)

INVESTIGATOR CONTACT INFORMATION	
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RESOURCES REQUESTED	
Resource Requested: *(Drug, Funding, or Drug & Funding)*	Drug & Funding
Estimated Study Budget: *(Enter total here - including direct, indirect cost and institutional overhead); -*	$ 600,048.86
Do you have additional funding sources for this project? *(If Yes, please explain)*	No
Dosage and Formulation:	10mg
Estimated Total Drug Supply for Study: *(number of tablets, vials)*	18250 vortioxetine 10mg 18250 matching placebo

Total # of Subjects:	100
Study Timeline *Planned Activation Study: (Month/Year)* *Study activation is final regulatory authority approved protocol and fully executed contract*	April 29, 2016
Study Activation to First Patient In: (Months) (n/a for non-clinical study)	3
First Patient In to Last Patient Out: *(Months) (n/a for non-clinical study)*	18
Monthly enrollment rate (days)(n/a for non-clinical study):	1 participant randomized per 2.5 working days (= 100 in one year)
Treatment duration (in months) (n/a for non-clinical study):	6
Number of Study sites/depots (n/a for non-clinical study)	1
Completion of Data Analysis: (# Months)	2
Completion of Final Study Report/Manuscript: (Month/Year)	8/1/17 (or earlier): provide report of acute phase study outcomes to sponsor. 2/1/18 (or earlier): provide report of one-year study outcomes to sponsor. 4/1/18 (or earlier): submit results to a peer-reviewed journal.
Publication Plan: (target journal, target conference)	Potential journals include NEJM, Lancet, JAMA, and Journal of the American Geriatrics Society. Above publication plan may be time-adjusted depending on date of funding; it assumes one year for recruitment, 6 weeks for acute phase, additional 22 weeks for long-term outcomes, and 8 weeks for data cleanup,

	analysis, and writing up of results.

STUDY PROPOSAL

Study Rationale:

Background:

We propose to test vortioxetine, in combination with a cognitive training program, to remediate age-related cognitive decline, in a randomized clinical trial. The vast majority of older adults will experience some deterioration in cognitive function as they age. This age-related cognitive decline varies widely between individuals, with individual differences related to preclinical Alzheimer's pathology, cerebrovascular changes, mood/stress, and genetic and other differences. Age-related cognitive decline can have substantial influence on quality of life, character of personal relationships, and the capacity for making informed decisions about health care, retirement, and other issues faced daily by millions of older adults. Cognitive training is beneficial for age-related cognitive decline; the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, a large randomized trial of a cognitive intervention in an older population with normal cognitive ability, showed that targeted cognitive training has beneficial and long-lasting effects on specific functions (Ball et al, JAMA 2002).

Rationale:

The need for combining vortioxetine with a cognitive training program is to increase the effect size of the cognitive benefit. Computerized cognitive training helps older adults to preserve and enhance their cognitive function – but with a small overall effect size (Lampit et al, PLOS Medicine 2014). The rationale for a combined intervention is based on preclinical animal models suggesting that combined interventions (i.e., pharmacologic + behavioral interventions) may have greater pro-cognitive benefits through synergistic actions. This assertion may be particularly relevant to vortioxetine, as its combination with cognitive training could robustly drive beneficial plasticity of the aging brain, resulting in significant improvement (or remediation) in memory and executive function of older adults with age-related cognitive decline. At the same time, cognitive training programs are automated and therefore offer a feasible and scalable combination with pharmaceutical treatment.

We propose doing so in a framework that allows for an understanding of contributors to age-related cognitive decline and how they predict individual differences in vortioxetine treatment

response.

