IISR GUIDE (to be completed in English) **STUDY INFORMATION** **Date: April 19th, 2017** **Protocol Version:3.1**	
Country(s) the study will be conducted in:	United States
Compound/Product: <Generic Drug Name>	Vortioxetine
Study Type :{ie, clinical interventional, clinical non-interventional, observational}	Clinical interventional
Study Title:	A Double-Blind, Placebo-Controlled Study of Vortioxetine in the Treatment of Binge Eating Disorder.
Indication:*List therapeutic area: {Gastroenterology, Diabetes/Metabolism, Hypertension, Central Nervous System, Respiratory, Other}*	Central nervous system

INVESTIGATOR CONTACT INFORMATION	
Number of Sites: ***(if there are sites multiple countries, name each country and number of sites in each country)***	1 – United States
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RESOURCES REQUESTED	
Resource Requested: *{Drug, funding or drug & funding}*	Drug and Funding
Estimated Study Budget: *(Enter total here – including direct, indirect cost and institutional overhead)*	$401,776
Do you have additional funding sources for this project? *(If yes, please explain)*	No
Dosage and Formulation:	10mg tablets and 20mg tablets
Estimated Total Drug Supply for Study: *(number of tablets, capsules, vials)*	10mg po qday (or placebo) for the first week and 10mg po qday (or placebo) for the final taper week (this means 14 days total taking 10mg tablets for 80 subjects = 1120 tablets [560 10-mg tablets and 560 placebos]) and 20mg po day for 11 weeks for 80 subjects (means 3080 tablets and 3080 placebos)
Total # of Subjects:	80 subjects (40 assigned to vortioxetine and 40 assigned to placebo)

Study Timeline: *Planned StudyActivation: (month/year)* *Study activation is final regulatory authority approved protocol and fully executed contract*	September 1, 2015
Study Activation to FirstPatient In (days, weeks, months):	September 7, 2015 (within one week of study activation)
First Patient In to Last Patient In *(days, weeks, months)*	20 months
Last Patient In to Last Patient Out (days,weeks, months)	13 weeks
Monthly enrollment rate:(days)	4 subjects per month
Treatment duration:(in months)	3 months (12 weeks of treatment and 1 week taper off)
Number of Study Sites/Depots: (depots are defined as shipment facilities for sites)	1
Completion of Data Analysis: (# months)	2 months
Completion of Final Study Report/Manuscript: (month/year)	October, 2017
Publication Plan: (target journal, target conference)	American Journal of Psychiatry ACNP

STUDY PROPOSAL

Background

Binge-eating disorder recently included in the DSM-5, is now recognized as a serious public health problem (Kessler et al., 2013). Binge-eating disorder is associated with obesity and psychiatric comorbidities, including depression, and may be predictive of metabolic syndrome (Mathes et al., 2009). Many patients are undertreated despite functional impairments and personal and social difficulties leading to a poor quality of life (Hudson et al., 2007). Binge-eating disorder is characterized by recurrent episodes of excessive food consumption accompanied by a sense of loss of control and psychological distress but without the inappropriate compensatory weight-loss behaviors of bulimia nervosa. Binge eating is seen in 23–46% of obese individuals seeking weight loss treatment and its severity relates to body mass index and predicts regain of lost weight.

Current treatments for binge eating disorder are often inadequate. Cognitive behavioral therapy has been shown to reduce binge eating but finding trained psychologists is difficult. Lisdexamfetamine was recently approved by the FDA for binge eating disorder (McElroy et al., 2015) but it carries risk of addiction and diversion and so will likely not be prescribed by most family physicians or psychiatrists. Other currently available medications, used off-label for binge eating disorder, include anticonvulsants, which may reduce binge eating but are often poorly tolerated (McElroy et al., 2012). Therefore, additional clinical trials are needed to identify effective pharmacotherapies.

