Abbott	Clinical Investigation Plan Cover Page

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BROADEN
A Clinical Evaluation for the Management of Patients with Major Depressive Disorder, Single or Recurrent Episode, with Deep Brain Stimulation
Study Document No: C-07-01
Version A
Date: 8-May-2023

Sponsor

Abbott Neuromodulation
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Plano, Texas 75024
United States

Clinical Protocol

Protocol Number: C-07-01, Revised with Amendment I-IX, 10/05/2011

Protocol Title: A clinical evaluation for the management of patients with Major Depressive Disorder, single or recurrent episode, with deep brain stimulation.

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Investigator _____ **Date** _____

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Study Monitor _____ **Date** _____

Table of Contents **Page No**

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Protocol Summary

Title: A clinical evaluation for the management of patients with Major Depressive Disorder, single or recurrent episode, with deep brain stimulation.

Test Articles: ANS Libra® Deep Brain Stimulation System

Objectives: To demonstrate the safety and efficacy of deep brain stimulation (DBS) to the subgenual white matter (Brodmann Area 25WM) as an adjunctive treatment for single or recurrent Major Depressive Disorder (MDD).

Patient Population: Patients who have single or recurrent Major Depressive Disorder (MDD) complying with specific inclusion/exclusion criteria.

Sample Size: A total of 201 patients will be randomized to treatment from up to 20 investigational sites.

Structure: Prospective, controlled, multi-centered, double blind, randomized, study with endpoint evaluation at 6 months post device implantation. Control group patients will not have the investigational device activated for the first 6 months of study.

Method of Assignment: All patients who meet the inclusion/exclusion criteria will be randomized.

Randomization: Randomization will be performed according to a computer generated scheme after device implant in a 2:1 ratio (Active Stimulation vs. Control Group).

Statistical Analysis: The primary endpoint, at least a 40% decrease from baseline to 6 months in Montgomery and Asberg Depression Rating Scale (MADRS) and no worsening in Global Assessment of Functioning, will be analyzed by logistic regression that includes the effects of treatment group, study site, and baseline MADRS, and will be tested at the 5% level of significance.

Adverse Events: Volunteered and solicited.

1 Introduction

Depression, also known as major depressive disorder (MDD), is a serious medical illness that affects a person's physical and mental state. When a person is clinically depressed, his or her ability to function both mentally and physically is drastically affected. This impaired functional and symptomatic state may last for weeks, months, or even years. Typical symptoms of depression include: an "empty" feeling, sadness and anxiety, tiredness, lack of energy or interest in activities, sleep disturbances, including early morning awakening or oversleeping, and thoughts of death or suicide, a suicide attempt. These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of their daily responsibilities. MDD is one of the leading causes of disability in the United States and established market economies worldwide (Murray et al. 1996). The World Health Organization (2006) estimates that at its worst, depression can lead to suicide, a tragic fatality associated with approximately 850,000 lives every year.

Major depressive disorder affects approximately 9.9 million American adults or about 5.0 percent of the U.S. population age 18 and older in a given year (Narrow 1998). While MDD can develop at any age, the average age of onset is the mid-20s (American Psychiatric Association – APA, 1994). Among this disease population, a large number of patients are consistently resistant to the many and different therapies utilized to treat depression. This subgroup is diagnosed as having treatment resistant depression (TRD) and treatment alternatives are desperately needed for this growing population of severely depressed patients.

Modern brain imaging technologies are revealing that in depression, neural circuits responsible for the regulation of moods, thinking, sleep, appetite, and behavior fail to function properly, and that critical neurotransmitters—chemicals used by nerve cells to communicate—are out of balance (Nestler et al. 2002). Genetic research indicates that vulnerability to depression results from the influence of multiple genes acting together with environmental factors (NIMH Genetics Workgroup). Ongoing studies of brain chemistry and of mechanisms of action with antidepressant medications continue to inform the development of new and better treatments.

Antidepressant medications are widely used and often partially effective treatments for depression (Mulrow et al. 1998). Available antidepressant drugs influence the functioning of certain neurotransmitters in the brain, primarily serotonin and norepinephrine, known as monoamines. Older medications such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), affect the activity of both of these neurotransmitters simultaneously. The disadvantage of these older medications is that they can be difficult to tolerate due to side effects or, in the case of MAOIs, dietary and medication restrictions. Newer medications, such as the selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs), appear to have fewer side effects than the older drugs, making it easier for patients to adhere to treatment. Unfortunately, no single medication is effective for all depressed patients as

various groups of patients will respond to one drug while other patients will require different agents. Fava (2003) states that treatment resistant depression typically refers to an occurrence of an inadequate response following adequate antidepressant therapy among patients suffering from unipolar depressive disorders; which further shows that adequate treatment strategy is extremely difficult for this group of depressed patients. A recent, overall assessment of the nation's largest real world study of treatment-resistant depression (Sequenced Treatment Alternatives to Relieve Depression – STAR*D) suggests that a patient with persistent depression can get well after trying multiple treatment strategies, but his or her odds of "beating" depression lessen as additional strategies are needed (Rush et al. 2006). The STAR*D study, which has studied thousands of patients, further proves that the task of finding the correct treatment for severely depressed patients, can be extremely daunting.

Certain types of psychotherapy can be an effective treatment option for depression. Cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT) have shown to be particularly useful. Approximately two thirds of adults with depression improve when they receive appropriate treatment with medication, psychotherapy, or the combination (Hollon et al. 2006), whereas only one third of treatments result in a full remission.

Despite available pharmacologic and psychotherapeutic treatments, a large number of depressed patients do not have an acceptable or sustained response to these treatments. Despite the advances in brain-neurobiology research and the growing number of available antidepressant therapies, fewer than 50% of these patients achieve remission, and up to 20% develop treatment resistant depression (Kennedy & Lam, 2003). Not only do these patients remain treatment resistant, they are also chronically and severely disabled.

For these severely ill patients who do not respond to psychotherapy and medication, Electroconvulsive Therapy (ECT), is often prescribed. Although this therapy has been shown to have short-term efficacy, many patients experience acute or sustained side effects as a result of the feature (Fink, 2001). Some patients indicate memory loss which can occur for days, weeks and even months after ECT sessions. More recently, other somatic interventions such as Transcranial Magnetic Stimulation (rTMS) and Vagus Nerve Stimulation (VNS) have become available, although sustained response rates are relatively modest according to research studies.

Although still investigational, the rTMS method appears to only provide temporary relief of symptoms; thus many aspects will need to be refined for programming parameters and targeting of regional locations when utilizing this technology, if it is ultimately approved by FDA. A recent FDA panel meeting addressing rTMS' safety and efficacy, showed that rTMS has a favorable safety profile but did not show efficacy at the specific primary endpoint of the clinical trial. The FDA panel recommended to FDA that this therapy not be approved for the treatment of Major Depressive Disorder (FDA Panel Meeting, January 2007).

Alternatively, vagus nerve stimulation has been used for the indication of Epilepsy

in the United States since 1997 (George 2000 and Sackeim et al. 2007). Due to the fact that many epileptic drugs also work for bipolar depressed patients, there was belief that there may be a correlation in the disease process between these two conditions (Elger 2000). These hypotheses led to clinical trials researching the use of the VNS system for major depressive disorder. VNS was ultimately evaluated and approved by the FDA in July of 2005, for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age and older, who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments (Cyberonics Labeling). VNS is now one of the limited new options for this depressed, treatment resistant patient population. Although this therapy was recently approved by the FDA, longer-term, well designed clinical trials are needed to confirm the safety and efficacy of this treatment alternative. Furthermore, since the VNS device has shown limited efficacy in small numbers of patients, it has certainly not proven to be the ultimate solution for treatment of these severely depressed patients.