The project will extend findings from the existing vortioxetine studies (particularly the geriatric depression study, the FOCUS and CONNECT studies, and preclinical work elucidating vortioxetine's pro-cognitive mechanisms of action). Specifically, data from this study will (1) inform projects currently under development, particularly in the area of mild cognitive impairment (MCI), and (2) clarify whether age-related cognitive decline is a potential target for a new indication. Along these lines, the FDA has indicated that approval for drugs for "pre-MCI" would be possible given a benefit for a cognitive outcome with an accelerated approval process, given the urgent need for disseminable treatments in the very early stages of cognitive decline (personal communication, George Nomikos; and Kozauer & Katz, NEJM 2013). (3) Most importantly, the project would pave the way forward for treatment approaches for this extremely common age-related syndrome that is expected to affect the majority of aging adults.

Finally, the project is led by a PI who has repeatedly shown the ability to meet ambitious recruitment and completion timelines and succeed in demonstrating benefits of pharmacological treatments for symptoms and cognition in older adults, in both industry-sponsored and government-funded studies.

Hypothesis:

(1) Hypothesis 1: Vortioxetine will boost the acute and long-term cognitive benefits of computerized cognitive training in older adults with age-related cognitive decline who receive computerized cognitive training.

H1a will test the hypothesis that participants randomized to vortioxetine will have a greater acute improvement in neuropsychological functioning than those randomized to placebo. This will be tested using acute (week 0 and week 4) data.

H1b will test whether participants randomized to vortioxetine will have a better long-term course in neuropsychological functioning than those randomized to placebo. This will be tested using all longitudinal data (week 0, week 4, week 12, and week 26).

Hypothesis 2: Vortioxetine will improve everyday functioning in older adults with age-related cognitive decline who receive computerized cognitive training.

H2 will test whether participants randomized to vortioxetine will have a better long-term course in

function (using the UPSA) than those randomized to placebo. This will be tested using all longitudinal UPSA data (week 0 and week 26).

Primary Aim/Objective:

Test the efficacy of vortioxetine for acutely improving neuropsychological functioning on the NIH Toolbox Cognitive Battery in 100 participants aged 65 and older with age-related cognitive decline, who will receive computerized cognitive training and will also be randomized 1:1 to vortioxetine or placebo.

Secondary Aim/Objective: (*if applicable)*

Test the long-term (26 week) efficacy of vortioxetine's benefits.

Test the functional benefits of vortioxetine.

Explore brain-based predictors (moderators) of vortioxetine treatment efficacy.

Primary Endpoints:

Our primary outcome measures will be the total fluid cognitive score from the NIH Toolbox as well as the speed of cognitive improvement. The NIH Toolbox will be carried out at baseline and after the lead-in phase (to establish a baseline and clarify inclusion into the study) and at 4, 12, and 26 weeks post-randomization.

Secondary Endpoints:

As a secondary outcome, we will assess participant function using the UCSD Performance-Based Skills Assessment (UPSA), which has been shown to be sensitive to the cognitive effects of vortioxetine.

Study Plan

The key design features are:

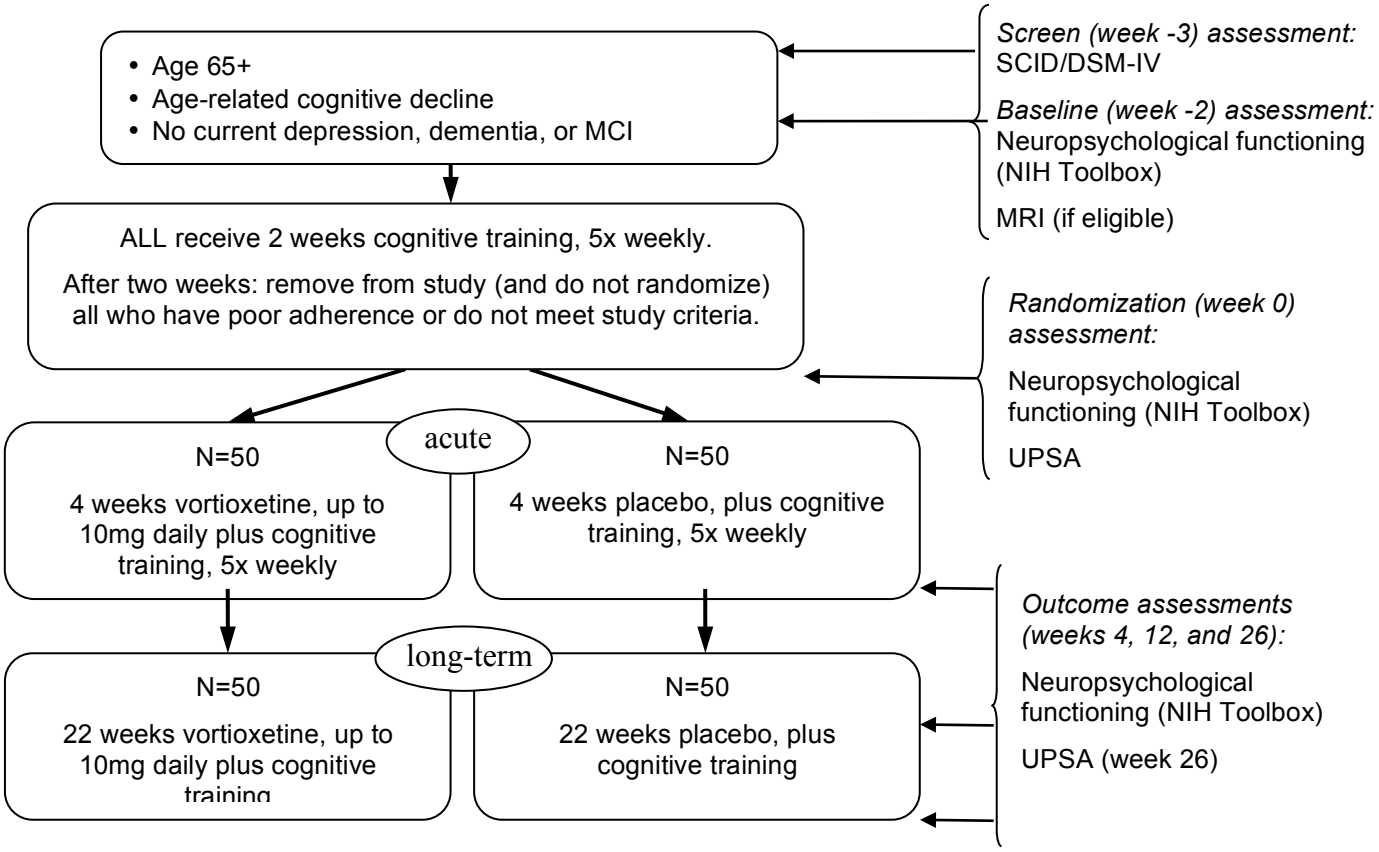
(1) Parallel-group randomized, double-blinded controlled trial of up to 10mg vortioxetine vs placebo, 50:50 randomization.

(2) Randomize 100 adults aged 65+ with age-related cognitive decline. A sample size of 100 balances power and feasibility concerns, allowing for a reasonably-powered preliminary examination of efficacy and exploration of individual differences while providing a finding within a near-term time frame (initial results at the end of one year of funding). This will require recruiting and consenting, in our estimate, approximately 120 individuals, with approximately 10% being

removed in the baseline and after lead-in phases.

(3) All participants receive cognitive training using a well-validated program, "Scientific Brain Training Pro" (www.scientificbraintrainingpro.com). Prior to randomization, all participants receive a training session with research staff and then an "open label lead-in" of two weeks of cognitive training (with their home computer), 5 times weekly for 30 minutes/day.