Consuming food is necessary for life and involves brain regions that are quite ancient in evolutionary terms. The intestinal tract itself is almost like a “second brain” in that it contains vast amounts of neurons used to transmit and process sensory information; indeed the intestinal tract contains more of the neurotransmitter serotonin than the brain itself. Peripheral signals from the body (including from the intestinal tract, but also from the blood stream – e.g. glucose levels) are transmitted to brain regions such as the hypothalamic nuclei to help regulate appetite/hunger and maintain equilibrium. Another key aspect of circuitry involved in eating involves the brain reward system, including the nucleus accumbens, which is regulated by neurotransmitters such as dopamine, opioids, noradrenaline, and serotonin. In humans, but to a lesser degree in other animals, there is also top-down control from the prefrontal cortices, which serve to regulate our behaviors and suppress our tendencies to crave rewards, and allow us to flexibly adapt our behavior rather than get stuck in repetitive habits. Thus, binge-eating most likely involves dysregulation of all three above domains regulating behavior: the primitive ‘peripheral-hypothalamic’ feedback system, reward circuitry, and top-down control circuitry. On a neurochemical level, binge eating may be related to dysfunction of the serotonergic, dopamine, glutamatergic, and norepinephrine systems (David et al., 2009; Johnson and Kenny, 2010; Latagliata et al., 2010). Thus, a medication to target binge eating needs to be multi-modal in terms of its pharmacology.

Rationale:

Rationale for evaluating this compound in this population/target organ. Provide overall reason the study is being proposed, including past study results that may have led to a decision to propose this study.

Vortioxetine has distinctive properties that make it a promising option for patients with

binge eating disorder. In vitro studies indicate that vortioxetine is an inhibitor of the 5-HT transporter and is a 5-HT1D, 5-HT3 and 5-HT7 receptor antagonist, a 5-HT1A receptor agonist and a 5-HT1B receptor partial agonist. Animal and in vitro studies indicate that several neurotransmitter systems may be impacted by vortioxetine, with the drug enhancing levels of 5-HT, noradrenaline, dopamine, acetylcholine and histamine in certain areas of the brain, as well as modulating γ-aminobutyric acid and glutamate neurotransmission (Gibb and Deeks, 2014). In addition, vortioxetine appears to improve executive functioning which in turn has the potential to improve top-down cognitive control (Mahableshwarkar et al., 2015). This suggests that vortioxetine could improve the symptoms of binge eating disorder by two complementary pathways. Finally, because of low rates of side effects, low likelihood of sexual dysfunction, and the potential for improved cognitive performance, vortioxetine should be a well-tolerated and in fact desired medication approach to binge eating.

Given the serious public health problems associated with binge eating disorder, and the likelihood of success of vortioxetine in treating the disorder, the aim of the present study was to examine the efficacy and safety of vortioxetine vs placebo in adults with moderate to severe Binge eating disorder, as indicated by at least 3 binge eating days per week for the 2 weeks before the baseline visit

Hypothesis:

State hypothesis for study objectives.

We hypothesize that vortioxetine will be more effective than placebo in reducing the number of binge eating days per week after 12 weeks of treatment when compared to baseline.

Primary Aim/Objective:

For clinical studies– eg, To evaluate the safety and efficacy of interventions with test medication on symptoms, signs and quality of life in patients with target condition.

The aim of the present study is to examine the efficacy and safety of vortioxetine vs placebo in adults with moderate to severe Binge eating disorder, as indicated by at least 3 binge eating days per week for the 2 weeks before the baseline visit.

Secondary Aim/Objective:*(if applicable)*

A secondary aim of the study is to examine the effects of vortioxetine vs placebo con overall functioning and quality of life.

Primary Endpoint(s):

The primary efficacy measure is the number of binge eating days per week based on clinician interview and confirmation of identified Binge eating episodes in self-reported Binge eating diaries. The primary efficacy end point is the change from baseline to week 12 on the log-transformed scale (Binge eating days per week) + 1.

Secondary Endpoint(s): *(if applicable)*

Secondary efficacy measures include the number of Binge eating episodes per week, 1-week Binge eating episode response status, and 4-week cessation from Binge eating (free from Binge eating episodes). Other secondary endpoints include the change in weight/BMI between baseline and study endpoint, the Clinical Global Impressions–Improvement Scale (CGI-I) rated global improvement of symptoms over time (results will be dichotomized as improved [CGI-I ratings of 1 or 2 very much/much improved] or not improved [CGI-I ratings of 3-7]). The self-reported Eating Inventory, also known as the Three-Factor Eating Questionnaire, the self-reported Binge Eating Scale, the Yale-Brown Obsessive Compulsive Scale modified for Bing Eating (YBOCS-BE), the Quality of Life Inventory, the Hamilton Depression Rating Scale and the Hamilton Anxiety Rating Scale.