For the most severely, treatment resistant of these patients, several invasive ablative neurosurgical procedures have also been available; although they are now infrequently used due to perceived side effects and the unfortunate irreversibility of the treatment. Well-established procedures involve the production of lesions that interrupt distinct frontal-cingulate, fronto-striatal, and thalamo-frontal white matter tracts, resulting in therapeutic benefit for some patients (Cosgrove et al. 1995; and Sachdev and Sachdev, 2005). Several of these procedures, including subcaudate tractotomy, cingulotomy and anterior capsulotomy have been found to be effective in some patients, although all involve the permanent destruction of neural structures. Furthermore, there is also a considerable time delay between surgery and symptom improvement.

Recently, destructive procedures to treat Parkinson's disease, such a thalamotomies and paladotomies have been replaced by applying high frequency electrical stimulation to these targets. Deep brain stimulation (DBS) has been found to have distinct advantages over ablation with the major advantage being its reversibility, as well as the option to modify specific stimulation parameters when necessary. Pathological studies further demonstrate that chronic DBS produces little to no tissue damage (Haberler et al. 2000). In theory, DBS can be seen as a potentially safe, effective, flexible and reversible alternative to ablative surgery for treatment resistant depression, if the optimal target can be defined and evaluated.

Functional neuroimaging studies have revealed changes in cortical (frontal, parietal), paralimbic (cingulate, insula) and subcortical (caudate, thalamus) activity following various types of treatments [medication, psychotherapy, sleep deprivation, ECT, repetitive transcranial magnetic stimulation (rTMS), ablative surgery] (Mayberg, 2003). Normalization of frontal abnormalities (both increases and decreases) is the best-replicated finding. Decreases in paralimbic regions, while variable, are also consistently reported. While there is not yet a common pattern that characterizes depression remission across all of the available treatment modalities, medications and all of the available somatic treatments such as ablative surgery, TMS and VNS, changes have been seen in the paralimbic

regions. Specifically, changes have been found in the hippocampus and ventral medial frontal/cingulate areas, having known projections through specific subcaudate tracts (Mayberg et al. 2000).

Regions affected by these white matter interruptions are widespread, as the subcaudate tractotomy is quite large. Specific tracts are less well characterized, but likely involve connections linking orbital frontal, subgenual cingulate, ventral striatum/caudate, thalamus brainstem, hypothalamus and hippocampus/amygdala. The precise optimal target(s) within the subcaudate that mediate antidepressant response is not known at this time. However, imaging studies suggest that disturbances involving more specific connections between the subgenual cingulate and medial frontal, ventral striatum, anterior thalamus, hippocampus, hypothalamus and brainstem may be particularly critical (Seminowicz et al. 2004). Brodmann Area 25WM (BA25WM), also known as the subgenual cingulate region, subgenual white matter, or Cg25, has been shown to be involved in both acute sadness and antidepressant treatment effects; hence indicating its role in modulating mood states (Mayberg et al. 1999). These findings further suggest that DBS may be most effective if these medial pathways are selectively modulated, as this hypothesis has been further verified in a preliminary study in treatment-resistant depressed patients. Mayberg et al. 2005, reported that in a small group of severe refractory depressed patients, DBS induced clinical response in 4 out of 6 patients, with 2 patients achieving full remission. Although these preliminary findings are encouraging, much larger, controlled clinical trials are necessary to show the safety and efficacy of deep brain stimulation of Brodmann Area 25WM.

Deep brain stimulation is considered safe, non-destructive and reversible. The frequency and severity of procedural risks and complications with DBS implantation for depression are expected to be similar to those for Parkinson's Disease and Essential Tremor. An extensive review of Manufacturer and User Facility Device Experience (MAUDE) reports, regarding deep brain stimulation from 1997 to present, has shown no evidence of tissue damage due to excessive electrical stimulation. To date, over 30,000 Deep Brain Stimulation devices have been implanted worldwide. Furthermore, a recent paper by Haberler et al. (2000) concluded that chronic DBS, defined as continuous deep brain stimulaton for up to 70 months, does not cause damage to neural tissue in Parkinson's Disease patients when applied at therapeutic levels.

Unfortunately, there are a limited number of new treatment options for the treatment resistant patient population. Considering the severity of treatment resistant depression and its debilitating effect on patients' and family's lives, Deep Brain Stimulation provides an optimistic opportunity for significant symptom relief and potential quality of life improvement, with minimal risk. Further, this evaluation of DBS' safety and efficacy, gives patients with treatment resistant depression an additional treatment option. The purpose of this proposed clinical study is to evaluate safety and efficacy of subgenual white matter (Brodmann Area 25WM) deep brain stimulation for the treatment of single or recurrent, Major Depressive Disorder, using standard psychiatric rating scales and questionnaires as outcome measures.

2 Objective

2.1 Primary Objectives

To demonstrate the safety and efficacy of deep brain stimulation (DBS) to the subgenual white matter (Brodmann Area 25WM) as an adjunctive treatment for Major Depressive Disorder (MDD), single or recurrent episode.

2.2 Secondary Objectives

To evaluate changes in the following: Hamilton Rating Scale for Depression (HRSD-17), the 30-item Inventory of Depressive Symptomatology (IDS-C30), Quick Inventory of Depressive Symptomatology (QIDS-SR), Young Mania Rating Scale (YMRS), Work and Social Adjustment Scale (WSAS), Quality of Life and safety.

2.3 Primary Variable

Primary Efficacy: Change from Baseline (defined as mean of 3 Montgomery and Asberg Depression Rating Scale (MADRS) scores) to the mean of months 4, 5, and 6 between treatment groups.
The primary endpoint will be defined as at least a 40% reduction in MADRS and no worsening in Global Assessment of Functioning (GAF).

2.4 Secondary Variables

- Change from baseline in GAF over time;
- Change from baseline in the MADRS over time;
- Change from baseline in the Hamilton Rating Scale for Depression - 17 item (HRSD-17) over time;
- Change from baseline in the Inventory of Depressive Symptomatology (IDS-C30) over time;
- Change from baseline in Quick Inventory of Depressive Symptomatology (QIDS-SR) over time;
- Change from baseline in the Work and Social Adjustment Scale (WSAS) over time;
- Change from baseline in Patient Global Impression of Severity over time;
- Change from baseline in Clinician Global Impression of Improvement over time;
- Change from baseline in quality of life over time;
- The incidence of all adverse events (i.e. hospitalization due to worsening depression, suicidal ideation or behavior, medical treatment, and device related events) that occur over study duration.
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) over time.

2.5 Other Variables

- Number of patients who have a 40% reduction in Baseline HRSD-17 over time;
- Number of patients who have a 40% reduction in IDS-C30 over time;
- Number of patients who have a 40% reduction in QIDS-SR over time;
- Number of patients in Remission (as defined by a score of ≤ 14 on the IDS-C30) over time;
- Number of patients in Remission (as defined by a score of ≤ 5 on the QIDS-SR) over time;
- Number of patients in Remission (as defined by a score of ≤ 10 on the MADRS) over time;
- Number of patients in Remission (as defined by a score of≤ 7 on the HRSD-17) over time.
- Change from baseline in the Young Mania Rating Scale (YMRS) over time;
- Number of patients with hypomania (defined as present when YMRS ≥ 15.);
- Change in the Neuropsychological Battery test results at 6 and 12 months;
- Change from baseline in the Health and Labor Questionnaire (HLQ) over time;
- Change from baseline in the Columbia Suicide-Severity Rating Scale (C-SSRS) over time

3 Study Design

3.1 Design

This study is designed as a prospective, multi-centered, double-blind, randomized, controlled 12-month pivotal study to evaluate the safety and efficacy of the ANS Libra® Deep Brain Stimulation System for patients with major depressive disorder who have failed at least 4 treatments in the current episode. The primary outcome assessment will occur at 6 months: however, all patients will be followed for 1 year. A total of 201 patients will be randomized from up to 20 sites.