Study design and schedule of procedures:



Description of the cognitive training program: Cognitive training techniques result in physiological adaptation of the brain as a result of neuroplasticity, leading to tissue growth and more efficient neurophysiological processing. These techniques increasingly rely on drill and practice computerized exercises, which include graded changes in difficulty level to adapt to the dynamic performance of the individual. That is, the participant's performance guides the task parameters and a trial-by-trial change in difficulty level is made to keep the activity challenging enough to stimulate neuroplasticity, but not so difficult that repeated failure produces discouragement and withdrawal. The training is feasible with older and even novice computer

users; the participant logs into the activity online through a simple interface that only displays a request for username and password and the exercises appear automatically through a pre-selected order. Thus, participants click “play” or “exit”, reducing the visual distractions and complexity that might be associated with computer use in general. There are 28 different cognitive exercises, each with 30 levels of difficulty. Training progresses from basic (i.e., processing speed, attention) to more complex (i.e., working memory, executive functions) cognitive functions. Difficulty levels change adaptively by increasing following consecutive trials of 80% success or better and decreasing following consecutive trials of 70% success or less. Feedback is provided after each trial and participants have access to visual displays of their progress on each task throughout their training period. A one-hour orientation and training session is completed with participants following baseline assessment. This includes psychoeducation to the purpose of improving cognition, which is integrated into the participant’s own profile of cognitive strengths and limitations and their self-defined goals for functioning. A manual is provided to participants with clear instructions, goals, and strategies for each of the exercises. The program has a moderated forum wherein participants share their cognitive strategies and how the tasks are relevant for everyday life skills.

Rationale for all participants to receive cognitive training: numerous studies already have demonstrated the cognitive benefits of cognitive training for older adults with age-related cognitive decline. This study would be the first to examine vortioxetine’s benefits when taken together with cognitive training. Combining medication with cognitive training is expected to synergize with the drug's putative pro-cognitive mechanisms of action; this should demonstrate greater cognitive benefits than has been shown in most of the existing studies with drug alone. Another advantage of this approach is that the project may be more appealing for individuals seeking help for their cognition.

Rationale for a lead-in phase: The lead-in phase (cognitive training only; no medication) allows for a confirmation of participants’ motivation and willingness/ability to carry out the cognitive training. For those unable or unwilling to do so, they can then be removed from the study at the end of the two-week lead-in phase, without penalizing the randomized controlled trial. Additionally, sequencing the treatments (providing cognitive training first and then medication later) is less taxing for participants than introducing two treatments simultaneously. Finally, those who hit a ceiling effect on neuropsychological testing after two weeks of training will be removed prior to

randomization. These advantages improve our ability to discern specific efficacy of vortioxetine.

(4) At Baseline visit (baseline visit = prior to first dose of vortioxetine or placebo), all eligible participants will receive a structural and resting-state functional connectivity brain MRI. This will examine brain markers of age-related cognitive decline that could be treatment response predictors. Doing so would clarify inclusion/exclusion criteria for future cognitive aging research with vortioxetine.

(5) The RCT has two phases, acute and long-term. The acute phase is four weeks long, during which participants receive either up to 10mg vortioxetine or placebo, and all participants also receive four weeks of cognitive training at home, 5 times weekly for 30 minutes/day, which our team has previously found to be an acceptable amount, even in very ill samples. The long-term phase would last an additional 22 weeks, during which participants remain (double-blinded) on their vortioxetine vs placebo assignment. During that time, participants will also continue to receive cognitive training (with their home computer), 5 times weekly for 30 minutes/day.

Schedule of assessments:

	Week of study					
	-3	**-2**	**0***	**4**	**12**	**26**
Outcome measures						
(Hypothesis 1) Cognitive battery		X	X	X	X	X
(Hypothesis 2) UCSD Performance-Based Skills Assessment (UPSA)			X			X
Baseline assessments						
Structured Clinical Interview for DSM-IV Disorders (to exclude major depression and other disorders)	X					
MRI (structural + resting state fMRI)		X				

* Note: week 0 = randomization visit.

Rationale for study length: the four-week acute phase allows for a rapid test of vortioxetine's benefits in the setting of co-administered cognitive training. Four weeks was chosen because it is

a sufficient length to achieve steady state concentrations of vortioxetine, and to expect neuroplasticity (and thus neuroplasticity enhancing) effects of the drug in combination with training.

