Cover Page – Study Protocol

Title: Vagal Nerve Stimulation for Treatment Resistant Major Depression

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A. Background and Study Aims

The goal of this background statement is to outline unmet needs in treating Major Depressive Disorder (MDD) and how non-invasive vagal nerve stimulation (nVNS) could help address those needs. MDD is a common and deleterious illness. The lifetime prevalence of MDD is about 16%. The World Health Organization (WHO) reports that MDD is one of the most common causes of disability in the world, costing society more per year than illnesses such as cancer, heart disease and diabetes. The majority of patients with MDD are poorly served because the treatment they receive is not effective. Thirty nine percent (39%) of patients who receive up to four sequential antidepressant trials continue to demonstrate clinically significant symptoms of MDD. The rate of suicide in severely ill MDD patients is high. Given this data, there is an unmet need to study new and potential therapies for MDD.

Implantable VNS (iVNS), the electrical stimulation of the nervous system to modulate or modify function, has been FDA approved in the United States since the late 1990s. Implantable VNS therapy has been approved for use in epilepsy and depression. It has also been used off-label to treat Parkinson's Disease, essential tremor, dystonia, OCD, severe hearing loss, high frequency hearing loss, obstructive sleep apnea, chronic pain, malignant pain, spasticity, urinary incontinence, and fecal incontinence. VNS therapy is similar to a pacemaker and consists of a small generator and lead implanted under the skin below the collarbone. An attached electrode passes stimulation to the vagus nerve, which in turn sends electrical pulses to the areas of the brain associated with mood regulation and other relevant brain structures. Regular therapeutic delivery adjusts levels of norepinephrine, gamma-aminobutyric acid, serotonin, and aspartate while also increasing blood flow to the thalamus and cortex.

When treating major depression with implanted VNS, the widely held belief is that chronic stimulation is required for therapeutic effect. In trials of implantable VNS in major depression, more patients respond at 12 months than at 3 months. Once depressed patients respond to VNS, the effects have been demonstrated to continue for up to five years with continued stimulation. This finding suggests that VNS gradually changes brain function through neuroplasticity.

electoCore has developed gammaCore™ , (non-invasive vagus nerve stimulator, nVNS) which is FDA approved for the acute and preventive treatment of cluster and migraine headache. It is approved for adults with cluster headache and \ for adolescents and adults (>12 years of age) with migraine. The portable hand-held nVNS device is external to the body and delivers similar results as the implantable nVNS device, without the need for surgery. The device is about the size of a smartphone and will be held to the neck during the nVNS therapy. Each discrete nVNS stimulation lasts two minutes. We plan to use the recommended dosing schedule used in preventing migraine, since the device has demonstrated safety at that dose/duration and has known effects on the brain. We propose using gammaCore™ (nVNS) to treat treatment resistant depression (TRD) for up to 6 months.

With this study, we will address the following scientific aims:

1) Demonstrate the antidepressant effects of nVNS in human adults with treatment refractory MDD as measured by standard rating scales.

2) Confirm gammaCore's™ safety profile in adult patients with TRD.

B. Approach

B1. Study Design

Participants will be medically stable and historically have failed to respond to one or more adequate trials of commercially available antidepressant drugs during the current depressive episode. Five adults with treatment resistant depression will participate in this pilot study. We plan to instruct the participant to self-administer nVNS based on guidance from the manufacturer. The study will use an open-label design. The initial phase will be 3 months and the participant will be seen for monthly follow-up office visits following the screening and baseline visits. If the participant improves after the 3 month trial, as determined by a 25% improvement on the primary outcome measure, the Montgomery-Asberg Depression Rating Scale (MADRS), the participant will continue using the device and be evaluated monthly thereafter.

Dosing will occur three times a day (morning, mid-day and night), each consisting of 2 consecutive 2-minute stimulations delivered on the same side of the neck.

At screening participants will undergo a Mini International Neuropsychiatric Interview (MINI), a physical examination, and ECG, vital signs, Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating scale (HDRS-17), Columbia-Suicide Severity Rating (C-SSRS), Antidepressant Treatment Response Questionnaire (ATRQ), Short form Health Survey (SF-36), and Clinical Global Impression (CGI-S). Laboratory assessment including CBC with differential, TSH with reflex T4, CMP, UA, and UDS will be done at screening. At screening, we will also administer the following self-reported questionnaires to characterize reward sensitivity and other personality features relevant to anhedonia: Social Anhedonia Scale, the Motivation and Energy Inventory and the Physical Anhedonia Scale. The screening period will last up to one week, at which point subjects will present for a baseline visit during which they will receive their device and training on its use.