Study Plan:

Eighty individuals with binge eating disorder will be recruited for a double-blind, placebo-controlled pilot study in which Vortioxetine or placebo is administered in a 1:1 fashion. All 80 subjects will have binge eating disorder per DSM-5 criteria for at least a year. Following baseline measures, subjects will receive Vortioxetine (10mg for one week and then 20mg thereafter) or inactive placebo. Participants will be seen one week after the baseline visit (assessing the 10mg dose), one week after that (assessing the 20mg dose), and then every 2 weeks for the remainder of the 12-week period. At week 12, subjects will start a 1-week taper off the medication and will be seen at week 13. Efficacy and safety measures will be performed at each visit.

The study will be conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice, all local ethical and legal requirements, and the World Medical Assembly (Declaration of Helsinki). The study protocol and procedures will be approved by the University of Chicago's institutional review board prior to any recruitment. Written informed consent will be required for study participation.

Study Population

80 male and female outpatients aged 18-65 with a primary diagnosis of binge eating disorder.

Subjects

Inclusion criteria:

1) Men and women age 18-65;

2) Primary diagnosis of Binge eating disorder;

3) At least 3 binge eating days per week for the 2 weeks before the baseline visit;

4) Ability to understand and sign the consent form.

Exclusion criteria:

1) Unstable medical illness based on history or clinically significant abnormalities on baseline physical examination (history of medical illness which is currently stable is allowed such as diabetes well controlled, treated hypothyroidism, hypertension, etc)

2) Current pregnancy or lactation, or inadequate contraception in women of childbearing potential

3) Subjects considered an immediate suicide risk based on the Columbia Suicide Severity rating Scale (C-SSRS) (www.cssrs.columbia.edu/docs)

4) Past 12-month DSM-5 major psychiatric disorder (psychotic disorder, bipolar disorder, major depressive disorder)

5) Past 6-month alcohol or substance use disorders

6) Illegal substance use based on urine toxicology screening

7) Initiation of psychological or weight-loss interventions within 3 months of screening

8) Use of any other prescription psychotropic medication (except a PRN hypnotic or PRN benzodiazepine)

9) Previous treatment with Vortioxetine

10) Currently taking OTC weight loss medications. If willing to stop these medications, the participant will not be excluded based on this criterion.

10) Cognitive impairment that interferes with the capacity to understand and self-administer medication or provide written informed consent

Stable medical conditions ('stability' based on history and clinical and physical examination) will not be reason for exclusion.

Concomitant medications, that have no psychotropic qualities, will be allowed.

Participants can be receiving psychotherapy if they have been in treatment for at least 3 months prior to study entry.

Concurrent formal weight loss interventions will not be allowed.

Study Drug(s):

Drugs, Dosages, and Regimens

Baseline visit will consist of all evaluations. For subjects who meet inclusion/exclusion criteria, they will be randomized at the end of their baseline visit.

All 80 subjects who are randomized to Vortioxetine (1:1 randomization) will receive 10mg/day or placebo during the first week of the study (the first dose will be started the day immediately after the baseline visit). All subjects will receive 10mg or placebo for 7 days and then will be evaluated with all measures at week 1 (7 days after baseline).

At the week 1 visit, subjects will be started on 20mg/day (or remain on placebo) for the remainder of the study. They will return at week 2 (corresponding to having been on 20mg/day for one week) and be evaluated with all measures. After week 2 visit, all subjects will be seen every two weeks for the remainder of the 12-week study period (this corresponds to visits at week 4, 6, 8, 10, and 12). Week 12 evaluation will be the study endpoint for purposes of efficacy.

All visits are as outpatients and include in-person assessments.

After study conclusion (at week 12), the dose will be tapered off during a 1-week follow-up period. All subjects will return at week 13 for final safety evaluation only.

Dosage changes/reductions will not be permitted. Because nausea, and possibly headache, are the most likely side effects anticipated at the 20mg dose, participants will be allowed the use of over-the-counter options such as Tylenol prn for headaches, or bismuth subsalicylate for nausea. The use of over-the-counter options will be tracked at each visit. If side effects continue and are intolerable, the participant will have to discontinue treatment. If that occurs, a detailed 'final visit' assessment will be conducted and the participant will be contacted two weeks following to assess side effect outcomes.

Treatment Duration, Visit Frequency, and Procedures

This is a 13-week study (12 weeks of acute treatment followed by a 1-week tapering phase). Subjects will be seen for a total of 9 study visits. All visits will include the full battery of assessments except week 13 which is only a safety evaluation.

Randomization

Participants are randomized (1:1) to receive placebo or vortioxetine by the investigational pharmacy at the University of Chicago. The study blind will be maintained by over-encapsulation, making placebo and active treatments appear identical in size, weight, shape, and color. Dosage changes and reductions will not permitted during the study and participants will be discontinued if they experienced intolerance.