The long-term phase duration (26 weeks) is chosen for several reasons. First, research with other neuroplasticity-enhancing intervention (namely, aerobic exercise) has suggested that longer duration of intervention may be necessary to see the full cognitive benefits. Therefore, it is possible that significant effects of vortioxetine in this context would not be apparent until 26 weeks. Second, this would provide valuable data on the long-term cognitive impact of vortioxetine, and the functional benefits that result.

With respect to adherence to 26 weeks of cognitive training, in our recent studies, we had success with this training period (5 to 7x per week) over a 12 week period with no evidence for substantial drop off during that period. (Bowie et al, J Nerv Mental Disease, 2013). Compliance over six months may be lower, but this is not expected to change study results and will be informative for future efforts to tie vortioxetine to cognitive-enhancing behavioral interventions.

Adherence monitoring to the cognitive training program and the study medication: the cognitive training program has built-in adherence monitoring. During the pre-randomization lead-in phase, we will use these data to determine whether or not to include participants in the RCT. During the RCT, we will use adherence monitoring to provide motivational feedback to participants to reinforce or increase adherence. We will examine medication adherence via self-report and pill count, which in our prior studies has provided >99% accurate data compared to a gold standard of blood tests of medication concentration.

Blinding measures taken to minimize bias: Subjects receive blinded study medication. Investigators will also be blinded; only the data manager will know treatment assignment. It is our goal to get key results to Takeda/Lundbeck as rapidly as possible. We will prepare an interim data analysis and a study report for Takeda/Lundbeck once the last participant has completed the acute phase, while keeping the rest of the team blinded. This would be the only such interim analysis. Prior to completing any final analyses for publication in a peer-reviewed journal, we will close the dataset and remove the blind.

Inclusion criteria: (1) Community-living men and women age 65 and older; (2) Age-related cognitive decline as defined by (a) self-reported cognitive dysfunction that is attributed to the aging process (in response to screening questions to the participant); (b) ability to complete cognitive battery, but still scoring less than 1 standard deviation above age-matched norms at both baseline and after the two-week cognitive training lead-in. Both a lower limit (to exclude dementia and mild cognitive impairment) and upper limit (to avoid ceiling effects) are needed. An upper limit of >1 standard deviation above age-matched norms reflects that with typical aging, older adults have declines in the domains of memory, executive functioning, and information processing speed compared to younger cohorts (thus have age-related cognitive decline).

Rationale for these age-related cognitive decline criteria: There is no clear consensus for how to define age-related cognitive decline for a clinical trial. Based on consensus definitions of age-related cognitive decline, and clinical trials by our group as well as other studies of vortioxetine, we propose three components: (1) the participant should endorse subjective difficulties with memory and/or concentration that are attributable to the aging process (rather than a lifelong problem such as ADHD); (2) At baseline, the participant should score below 1 standard deviation above the mean score of their age group in the NIH Toolbox total fluid cognition score, but still be able to complete the cognitive battery (as this inability to do so would indicate mild cognitive impairment); (3) After the initial two-week lead-in of cognitive training, the participant should continue to score below 1 standard deviation above the mean of their age group (to exclude individuals who "respond" to either simply repeating the neuropsychological testing or to brief cognitive training). These components should maximize our ability to detect a signal with vortioxetine in the RCT.

Exclusion criteria: (1) Known dementia or other clinical neurodegenerative illness (e.g., Parkinson's disease, cerebrovascular disease) per self-report, informant report, medical records, or neuropsychological testing. (2) Any current psychiatric disorder. (3) Medical conditions that suggest shortened lifespan, such as metastatic cancer; or would prohibit safe participation in the interventions, including cardiovascular disease or musculoskeletal conditions; or with the assessments. (4) Sensory impairment that would prevent participation. (5) IQ < 70 as estimated by the Wechsler Test of Adult Reading. (6) Alcohol or substance abuse within 6 months. (7) Concurrent cognitive training, such as brain-training software, or other interventions expected to affect neuroplasticity. (8) Psychotropic medications or those with likely CNS effects (none within 4

weeks prior to study entry).