Each potential patient will be pre-screened according to the inclusion/exclusion criteria. A narrative of what study participation entails, will be used to educate potential participants on study requirements. Prior to on-site baseline evaluations, the patient will sign the informed consent. Patients will then undergo 3 baseline evaluations, with each of these evaluations to occur no less than 2 weeks apart from each other. The first 2 baseline visit evaluations will be performed by separate psychiatrists in order to confirm the patient's diagnosis. The patient must score an average ≥ 22 on the MADRS, across 3 evaluations. All patients will be scheduled for surgery, to occur no less than two weeks and no more than 1 month after final baseline evaluation, to implant the ANS Libra® Deep Brain Stimulation system. After device implantation, patients will be randomly assigned to 1 of 2 groups in a 2:1 ratio

(Active Treatment Group & Control Group).

Group 1: DBS Active Treatment Group – implanted with investigational device and activated for stimulation.

Group 2: DBS Control Group – implanted with investigational device, but will not receive active stimulation for the first 6 months of the study. At the end of 6 month visit, these patients will have the investigational device programmed and activated.

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Study Visit Schedule

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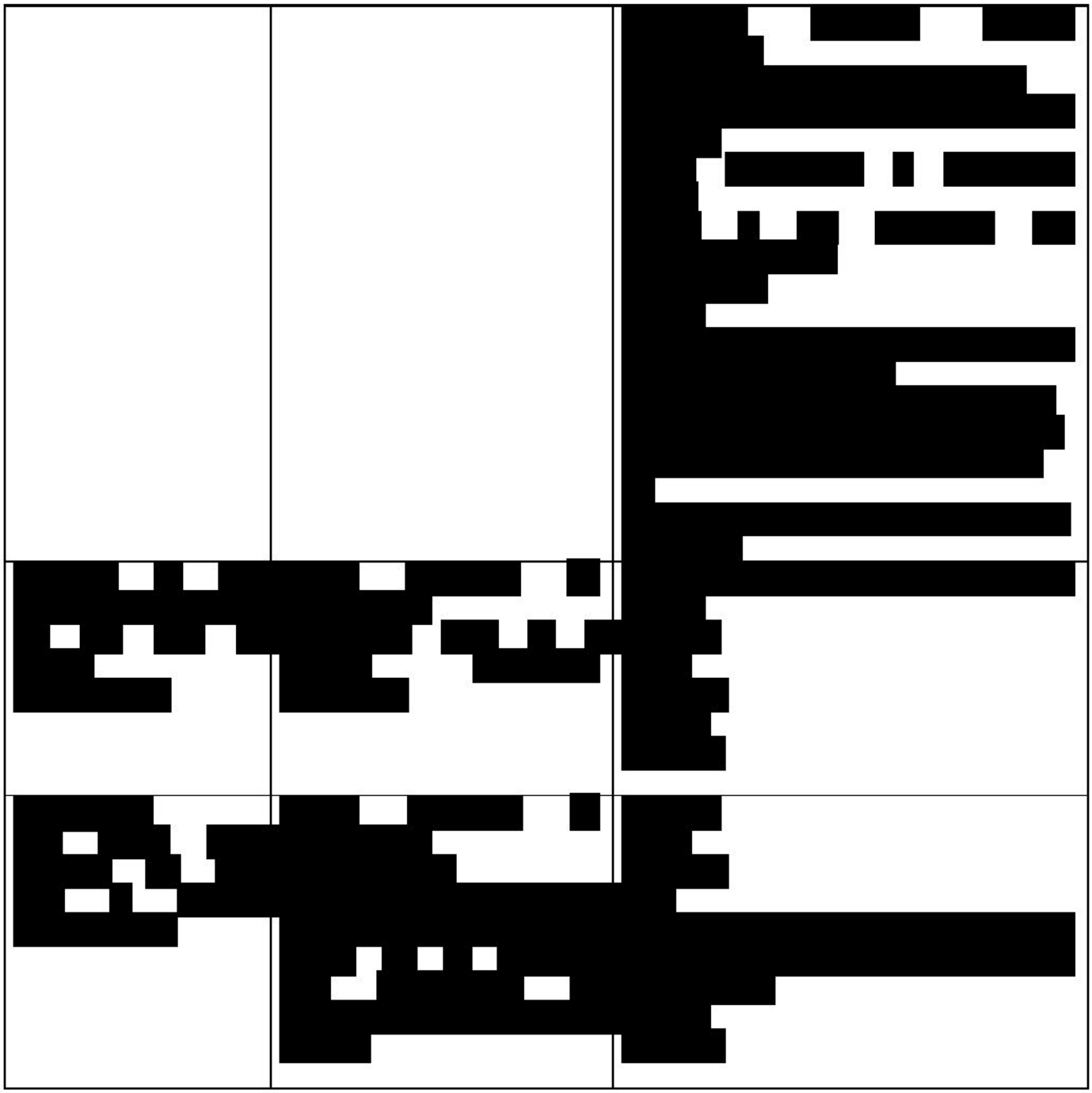