Participants will be seen on site monthly during the study. Treatment effects will be measured using standard rating scales including the HDRS-17, MADRS, SF-36, CSSR-S, CGI-I, CGI-S, which will be completed at each visit. The following scales will be completed at every other visit following the screening and baseline visits: Social Anhedonia Scale, the Motivation and Energy Inventory and the Physical Anhedonia Scale. At each study visit safety assessments including vital sign assessment and adverse event assessment will be completed. Subjects will also undergo physical examination and an ECG for safety during screening, after 3 months of treatment and at the end of 6 months of treatment.

To assess potential changes in cognition, three tests of cognition will the administered at baseline, month 3, and month 6. The Digit Symbol Substitution Test will measure psychomotor performance. The Digits Forward and Backward Test measures attention and working memory. The Reys Auditory and Verbal Learning Tasks evaluates verbal learning.

Additional design elements are as follows:

Analysis plan: The data will first be screened for outliers and structural problems using analytical and graphical methods. If there are violations of normality assumptions, we will determine if power transformations can address this. Otherwise, we will analyze the data using non- and semi parametric methods.

The primary analysis approach will be a generalized linear mixed model. This approach allows modeling within subject correlations of the data in a repeated measurement design and provides unbiased parameter estimates. Time will be modelled as a within subject variable. The main variable of interest in the model will be the time*Tx interaction term. To account for baseline differences between participants we will include random effect terms for each subject.

B2. Inclusion/Exclusion Criteria

Participants will be recruited from the outpatient clinic at the University of Alabama at Birmingham Department of Psychiatry and Behavioral Neurobiology. All recruiting efforts will be coordinated through the existing infrastructure of the Depression and Suicide Center.

Inclusion Criteria:

1) Age 18-75 years old
2) Sufficient fluency in English to understand testing procedures and provide written informed consent
3) A Hamilton Depression Rating Scale total score ≥ 18
4) A DSM 5 diagnosis of MDD based on the MINI.

Exclusion Criteria:

1) Evidence of alcohol or other substance use disorder in the past 3 months
2) For females: current pregnancy or lactation (women of reproductive potential must have a negative urine pregnancy test at screening).
3) Depressed patients who have failed at least one adequate antidepressant trial during the current depressive episode based on the ATRQ.
4) Diagnosis of other primary psychiatric disorder (defined in this case as being the main focus of treatment) as determined by the MINI, such as: bipolar disorder, personality disorders, psychotic disorders, post-traumatic stress disorder, obsessive-compulsive disorder, dissociative disorders, eating disorder, or cognitive task due to neurological conditions
5) Systolic blood pressure < 150 and/or diastolic blood pressure < 90 at screening
6) Post-partum state (being within 2 months of delivery or miscarriage)
7) Imminent suicide or homicide risk as determined by the investigator
8) Being treated with one of the following medications: benzodiazepines or other CNS depressants.
9) No clinically significant neurological disease based on medical history (e.g., epilepsy) or significant head injury.
10) Any of the following disorders are exclusionary: Rheumatoid arthritis; Lupus erythematosus; Autoimmune hepatitis; Autoimmune peripheral neuropathy; Autoimmune pancreatitis; Behcet's disease; Crohn's disease; Autoimmune glomerulonephritis; Grave's disease; Guillain-Barre syndrome; Hashimoto's thyroiditis; Autoimmune polymyositis or polymyalgia; Myasthenia gravis; Narcolepsy; Polyarteritis nodosa; Scleroderma; Sjogren's syndrome; Transverse myelitis; Wegener's granulomatosis; History of seizures (only childhood febrile seizures are allowed)
11) The presence of clinically significant laboratory findings in the opinion of the investigator including, but not limited to, clinically significant anemia or transaminase elevation is considered exclusionary.
12) If the UDS is positive, the subject would be excluded if, in the opinion of the investigator, the positive UDS meant the subject has an active substance use disorder.
13) Patients with prior exposure to VNS therapy whether using an implantable or external device will be excluded.
14) An active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device
15) A metallic device, such as a stent, bone plate, or bone screw, implanted at or near the neck
16) An open wound, rash, infection, swelling, cut, sore, drug patch, or surgical scar(s) on the neck at the treatment location
17) Patients diagnosed with narrowing of the arteries (carotid atherosclerosis)
18) Patients who have had surgery to cut the vagus nerve in the neck (cervical vagotomy)
19) Patients with clinically significant hypertension, hypotension, bradycardia, or tachycardia

B2. Assessments of clinical symptoms, cognition and functioning
Depressive symptoms will be assessed with the Hamilton Depression Rating Scale 17 item version and the Montgomery Asberg Depression Rating Scale. We will also administer the following self-reported questionnaires to characterize reward sensitivity and other personality features relevant to anhedonia: Social Anhedonia Scale, the Motivation and Energy Inventory and the Physical Anhedonia Scale.

C. References

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