Rationale for exclusion of patients with depression: There are methodological and safety reasons for this exclusion. As previous studies of vortioxetine in older and younger adults with MDD have shown a cognitive benefit, we believe the next step is to examine cognitive benefits in a non-depressed sample, to further demonstrate independence of cognitive benefits from vortioxetine's antidepressant benefit. Additionally, a non-psychiatrically ill population can remain safely off of antidepressants and other psychotropics for the duration of the RCT.

Clarification of medical and medication exclusions: We will exclude the following medical conditions: any acute condition (e.g., active infection), uncontrolled condition (e.g., ongoing/unstable angina, poorly controlled diabetes or hypertension), progressive condition (e.g., stage 3 or 4 heart failure, or any neurodegenerative condition such as Parkinson's), life-threatening or life-shortening conditions (e.g., metastatic cancer), or any that is expected to affect cognitive function (e.g., hyper- or hypo-thyroidism) or ability to participate in the study (e.g., severe arthritis such that the participant could not carry out the neuropsychological tests).

We will exclude all medications that have known or likely CNS effects. These include not only all medications approved for psychotropic indications (e.g., antidepressants, antipsychotics, benzodiazepines, mood stabilizers), but also centrally-acting anticholinergics (e.g., oxybutynin), antihistaminergics (e.g., diphenhydramine), opioids (e.g., methadone) dopaminergic agents (e.g., ropinirole), and other medications with neuropsychiatric side effects (e.g., interferon), unless the use of the medication is rare and it can be avoided for at least 24 hours prior to cognitive tests.

Safety Reporting (please do not change the safety section of the template)

Institution/Investigator is solely responsible for reporting all Adverse Events and Serious Adverse Events to regulatory authorities, investigators, IRBs or IECs and Takeda, as applicable, in accordance with national regulations in the countries where the study is conducted.

Regardless of expectedness or causality, all SAEs must also be reported in English to Takeda Pharmacovigilance or designee:

> ***Fatal and Life Threatening SAEs*** *within 24 hours of the sponsor-investigator's observation or awareness of the event*
>
> ***All other serious (non-fatal/non life threatening) events*** *within 4 calendar days of the sponsor-investigator's observation or awareness of the event*

Takeda requires that all information be communicated to Takeda's Pharmacovigilance Department as outlined in the study contract.

All reported adverse drug reactions and safety issues related to Takeda compound must be included in the final study report.

Describe procedures for reporting Adverse Events and Serious Adverse Events.

Definitions:

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a medicinal product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. This includes adverse reactions which arise from: use of a medicinal product within the terms of the marketing authorization; use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors; and occupational exposure.*

** This corresponds to the exposure to a medicinal product for human use as a result of one's occupation, such as nurses who may handle products routinely in their occupational setting.*

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- *Results in **death.***
- *Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).*
- *Requires inpatient **hospitalization or prolongation of an existing hospitalization** .*
- *Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).*
- *Is a **congenital anomaly/birth defect**.*
- *Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy),*

pathogenic or nonpathogenic, is considered an infectious agent.

An IMPORTANT MEDICAL EVENT also includes any event described in Takeda Medically Significant AE List below:

Acute respiratory failure/acute respiratory distress syndrome	*Anaphylactic shock*
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	*Acute renal failure*
Malignant hypertension	*Pulmonary hypertension*
Convulsive seizures	*Pulmonary fibrosis*
Agranulocytosis	*Confirmed or suspected endotoxin shock*
Aplastic anemia	*Confirmed or suspected transmission of infectious agent by a medicinal product*
Toxic epidermal necrolysis/Stevens-Johnson syndrome	*Neuroleptic malignant syndrome/malignant hyperthermia*
Hepatic necrosis	*Spontaneous abortion/stillbirth and fetal death*
Acute liver failure	

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to the Takeda Pharmacovigilance or designee immediately. The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Takeda Pharmacovigilance or designee will request this information from the sponsor-investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Takeda Pharmacovigilance or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Product Complaints and Medication Errors

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda and report the event.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact Takeda (see below) and report the event.