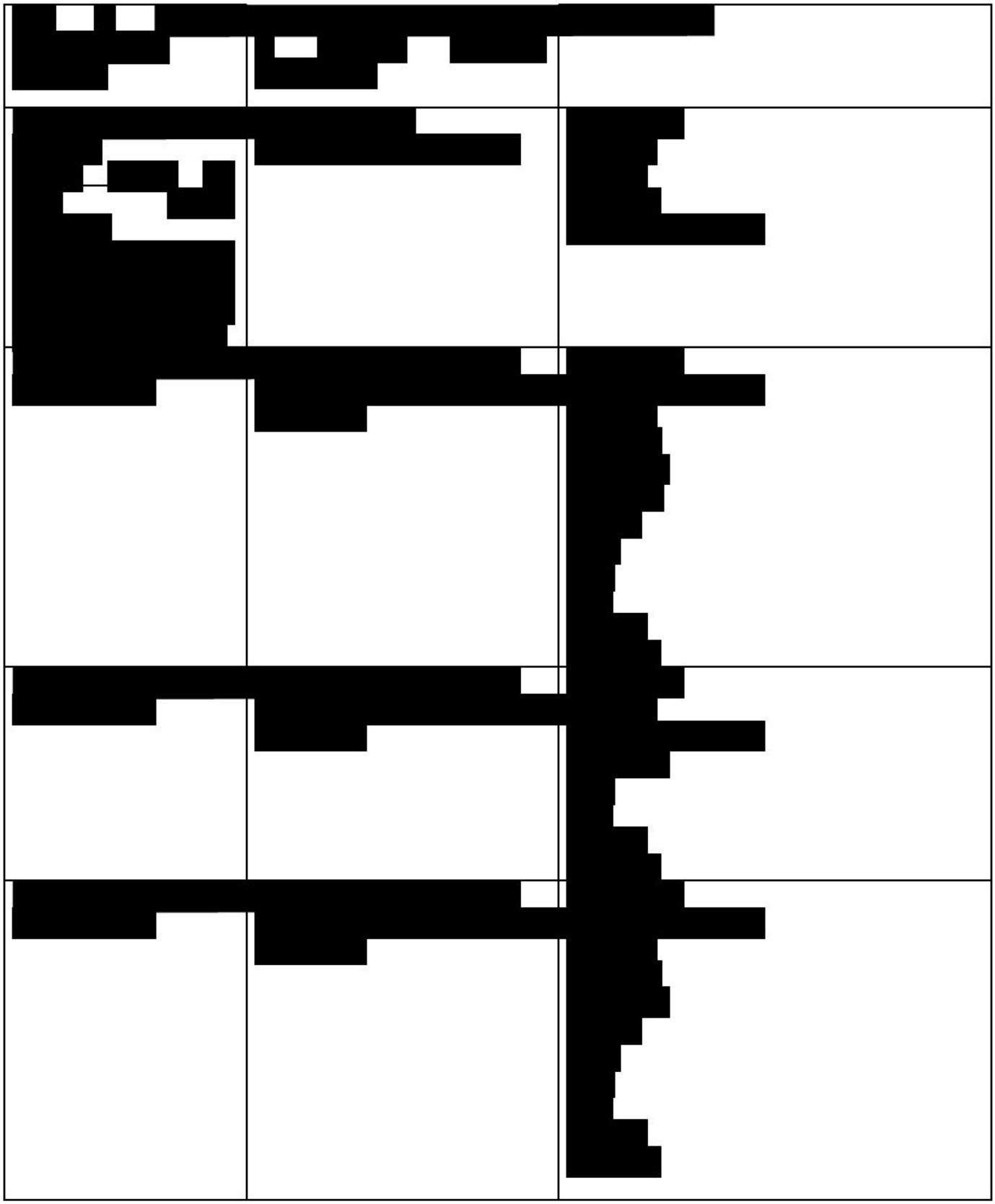

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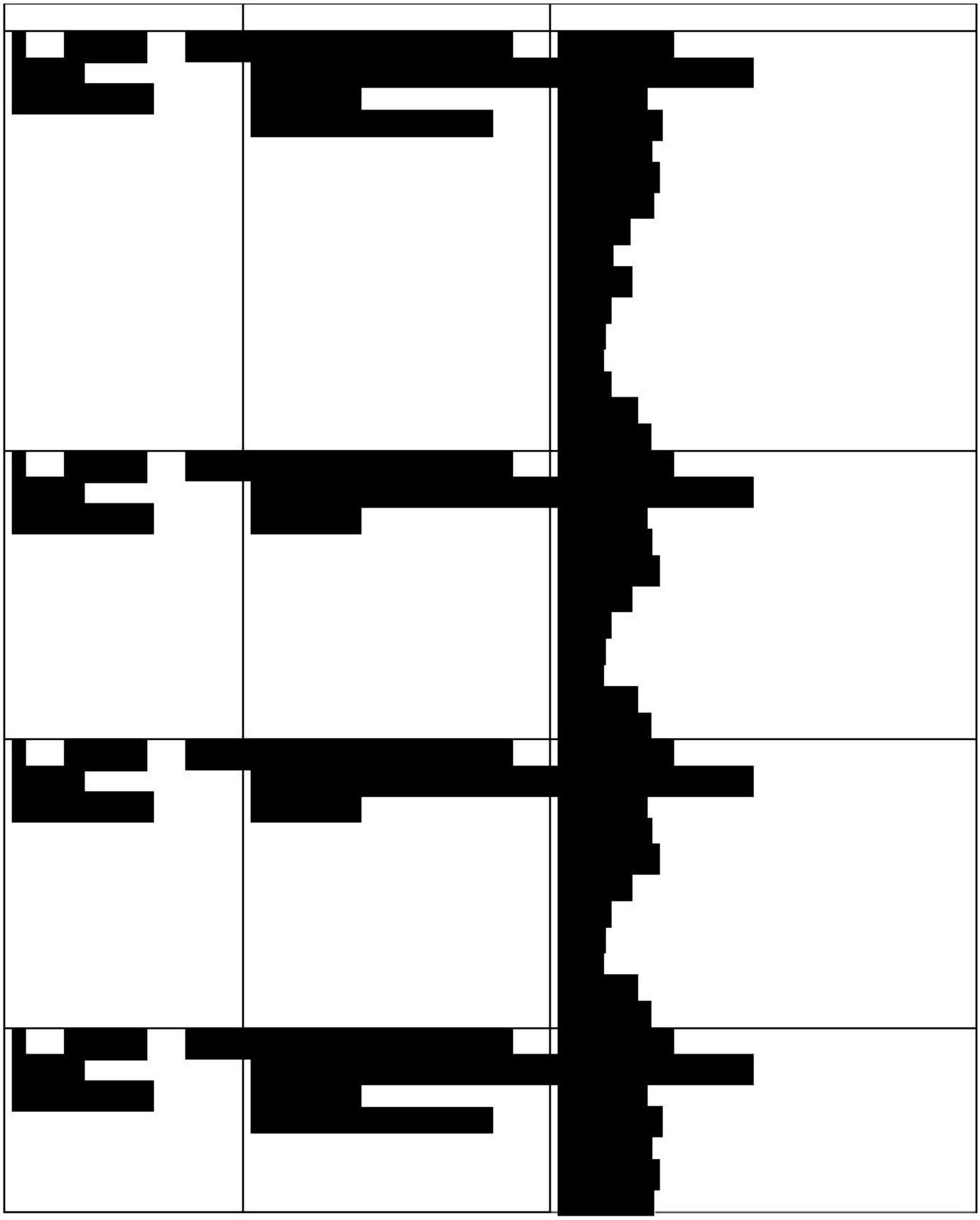

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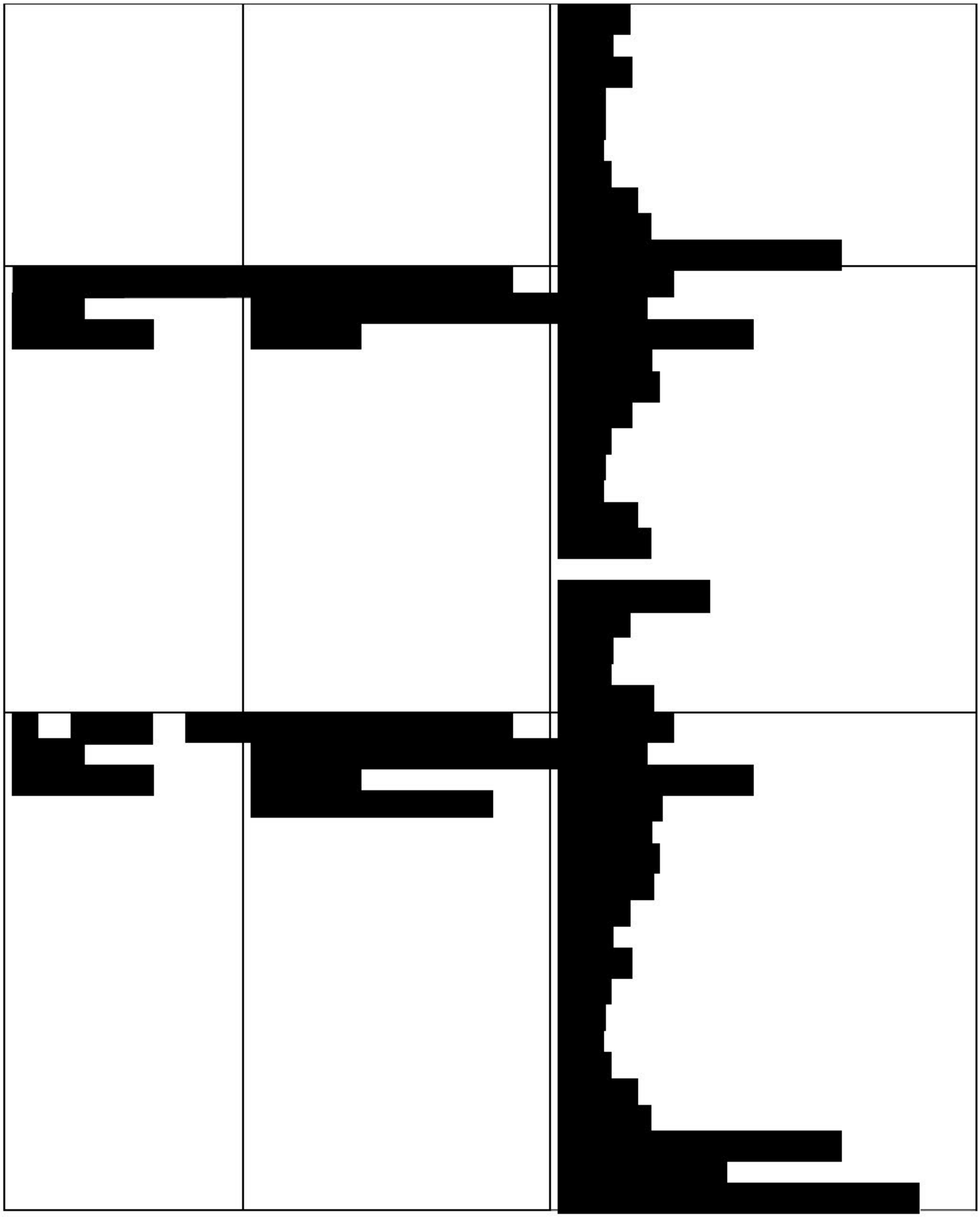