Baseline Visit Assessments

Those subjects who appear appropriate for the study, based on telephone screening, will be invited for a baseline assessment. The duration of the baseline assessment will be approximately 2-3 hours and will include the following: Informed consent, Demographic data, Concomitant medications (no psychotropic medications will be allowed), Family history data, Medical evaluation including physical examination, EKG, weight, and vital signs, Urine pregnancy test (for women of childbearing years) and urine drug screen, and a psychiatric evaluation (using the following measures: MINI International Neuropsychiatric Interview (Sheehan et al., 1998); Neurocognitive assessments of impulsivity; Depressive symptoms will be rated with the 24-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960); Anxiety symptoms will be assessed using the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959); Psychosocial functioning will be evaluated using the patient-rated version of the

Sheehan Disability Scale (SDS) (Sheehan, 1983); Quality of Life Inventory (QOLI) (Frisch et al., 1993); Compulsivity will be assessed using the Cambridge Chicago Trait Scale (Cambridge CHI-T Scale) (Grant & Chamberlain, 2016), the Lie Acceptability Scale (Goosie, 2014), The Narcissistic Personality Inventory (Raskin & Terry, 1988), The Social Desirability Scale (Crowne & Marlowe, 1960), and the Columbia Suicide Severity Rating Scale (C-SSRS)). If subjects consent, a blood sample will be collected to check for diabetes by measuring blood glucose levels.

At baseline, binge eating will be assessed using the following: Binge eating diary, Clinical Global Impressions–Severity Scale, the Three-Factor Eating Questionnaire, Self-Reported Binge Eating Scale, and the Yale-Brown Obsessive Compulsive Scale modified for Binge Eating (YBOCS-BE). Baseline labs, as well as interim labs, may be ordered based on clinical and medical evaluation.

Weight will be recorded using a calibrated scale with the participants not wearing shoes, rounded to the nearest 0.5 pounds, and converted to kilograms (to convert, multiply by 0.45) for data reporting.

Following-Up Visit Assessments

All follow-up visits will include safety measures (adverse events, vital signs, C-SSRS), weight, binge eating measures, Clinical Global Impressions–Improvement Scale, and other psychiatric measures.

Medical evaluation including physical examination will be performed again at study endpoint.

At study completion, participants will be made aware of all available options for follow-up care in the community.

Safety Assessments

Safety and tolerability will be assessed using spontaneously reported adverse events data, Columbia–Suicide Severity Rating Scale (C-SSRS) vital signs, and by evaluating premature termination. Safety assessments (C-SSRS, sitting blood pressure, heart rate, adverse effects, and concomitant medications) will be documented at each visit. Subjects who are an immediate suicide risk will be removed from the study and appropriate clinical intervention (e.g. hospitalization) will be arranged. Urine pregnancy tests will be performed at the initial visit. Subjects who have a positive urine pregnancy test will be excluded from the study. Assessment of side effects will be done at each visit. AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (Med- DRA) Version11.1. The incidences of all AEs will be summarized descriptively.

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 and pregnancy reports must also be reported in English by facsimile 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*

<u>Takeda Safety Reporting Contact Information</u>

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.

Reporting Adverse Events and Serious Adverse Events

- *Any unanticipated problem will be reported by telephone within 24 hours to Takeda. A full written report will be sent to the Institutional Review Board (IRB) at the University of Chicago and Takeda within 10 working days of the event.*
- *Any other adverse event will be summarized in the IRB and Takeda annual progress reports.*
- *The PI will inform either Takeda or the IRB at the University of Chicago of actions taken by the other organization as a result of their continuing review.*

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. Please refer to study contract for Takeda pharmacovigilance contact information.

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. Please refer to study contract for Takeda pharmacovigilance contact information.

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.