Phone: 1-877-TAKEDA7 (1-877-825-3327)

E-mail: medicalinformation@tpna.com

FAX: 1-800-247-8860

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to Takeda Pharmacovigilance.

We will assess all participants prior to randomization with medical history and physical examination and routine safety laboratories (electrolytes, liver/kidney function, thyrotropin). We do not anticipate routine assessment during the RCT with safety laboratories or physicals, as vortioxetine is an FDA-approved medication at this dose and such routine monitoring is not recommended with its clinical use. We will assess and record vital signs at all in-person visits and, post-randomization, will assess for study medication side effects at all visits. We will assess for and record adverse events (serious and nonserious) throughout the RCT.

Statistical Analysis

The PI and his research team will carry out all data analyses (although the data will be available to the sponsor) and publish findings from the study. Efficacy analyses will be: primary – neurocognitive changes; secondary – functional changes.

The rationale for the study design and its sample size of 100 is based on achieving the greatest possible statistical power within the feasibility confines of a single-site study. Based on this sample size, we would have 80% power (at 2-tailed $p<0.05$) to detect a moderate effect size ($d=0.55$) for greater cognitive improvement in the vortioxetine group compared to the placebo

group.

We will use the intention-to-treat principle in examining vortioxetine's efficacy. All data from all randomized participants will be included. Given the common occurrence of non-treatment related dropout/nonadherence in this age group, we reduce the likelihood of these methodological problems by our screening/exclusion procedures, the lead-in phase, and the relatively short (4 week) acute RCT phase.

Our primary analytic strategy will be mixed effects models, where the treatment group by time interaction (from baseline to post treatment) will be the key analysis. This is the preferred strategy to a remission analysis as it provides greater statistical power than a categorical endpoint. Mixed effect models are also optimal for the intent-to-treat principle, as missing data are taken into account by the models.

H1a will test the hypothesis that participants randomized to vortioxetine will have a greater acute improvement in neuropsychological functioning than those randomized to placebo. This will be tested using acute (week 0 and week 4) data.

H1b will test whether participants randomized to vortioxetine will have a better long-term course in neuropsychological functioning than those randomized to placebo. This will be tested using all longitudinal data (week 0, week 4, week 12, and week 26).

H2 will test whether participants randomized to vortioxetine will have a better long-term course in function (using the UPSA) than those randomized to placebo. This will be tested using all longitudinal UPSA data (week 0 and week 26).

We will also explore predictors of cognitive improvement using brain MRI data. While this will be a more exploratory set of analyses, depending on results from H1a and H1b, we will examine whether MRI-derived data on (a) volumetric (b) white matter hyperintensities (c) connectivity within and between relevant cognitive circuits predicts both acute and long-term course of cognitive change in the vortioxetine vs. placebo groups.

Data Management Plan

The PI, Study Coordinator and/or other designated research staff will be responsible for data collection, error resolution, data entry and protecting the integrity of the data.

Source Data: Source data includes information in original records or copies of clinical findings,

observations, ratings, or other activities in a study necessary for the reconstruction and evaluation of the study.

Procedures: Source data received by the delegated individual responsible for data management should be reviewed for any missing data, incomplete fields or data outside the normal ranges in a timely manner. If any discrepancies are raised at this point, these must be clarified and any queries recorded immediately. Any amendments made on the original data collection sheet will be documented, initialed and dated by the individual/s using a single line through method so as not to obscure the original data collected. No correction fluid should be used.