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3.2 Baseline Evaluations

A thorough review of medical records, over at least the previous two years for each patient, will be necessary to review treatment history and any non-compliance to treatment issues. These baseline measurements will be taken after the patient signs the informed consent and complies with all the inclusion/exclusion criteria, prior to device implantation and randomization to treatment. Patient baseline measurements include the Montgomery and Asberg Depression Rating Scale (MADRS); the Hamilton Depression Rating Scale - 17 item (HRSD-17); the Self-Rated Quick Inventory of Depressive Symptomatology (QIDS-SR); Subsection for cluster B personality disorder of the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II); Systematic Assessment for Treatment Emergent Events (SAFTEE); the 30 item Inventory of Depressive Symptomatology (IDS-C30); the Young Mania Rating Scale (YMRS); the Work and Social Adjustment Scale (WSAS); Global Assessment of Function (GAF); the short form Quality of Life Enjoyment and Satisfaction Questionnaire (QOL); Clinical Global Impression of Severity and Improvement (CGI); Patient Global Impression Index (PGI); Health and Labor Questionnaire (HLQ); Hamilton Anxiety Rating Scale (HAM-A) and Columbia Suicide-Severity Rating Scale (C-SSRS). Two different psychiatrists will confirm the diagnosis of MDD via DSM-IV-TR criteria. Previous medical history and psychiatric history will be assessed and recorded including the M.I.N.I. Plus, MMSE, and psychotherapy treatments. A Neuropsychological Battery will be performed after Baseline #3 if patient has met MADRS study inclusion criteria. Portions of these baseline sessions may be videotaped. An initial MRI will occur after Baseline #3 in order to (1) exclude patients presenting with brain abnormalities that might be contributing to severity and treatment resistance of depression or which would not be compatible with the surgery; and (2) to perform surgical lead placement targeting and surgical pre-planning.

3.3 Justification for Study Design

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[redacted]

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[redacted]

1. [redacted]

[redacted]

[redacted]

3.4 IPG Implantation

The ANS Libra Deep Brain Stimulation (DBS) System consists of an Implantable Pulse Generator (IPG) designed to be connected to 4 or 8 electrode leads and extensions and programmed by an external programmer. The DBS system for the purposes of this study is to be used for the treatment of severe major depressive disorder. The ANS pulse generator is implanted in a subcutaneous pocket, and receives radio frequency (RF) programming signals by means of the external programmer. The ANS IPG decodes the programmed information and delivers stimulation pulses to a selected combination of output electrodes, on the lead. The Implantation Visit will be classified as "Week 0".

3.5 Patient Evaluation

[redacted]

[redacted]

[redacted]

4 Test Articles

4.1 System Components

The components of the DBS System to be used in this study include an Implantable Pulse Generator (ANS, Libra and LibraXP DBS IPG), leads (ANS, Libra DBS Lead Kits), extensions, the ANS MTS trial stimulator, the clinician programmer, the patient controller (ANS, QuikLink Controller). The Libra system is comprised of implanted and non-implanted components that include:

- Implantable Pulse Generator (IPG) – generates low-current electrical pulses.
- Lead - contains electrodes to deliver stimulation
- Lead Extension – make the electrical connection between the lead and the generator
- Trial Stimulator - for intraoperative and post operative testing
- Clinician Programmer – for programming the generator
- QuikLink Patient Controller - controls off/on function and amplitude

4.2 Regulatory Status

[redacted]

5 Patient/Subject Selection

5.1 Inclusion Criteria

Patients enrolled in this study must comply with the following inclusion criteria:

1. Men and women (non-pregnant) age is 21-70 years;
2. Diagnosed with non-psychotic major depressive disorder, single or recurrent episode by DSM-IV-TR criteria derived from the MINI;
3. First episode onset before age 45;
4. Current episode ≥ 12 months duration;
5. In the current episode: Documented resistance (i.e. persistence of the major depressive episode) to a minimum of 4 adequate depression treatments from at least 3 different treatment categories (e.g. SSRI's, SNRI's, TCA's, MAO-inhibitors, Mirtazipine, Nefazodone, Trazodone, Bupropion, lithium augmentation, thyroid augmentation, ECT); Adequacy of treatments as defined by a score of at least 3 according to the amended Antidepressant Treatment History Form (ATHF) criteria;
6. In Lifetime: Received a course of psychotherapy for depression;
7. Montgomery Asberg Depression Rating Scale (MADRS) of ≥ 22 at 3 separate baseline visits, rated by 2 separate psychiatrists, Baseline 2 and Baseline 3 MADRS scores cannot be separated by > 6 weeks and cannot improve ≥ 20%;
8. Global Assessment of Function, score <50;
9. Modified mini-mental state examination (MMSE) score ≥24;
10. No change in current antidepressant medication regimen or medication free ≥4 weeks prior to study entry (with exception to sleep, cholesterol, blood pressure, sexual dysfunction, non-migraine headache medication, or medication for other medical reasons not related to depression, in which changes to dose or type will be allowed during course of study);
11. Able to give informed consent in accordance with institutional policies;
12. Able to comply with all testing and follow-up requirements as defined by the study protocol;
13. Must be determined medically stable by surgeon, to undergo deep brain stimulation surgical procedure.
14. Must have platelet count, PT and PTT within normal limits of the laboratory.
15. During last 6 months in the current episode documented treatment under the care of a licensed psychiatrist/psychologist.

5.2 Exclusion Criteria

Patients will be excluded from participation in this study if they meet any one of the following criteria:

1. A diagnosis of a bipolar I or bipolar II disorder by DSM-IV-TR criteria, derived from the MINI;
2. Meets criteria for borderline or antisocial personality disorder in the last 12 months by DSM-IV-TR criteria, derived from the Cluster B Personality Disorders Sections 301.7 – 301.83, and screened via SCID-II at Baseline visit;
3. In the current depressive episode, has been diagnosed with General Anxiety Disorder (GAD) - as defined by the DSM-IV-TR, and GAD is the primary diagnosis;
4. Has an intracranial Central Nervous System (CNS) disease that impairs motor, sensory or cognitive function or that requires intermittent or chronic medication (e.g., Parkinson's Disease, chronic migraine, stroke, Huntington's, head trauma, etc.) with exception to non-migraine headaches;
5. Has been diagnosed with fibromyalgia or has a current condition which requires chronic pain narcotic usage (e.g. morphine, methadone);
6. Has been currently diagnosed with chronic fatigue syndrome;
7. Substantial suicidal risk as defined by (1) MADRS item 10 score of 5 or 6, (2) a current plan and intent, (3) clinician judgment that there is a clear immediate intent for self-harm, (4) more than 3 suicide attempts within the last 12 months;
8. Co-morbid obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, bulimia or anorexia nervosa if previously present, must be in remission for 6 months as defined by DSM-IV-TR criteria, derived from the MINI;
9. Alcohol, medication, or illegal substance dependence or abuse within last 12 months derived from the MINI;
10. Diagnosis of sleep apnea confirmed by a sleep test that is not adequately treated;
11. Advanced cardiovascular disease which renders anesthesia and surgery as unsafe as determined by neurosurgeon;
12. Clinically relevant abnormality (e.g. tumor or growth) on study MRI;
13. Has cardiac pacemaker/defibrillator or other implanted active stimulator;
14. Has a medical condition requiring a repetitive MRI body scan;
15. Requires chemotherapy for the treatment of malignancy or requiring chronic oral or intravenous (immunosuppressive or) steroid therapy;
16. Is unable to comply with study visit schedule and timeline;
17. Past ablative or relevant intracranial surgery;
18. A female lactating or of child bearing potential, with a positive pregnancy test or not using adequate contraception;
19. Lifetime psychotic disorders, schizophrenia, or schizoaffective disorder defined by DSM-IV-TR;

20. Psychotic features in current depressive episode as diagnosed by DSM-IV-TR criteria;
21. Other medical conditions likely to require hospitalization within the next year;
22. Received ECT within 3 months prior to enrollment, or requires ECT for the duration of the study;
23. Has a history of epilepsy or history of status epilepticus;
24. Plans to use diathermy;
25. Has any metallic implants such as aneurysm clips or cochlear implants;
26. Currently participating in another investigational device, drug or surgical trial.