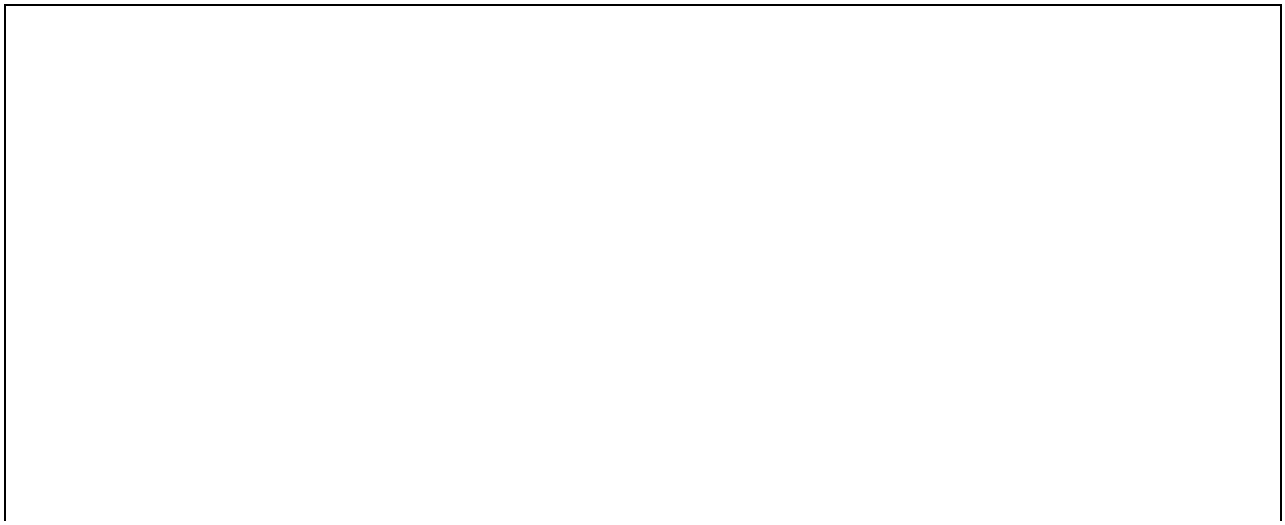
A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential 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.



Statistical Analysis:

Design/Randomization

The study is a double-blind, placebo-controlled study. Participants will be randomized (1:1) to receive vortioxetine or placebo by the University of Chicago Investigational pharmacy in block sizes of eight, using computer-generated randomization with no clinical information.

Efficacy Analysis

For statistical analysis, the full-analysis set will be defined as all participants who took at least 1 dose of the study drug and had at least 1 post-baseline primary efficacy assessment. The safety-analysis set will be defined as all randomized participants who took at least 1 dose of the study drug and completed at least 1 follow-up safety assessment.

We will compare the baseline characteristics of both groups using Fisher's exact test for categorical variables and the t test for continuous variables. We will calculate adherence to treatment, based on the number of capsules returned at each visit, as the number of capsules taken divided by the number of days in the study × 100%.

Primary endpoint analysis

The primary outcome measure will be the change from baseline in frequency of binge eating episodes (binges/week), defined as the mean number of binges per week in 2-week intervals. If the visit interval is less than 2 weeks, the mean number of binges per week will be estimated based on the number of binge days in the interval since the last visit.

Between group comparisons will use a mixed-effects model for repeated measures, including fixed factors for treatment and visit, the interaction of treatment and visit, a covariate of the log-transformation ([baseline number of BE days per week] + 1), and the interaction of the baseline covariate and visit using visit as a categorical variable. Mixed-effects models for repeated measures estimates differences from placebo in the change from baseline of the log-transformed scale ([BE days per week] + 1) at week 12 (primary end point). Based on previous research, log-transformation should reduce skewness (McElroy et al., 2007).

Secondary endpoints analyses

Secondary outcome measures will include the change from baseline in frequency of binge days (or mean days per week when the participant had one or more binges), weight, body mass index, global improvement, Three-Factor Eating Questionnaire, and Impact of Weight on Quality of Life.

We will also analyze changes from baseline in log-transformed BE episodes, TFEQ factor scores, and YBOCS-BE total score to week 12 using the mixed-effects model for repeated measures. Pairwise $\chi 2$ statistical tests will evaluates dichotomized CGI-I ratings at week 12 for placebo vs treatment group.

Response categories will be tabulated based on the percentage decrease in frequency of binges from baseline to endpoint, which will defined as follows: complete=cessation of binges; marked=75% to <100% decrease; moderate=50% to <75% decrease; and none=<50% decrease.

We will calculate effect sizes for the primary analysis of binges per week and weight using Cohen's d. Finally, we will perform a Spearman rank correlation to assess the association between the change in frequency of binges from baseline to week 12 and the change in weight from baseline using completers.

Safety analyses

Adverse events will be collected at baseline visit. We will evaluate differences between groups in the incidence of treatment-emergent adverse events using Fisher's exact test. Descriptive statistics will be used to evaluate changes in laboratory values, blood pressure and heart rate.