On completion of the above process, a delegated member of the research team will enter the data into REDCap (Research Electronic Data Capture data capture software developed by Vanderbilt University for clinical researchers). This web-based software allows researchers the ability to perform checks on the data during the entry process, as well as while the data is in the system. Additional benefits of REDCap are: Support of Multiple Data Types, Textbox Data Validation, Audit Trails / Data Logging, Data Quality Module, Double Data-Entry, Branching Logic to conditionally show/hide fields, Custom Reports, and Study Calendar tool.

REDCap includes data import and export tools. Exported data can be done so with the removal of identifying information, and to any of the following software packages: CSV/Microsoft Excel, SPSS, SAS, R, Stata.

Data collection safety and confidentiality: Procedures designed to maintain data confidentiality include (1) formal training sessions for all research staff emphasizing the importance of confidentiality, (2) specific procedures developed to protect participants' confidentiality, and (3) formal mechanisms limiting access to information that can link data to individual participants.

Electronic records (computer files, electronic databases, etc.): All electronic records will be collected and maintained in compliance with Washington University approved policy and practice. The risks of breaching confidentiality will be strictly limited by the use of locked and restricted access to data, as well as the use of participant ID numbers rather than names in the data base. All sensitive electronic information is kept in password-protected files on a password-protected computer. All other data will be entered and secured in a WUSM database system.

Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.): The risks of breaching confidentiality will be strictly limited by the use of locked and restricted

access to data, as well as the use of participant ID numbers rather than names in the data base. Medical records containing PHI and research records are kept in a locked cabinet behind two locks. All research records are kept and transported in closed containers (e.g., sealed envelope, closed bag, closed wheeled cart, etc.), all in compliance with Washington University approved policy and practice. No identifiers are included in any reports generated by this study.

Publication Plan (i.e., abstract, presentation, journal, conference, etc.)

Our plans are as follows.

8/1/17 (or earlier): provide report of acute phase study outcomes to sponsor.

2/1/18 (or earlier): provide report of one-year study outcomes to sponsor.

4/1/18 (or earlier): submit results to a peer-reviewed journal and for presentation at conferences.

Potential journals include NEJM, Lancet, JAMA, and Journal of the American Geriatrics Society. Potential national conferences include the Gerontological Society of America and the American Association for Geriatric Psychiatry. The above publication plan may be time-adjusted depending on date of funding; it assumes one year for recruitment, 6 weeks for acute phase, additional 22 weeks for long-term outcomes, and 8 weeks for data cleanup, analysis, and writing up of results.

Ethical and Regulatory Considerations

Prior to initiating the study, the Principal Investigator will obtain written approval to conduct the study from the Washington University Institutional Review Board and send a copy to Takeda (gma.externalresearch@takeda.com). Should changes to the study become necessary, copies of written approvals from appropriate institutional ethical and/or regulatory committees will be sent to Takeda (gma.externalresearch@takeda.com).

The Principal Investigator will register the study with clinical trials.gov prior to randomizing subjects.

If an IND is required, the Principal Investigator will work with the FDA to obtain or prove exemption.

References

Ball K, Barch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, Morris JN, Rebok GW, Smith DM, Tennstedt SL, Unverzagt FW, Willis SL; Advanced Cognitive Training for Independent and Vital Elderly Study Group. Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA. 2002 Nov 13;288(18):2271-81.

Bowie CR, Gupta M, Holshausen K, Jokic R, Best M, Milev R (2013): Cognitive remediation for treatment-resistant depression: effects on cognition and functioning and the role of online homework. J Nerv Ment Dis. 201(8):680-5.

Kozauer N, Katz R. Regulatory innovation and drug development for early-stage Alzheimer's disease. N Engl J Med. 2013 Mar 28;368(13):1169-71.

Lampit A, Hallock H, Valenzuela M. Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. PLoS Med. 2014 Nov

18;11(11):e1001756
Supporting documentation/tables and graphs Tables/figures are embedded within the protocol.
Attach a detailed Budget for all study related costs. Budget is provided (separate document)