6 Subject Assignment to Treatment and Blinding

[redacted]

7 Methods and Procedures

7.1 Informed Consent

Written Informed Consent will be obtained from each patient prior to enrollment into the study. All potential patients/subjects will be properly informed as to the purpose of the study and the potential risks and benefits known, or that can be reasonably predicted or expected. The Investigator will retain the original copy of the Informed Consent Form signed by the patient, a duplicate will be provided to the patient and a document signed by the Investigator confirming receipt of patient consent will be returned to the Sponsor. Only the consent form approved by the IRB/IEC will be used. (Appendix A: Sample Informed Consent)

7.2 Screening/Baseline

Study candidates will be screened according to the inclusion/exclusion criteria prior to enrollment in the study. All study participants must provide informed consent. Evaluations will include the following:

- Confirmation of MDD via DSM-IV-TR criteria will occur combined with extensive medical record review by evaluating psychiatrist;
- Montgomery and Asberg Depression Rating Scale (MADRS);
- Demographics and prior history;
- Medical system review;
- Brief physical exam, neurological exam;
- Pregnancy test (if necessary);
- Family history, medication history – antidepressant treatment history form (ATHF - modified);
- MINI Plus;
- HRSD-17;
- SAFTEE;
- Mini Mental State examination (MMSE);
- Subsection for cluster B personality disorder of the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) ;
- Inventory of Depressive Symptomatology (IDS-C30);
- Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR);
- Work and Social Adjustment Scale (WSAS);
- Short form Quality of Life Enjoyment and Satisfaction Questionnaire (QOL);
- Young Mania Rating Scale (YMRS);
- Clinical Global Impression of Severity and Improvement (CGI);
- Patient Global Impression Index (PGI);
- Health Labor Questionnaire (HLQ);
- Hamilton Anxiety Rating Scale (HAM-A);
- Columbia Suicide-Severity Rating Scale (C-SSRS).

7.2.1 Baseline 2/Baseline 3

A second baseline will be performed no less than 2 weeks and no more than 4 weeks after Baseline #1. Evaluations will include the following:

- Confirmation of MDD via DSM-IV-TR criteria will occur combined with extensive medical record review by evaluator;
- Montgomery and Asberg Depression Rating Scale (MADRS);
- The Quick Inventory of Depressive Symptomatology (QIDS);
- Systematic Assessment for Treatment Emergent Events (SAFTEE-SI);
- Hamilton Anxiety Rating Scale (HAM-A);
- Columbia Suicide-Severity Rating Scale (C-SSRS).

A third baseline will be performed no less than 2 weeks and no more than 6 weeks after Baseline #2. Evaluations will include the following:

- Montgomery and Asberg Depression Rating Scale (MADRS);
- The Quick Inventory of Depressive Symptomatology (QIDS);
- Systematic Assessment for Treatment Emergent Events (SAFTEE-SI);
- Hamilton Anxiety Rating Scale (HAM-A);
- Columbia Suicide-Severity Rating Scale (C-SSRS);
- Neuropsychological Battery – performed only <u>if</u> patient meets eligibility for study participation after scoring ≥ 22 on three baseline MADRS evaluations.
- MRI scan will be performed after patient has meet eligibility requirements (to exclude brain abnormalities, plan for surgery, and targeting);

The patient will also be assigned a case manager to follow each patient's care for the duration of the study.

*If the patient does not have three MADRS values ≥ 22, they will be considered a screen failure and <u>may not</u> be re-evaluated for study participation for a minimum of 6 months.

7.2.2 Outcome measures

<u>Montgomery and Asberg Depression Rating Scale (MADRS)</u>
The Montgomery and Asberg Depression Rating Scale is a 10 item severity scale constructed to be sensitive to change with treatment. It was designed to be sensitive for individual items and is therefore useful for measuring differential profiles of action. Ratings of patients on a 65 item comprehensive psychopathology scale were used to identify the 17 most commonly occurring symptoms in primary depressive illness, and ratings on these 17 items for 64 patients participating in studies of four different antidepressant drugs were used to create a depression scale consisting of

the 10 items which showed the largest changes with treatment and the highest correlation to overall change. (Montgomery & Asberg 1979) An interrater evaluation will also be performed on multiple study visits to increase consistency and reduce variability.

Hamilton Rating Scale for Depression (HRSD-17)
The Hamilton Rating Scale for Depression is a 17-item scale that evaluates depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms. The HRSD-17 was one of the first rating scales developed to quantify the severity of depressive symptomatology. First introduced by Max Hamilton in 1960, it has since become the most widely used and accepted outcome measure for evaluating depression severity. It provides ratings on current DSM-IV symptoms of depression, with the exceptions of hypersomnia, increased appetite, and concentration/indecision. The HRSD-17 was designed to be administered by a trained clinician using a semi-structured clinical interview. The 17-items are rated on either a 5-point (0-4) or a 3 point (0-2) scale.

Inventory of Depressive Symptomatology (IDS-C30)
The construction of the IDS-C30 was intended to remedy deficits in the Hamilton Scale for Depression (HRSD-17) and Montgomery and Asberg (MADRS) depression rating scales by, among others, including all nine symptom domains needed to diagnose a DSM-IV major depressive episode in order to assess symptom remission, improve ability to detect milder levels of symptoms than the HRSD-17, and provide unconfined and more equivalent weighting among items. There are two versions of the IDS with identical items: a clinician rating (IDS-C30) and a self-report (IDS-SR30). Items were selected to represent mood, cognitive, vegetative, anxious, and endogenous symptoms common in depression. Each of the 30 items is rated from 0 to 3, with increasing severity represented by a higher rating. (Rush et al. 1996)

The Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR) is a 16-question shortened self-test, derived from the 30-item IDS, which measures 9 different criterion domains of major depression. Each of the 4 possible answers to each quiz is given an ascending numerical value from 0-3.

Systematic Assessment for Treatment Emergent Events (SAFTEE-SI)
The SAFTEE is a structural clinical interview developed by the National Institute of Mental Health which exams possible treatment-emergent side effects for clinical studies. The SAFTEE-SI looks at specific adverse symptoms for a particular treatment.

The Mini-International Neuropsychiatric Interview (M.I.N.I.) Plus
The MINI is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM-IV and ICD-10 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 multi-centered clinical trials and epidemiology studies and to be used as a first step in outcome tracking in non-research clinical settings. The MINI Plus is a more detailed edition of the MINI.

The mini-mental state examination (MMSE) or Folstein test is a brief 30-point questionnaire test that is used to assess cognition. It is commonly used in medicine to screen for dementia. In the time span of about 10 minutes, it samples various functions, including arithmetic, memory and orientation. It was introduced by Folstein *et al* in 1975 and is widely used with small modifications.

Structural Clinical Interview for Personality Disorders (SCID II)
The SCID-II is a semi-structured interview for making DSM-IV Axis II (Personality Disorder) diagnoses and is designed to be administered by a clinician or trained mental health professional. A SCID II takes 1/2 to 1 hour to administer. There are 3 components to the SCID-II. The interview itself covers the 11 DSM-IV Personality Disorders. The SCID-II Personality Questionnaire is available as a screening tool to shorten the time it takes the clinician to administer the SCID-II. After the subject fills out the Personality Questionnaire (which usually takes 20 minutes), the clinician simply circles the numbers to the left of the SCID-II items that correspond to items answered "yes" on the questionnaire. When the SCID-II is administered, the clinician needs only to inquire about the items screened positive on the questionnaire. The assumption is that a subject who responds with a "no" on the questionnaire item would also have answered "no" to the same question had it been read aloud by the interviewer. For this study, only the subsection for Cluster B will be administered.