Sample Size

The sample size was calculated for the primary endpoint of change from baseline in binge eating days per week. For 80% power to compare the change from baseline in binge eating days per week on the log-transformed scale, assuming an effect size of 0.6 to 0.7 between treatment group and the placebo group, 40 participants will needed in each treatment group based on a 2-group t test at the .05 level of significance. Given the particularly low rates of adverse events reported with Vortioxetine, as well as its more positive side effect profile in terms of sexual side effects compared to other antidepressants used in binge eating disorder, we expect few drop-outs from the study and therefore a smaller sample is needed.

Feasibility

Given our past experience and the pacing of the study, we feel the goal to enroll 80 subjects in 20 months is practical and attainable. Given no-shows and rescheduling, and the time required for recruitment, telephone and in-person screening, and related issues inherent in any human study, the current goal of averaging at least 4 subjects per month is reasonable based on the fairly high prevalence of binge eating disorder, the number of subjects calling our outpatient clinic, and the large recruitment area of metropolitan Chicago. We will also employ our standard participant friendly provisions, including scheduling sessions in late afternoon/early evening and weekends, incorporating technological advances for contacts and reminders, and providing adequate compensation for participants' time.

Data Management Plan:

Data collected will consist of demographic data, subjective (self-report questionnaires, interview responses, ratings), and physiological (weight, heart rate and blood pressure). Access to individually identifiable private information about human subjects will be limited to Drs. Grant and Lee and their staff and will be collected specifically for the proposed research project. All collected data will be stored utilizing a 4-digit subject identification code, linked to separately stored identifying information via a coded log

only available to the PIs.

The gender ratio of adult binge eating disorder has been estimated to be approximately 1:1 We will also make every effort to include a racially/ethnically diverse study population. The year 2010 Chicago census is 2,695,598 (US Census Bureau, 2011). The year 2010 Chicago race distribution is as follows: white 47.1%, African/African-American 33.9%, Asian/Asian-American 6.2%, Native American 1.0%, or other race/not identified (11.8%). A total of 28.9% of the population also identified as Hispanic/Latino allowing for a diverse population sample (year 2010, US Census Bureau, Chicago, IL). We will make every effort to ensure that members of both genders and diverse racial, ethnic, and socioeconomic groups are adequately represented in the proposed study.

The PI will implement the following procedures to ensure data integrity and the safety of participants during the study: A number of elements of the research plan are intended to minimize the risks of study participation. For example, the study exclusion criteria exclude patients who are experiencing clinically significant suicidality or require a higher level of care than outpatient. If this is indicated, the PI will evaluate them and refer them for immediate non-study treatment (for example, inpatient or additional pharmacologic treatment). The PI will carefully monitor ratings on the Columbia Suicide Severity Rating Scale and the Hamilton Depression rating Scale; any participant endorsing suicidal thoughts, will be immediately evaluated by the PI and referred to a higher level of care if clinically indicated. The PI will evaluate patient safety at each visit and resolve any safety issues more frequently if necessary, as such issues arise. The PI will also be responsible for preparing written summary reports of adverse events and will prepare a written report summarizing any decisions that are made pertaining to participant disposition. Data integrity and confidentiality will be safeguarded as discussed above in the Data Management and Statistical Analysis section under Methods.

Timetable: Our research team has a history of excellent recruitment for research studies Our university clinic has active impulsivity and eating disorders clinics. The current goal of averaging at least 4 subjects per month is based on the number of calls we receive each month asking for treatment for this disorder. Generally the clinic received 10-15 calls per month for BED. Of these calls, we anticipate that approximately 30% would meet criteria for study entry. The study will recruit in month 1 of YR1 and end recruitment in month 20 of YR2. We estimate that immediately upon having IRB approval, we will embark on full data collection, including recruitment, telephone and in-person screening. We estimate averaging 4 subjects per month. Recruitment will be until month 20 for 80 subjects.

Ethical and Regulatory Considerations:

Prior to initiating the study, the Investigator must obtain written approval to conduct the study from appropriate institutional ethical and/or regulatory committee 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 must be sent to Takeda (gma.externalresearch@takeda.com).

If research involves human subjects, the Investigator must register the study with clinical trials.gov and other appropriate entities, as necessary.

An IND or CTA may be required. The investigator is responsible to work with regulatory authority to obtain or prove exemption

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Supporting documentation/tables and graphs:

Timetable of visits is attached.

Detailed Budget for all study related costs:

Please refer to the budget template accompanied with the notification letter from Takeda and include with your protocol submission.