The Young Mania Rating Scale (YMRS)
The YMRS is an 11-item instrument used to assess the severity of mania in patients with a diagnosis of bipolar disorder. The 11 items are: Elevated Mood, Increased Motor Activity Energy, Sexual Interest, Sleep, Irritability, Speech (Rate and Amount), Language - Thought Disorder, Content, Disruptive - Aggressive Behavior, Appearance, and Insight.
Ratings are based on patient self-reporting, combined with clinician observation (accorded greater score). (Young 1978)

Quality of Life Enjoyment and Satisfaction Questionnaire (QOL)
The short form of the Quality of Life Enjoyment and Satisfaction Questionnaire is a self-report form composed of 16 items each rated on a 5-point scale that indicates the degree of enjoyment or satisfaction experienced during the past week. A total score of items 1 to 14 is computed and expressed as a percentage of the maximum possible score of 70. The 14 items evaluated each subjects' satisfaction with his or her physical health, social relations, ability to function in daily life; ability to get around physically; mood; family relations; sexual drive and interest; ability to work on hobbies, work, leisure time activities; economic status; household activities; living/housing situation; and overall sense of well being. (Rapaport et al. 2005)

Work and Social Adjustment Scale Self Report (WSAS)
The WSAS-SR is used to measure functional impairment attributed to a identified problem (Mundt, 2002). There are 5 questions that are associated with work, home, social leisure, private leisure and ability to form and maintain relationships.

Global Assessment of Functioning (GAF)
The Global Assessment Scale is a hypothetical continuum of mental health illness that looks at psychological, social and occupational functioning. The GAF scale is divided into 10 ranges of functioning in which the clinician picks a single value that best reflects the individual's overall level of functioning. The GAF does not include "impairment in functioning due to physical (or environmental) limitations." (American Psychiatric Association – APA, 1994)

Clinical Global Impression of Severity and Improvement (CGI)
The CGI is used to measure the global impression of a treatment response in a psychiatric patient's illness by a clinician (Guy 1976). Two of three sub-scales are being used to measure severity of the illness and improvement of the illness. Items in the two-subscales being administered are rated on a seven-point scale ranging from "1=normal" to "7=extremely ill" for severity subscale and "1=very much improved" to "7=very much worse" for improvement sub-scale.

Patient Global Impression Index (PGI)
The PGI is used to measure the global impression of a treatment response in a psychiatric patient's illness by the patient. Two sub-scales are being used to measure severity of the illness and improvement of the illness. Items in the two-subscales being administered are rated on a seven-point scale ranging from "1=normal not ill at all" to "7=among the

most extremely ill" for severity sub-scale and "1=very much improved" to "7=very much worse" for improvement sub-scale.

Health and Labor Questionnaire (HLQ)
The HLQ is designed to collect quantitative data on the relation between illness and treatment and work performance. The HLQ data permits the estimation of production losses (costs) of paid and unpaid labor. It contains also an indicator for impediments for paid and unpaid labor, one of the indicators for quality of life. The HLQ is divided into 4 modules to collect data about absence from work, reduced productivity at paid work, unpaid labor production and impediments to paid and unpaid labor. The modular structure permits the omission of questions that are not applicable to the study population. The questionnaire is suitable for self-assessment.

Hamilton Anxiety Rating Scale (HAM-A)
A 14 item test designed to assess the severity of anxiety symptoms. All questions are rated on a 5 point (0-4) scale, with 7 questions on psychic anxiety and 7 questions on somatic anxiety. Total scores range from 0 to 56. Patients with anxiety and panic disorder tend to have a score greater than 20.

Columbia Suicide-Severity Rating Scale (C-SSRS)
The C-SSRS is a semi-structured clinical interview that utilizes a set of prompts and questions to help an interviewer get more complete information on events suggestive of suicidality. This prospective tool aims to standardize terminology and articulate suicidality assessment in a straightforward manner.

7.2.3 Neuropsychological Battery

Neuropsychological Examination: The following neuropsychological tests will be performed and evaluated at or after baseline #3, 6 months, and 1 year visits during the study to assess the safety of Deep Brain Stimulation. The following is a description of all the tests to be performed:

Attention/Working Memory

Wechsler Memory Scale –Working Memory Index Test (Wechsler, 1997)

Letter-Number Sequencing
Examinees are presented with strings of alphanumeric sequences (e.g., 6-B-3-Z) of increasing length (2-8 letter-number pairs). The task

of the examinee is to repeat the letters and then the numbers in alphabetical and numerically ascending order. This test of working memory thus requires re-sequencing of information while holding in memory the original sequence. This task takes 3-5 minutes to complete.

Stroop Color and Word Test (Golden, 1978)
This version of the well-known Stroop test has 3 parts, each consisting of 1 page of 100 stimuli (arranged in 5 columns of 20 items). The first sheet contains the words red, green, and blue, printed in black ink, in random order with the constraint that a word cannot be followed by the same word. The examinee is asked to read the words, and the variable of interest is how many items are completed correctly in 45 sec. On page 2 are 100 "XXXX" printed in either red, green or blue ink, with the constraint that a given item number could not correspond to the same color on the first page, and the same color cannot occur on consecutive items. The examinee is given 45 sec to name the color of the ink in which each stimulus is printed. On the final part, the page consists of the words red, green, and blue, and each word is printed in red, green, or blue ink, but in a manner that the word and color ink are always incongruent. The score is the number of items completed correctly in 45 sec. The whole test takes about 5 minutes.

Ruff 2 & 7 Selective Attention Test **(Ruff & Allen, 1996)**
This test of sustained and selective attention consists of 20 15-second trials during which patients cross out 2 target stimuli (the numbers 2 and 7) among three rows of either numeric or alphabetic stimuli (each row contains 10 targets and 40 distracters in quasi-random order). The targets embedded among letters are considered "automatic" conditions (because the patient can identify targets simply by the category they belong to), whereas the tasks embedding the targets among numbers are considered "Controlled" conditions requiring effort and working memory since targets and distracters belong to the same stimulus category (numbers). The test evaluates both accuracy (considering errors of omission and commission) and speed. Normative data (based on 360 persons) are available for ages 16-70 years, stratified by education. Test-retest reliability is estimated to be .89 for speed, and .59 to .69 for accuracy on automatic and controlled search tasks (with stability coefficients ranging from .76 to .93). The test is typically completed in 5 minutes.

Executive Functions

Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Tests

The D-KEFS contains 3 verbal fluency tests assessing timed oral production of items from lexical and semantic categories. In the Letter fluency task the patient is asked to say as many words as possible (excluding proper names and numbers) beginning with a given letter of the alphabet. There are 3 trials, each using a different letter, of 60 seconds each. In the Category Fluency task, the examinee is asked to say as many words as possible belonging to a category (such as animals) in 60 seconds. There are 2 trials using different categories. On the final task (Category Switching), the patient is asked to orally generate consecutive words from 2 alternating categories for 60 seconds. The tasks can be completed in about 8-10 minutes.

The tests are normed on over 2000 individuals, are standardized, are applicable to persons up to 89 years of age, and are co-normed with the WASI. This co-norming feature means that cognitive strengths and weaknesses can be ascertained with confidence given comparability of scores and normative data. Another strength of this instrument is the availability of alternate forms, thus minimizing practice effects (although not eliminating possible familiarity and carry-over effects). Test-retest data are available to facilitate interpretation of score changes over time.

Memory

Hopkins Verbal Learning Test – Revised (HVLT-R; Brandt & Benedict, 2001)

This verbal learning test has six equivalent, alternate forms, making it ideal for repeat administration. It is normed on persons aged 16-92 years and was designed to be tolerated by even significantly impaired individuals. The examinee is provided 3 learning trials to remember an orally presented 12-word list (four nouns from each of 3 semantic categories). Following a 20-25 minute interval, delayed recall and yes/no recognition are assessed. The test takes about 15 minutes excluding the delay interval which is preferably filled with intervening visuospatial tasks. Test-retest reliability is weaker for recognition and retention (.40 and .39; probably limited by skewed
Score distributions), but adequate for recall (.66-.74). Test-retest gains, even when persons were tested as little as 2 weeks apart, were only about 0.5 standard deviations.

Brief Visual Memory Test – Revised (BVMT-R; Benedict, 1997)

Like any of its word list learning analogs (e.g., the HVLT-R), this test involves multiple trial learning followed by delayed recall and recognition trials. However, the stimuli are abstract line drawings rather than words. The patient is shown a set of 6 abstract line drawings (in a 2x3 array) for 10 seconds and is then asked to draw

them in their correct location. This procedure is repeated for a total of 3 learning trials. After 25 minutes, delayed recall and recognition (identifying which 6 of 12 drawings were seen) trials are administered. The brevity of the task and the availability of 6 alternate forms make the test useful for repeated administrations. It is normed for persons aged 18-79 years. Reliability coefficients exceed .90, and test-retest reliability ranges from .60 to .84. Excluding the delay, which is filled with verbal tests, the BVMT-R can be completed in 15 minutes.

Self and Informant Rating of Executive Functions

Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A; Roth et al. 2005)

The self-and informant-report forms consist of 75 items asking the person to report the frequency (never, sometimes, or often) with which certain behaviors have occurred during the month prior to evaluation. The behaviors measured relate to a variety of executive functions (e.g., self-monitoring, emotional control, behavioral inhibition and shifting, planning and organization) and are expressed in 2 indices (Behavioral Regulation Index and Metacognition Index) and an overall summary score (Global Executive Composite). There are also 3 response validity scales. Normative data are available for 1,050 persons for self-report and 1,200 informant reports. The test can be used with adults aged 18-90 years. Test-retest reliability for self-report clinical scores ranged from .82 to .93 over an average re-test interval of about 4 weeks, while informant report test-retest reliability ranged from .91 to .94. Test-retest values were still higher for the summary indexes. Patients and informants usually complete these forms in about 15 minutes.

Testing order:

The above tests should be performed in the following order:

1. HVLT-R immediate recall (3 trials);
2. Ruff 2 & 7;
3. Stroop;
4. Fill rest of 20-25 minute delay with starting the BRIEF;
5. HVLT-R Delayed recall and recognition;
6. BVMT-R Immediate recall (3 trials);
7. DKEFS verbal fluency tests;
8. Letter-Number Sequencing;
9. Continue the BRIEF as needed to fill the BVMT-R delay;
10. BVMT-R Delay recall and recognition;
11. Finish BRIEF.

7.3 DBS System Implantation

The DBS system implant visit should be performed no less than 2 weeks and no more than 1 month after the baseline #3 visit.

Implantation of the DBS system will be performed according to standard surgical procedure for Brodmann Area 25WM (Cg25) DBS implantation.

Pre-Operative Imaging: High resolution, 3D T1 weighted images will be obtained. On or before the day of surgery patients will have a stereotactic frame or appropriate bone fiducials applied using local anesthesia. Additional CT imaging for fusion is optional, as is the use of IV contrast.

Pre-Operative Planning: Standard software (e.g. Framelink, Brainlab, or other) is used to reconstruct the images in axial, coronal, and sagittal views, relative to the AC-PC plane.

The sagittal images will be used first. Surgeon will select an image several millimeters (mm) off midline clearly showing the white and gray matter of the cingulate gyrus. A tentative target point is selected at the center of the subgenual cingulate (Brodmann Area 25WM).

Next, the surgeon will convert to the coronal images perpendicular to the AC-PC plane. The midpoint of the subgenual cingulate gyrus is typically found in the coronal image containing the anterior-most section of the caudate nucleus. Thus the A-P position of the target can be confirmed by scanning a few images anterior and posterior to confirm proximity to this section.

Precise targets can then be selected bilaterally in this same coronal section. A point is selected on each side at the border of the white and grey matter, midway between the superior and inferior banks of the cingulate gyrus. The intended site is approximately 5-7 mm from the midline and 10 mm below the corpus callosum. After targets have been selected, the appropriate frame coordinates can be calculated and used for the stereotactic procedure.

Entry points can also be selected on the stereotactic planner if desired. This practice is variable at different centers. If entry planning is performed it is recommended that an entry site that is slightly anterior to the more typical burr hole used for STN-DBS. This is necessitated by the more anterior nature of this target. Anterior entry (~2cm anterior to the coronal suture) will avoid a difficult approach angle.

DBS Implantation: After sterile preparation of the operative field, burr holes are placed under local or general anesthesia. Again the slightly more anterior entry is recommended. A lateral position of 2-3cm from midline is also recommended. Dura and pia are opened under direct visualization. The

remainder of the operation is performed using an appropriate stereotactic frame or frameless guidance system.

One or more cannulas are inserted to the target coordinate. Microelectrode recording may be performed, at this point, to confirm the location of the grey-white junction within the target area. This procedure is optional.

A DBS electrode will be inserted into the target under fluoroscopic visualization. Once the electrode has been placed in the calculated target intra-operative diagnostic testing will be performed; however, no active deep brain stimulation will be delivered to the patient in order to protect the study blinding process. After confirmation of position the end of the lead is protected and excess lead is coiled in a sterile subgaleal pocket made by blunt dissection. The procedure is then repeated for the contralateral side.

Intraoperative Device Diagnostic Testing: The implanted leads will be tested for proper connectivity as well as impedance; however, no active stimulation will be delivered, so as to not break the blinding of the study.

IPG Implantation: The second stage of the operative procedure involves the implantation of lead extensions and the IPG. This will be performed immediately following the above procedure. The patient is given a general anesthetic and a sterile preparation is performed. The lead ends are accessed either by reopening the scalp incision or by making a smaller incision over the subgaleal pocket. The lead extension is then tunneled subcutaneously to a second incision just below the clavicle (can be left or right depending on patient preference). The extension wire is attached to the DBS leads proximally and to the battery distally. The implantable pulse generator is placed in a subcutaneous pocket that is made below the clavicle. Excess wire is coiled behind the IPG. Once again, a device diagnostic test will occur but no active stimulation will be delivered to the patient at this time.

Lead Localization: The lead will be imaged post-implantation to confirm lead location according to current neurosurgical procedures and/or CT scans. These images must be given to the Sponsor for future analysis.

7.4 Concomitant Treatments

All patients will have the ability to maintain their depression medication regimen as well as regularly scheduled psychotherapy to ensure study and therapy controls are maintained. For the 1-year study, all psychiatric care/decisions must be transferred to the study psychiatrist. For the first 6 months of the study, patients will not be able to add new medications (excluding sleep aids and other meds to manage non-depression related conditions) nor increase current antidepressant medication doses.

Medication additions:
For temporary insomnia, zaleplon, zolpidem, zopiclone, or chloral hydrate (a single dose nightly) or trazodone (< 100 mg) may be used, for a maximum of 14 nights during the study. Lorazepam (< 2 mg/d) may also be administered for treatment emergent anxiety for up to 14 days.

Rescue medications:
The study psychiatrist should first identify a need for a rescue based on his/her clinical judgment of worsening depression. In the event that a patient needs to be "rescued" due to a severe worsening of their depression (defined as patients who score 25% worse than their baseline average on the MADRS or worsening of suicidal ideation), prior to the completion of 6 months in the study, appropriate intervention may be initiated at the principal investigator's discretion considering the protocol-specified guidance. The following guidance should be adhered to when the rescue protocol is initiated:

<u>If a patient is rescued based on a 25% worsening of their MADRS score compared to the average MADRS Scores:</u>

- The patient will be considered a treatment failure.
- The visit will serve as the patient's endpoint data and the patient will be exited from the study. All end-of-study procedures should be performed.
- At the principal investigator discretion, medications may be added or changed as deemed in the best medical interest of the patient.
- Patients who were in either the control group or received active stimulation should enter a separate open-label protocol for long-term follow-up.

<u>If a patient is rescued based on a worsening of suicidal ideation</u>

- A patient who shows imminent suicidal intent but does not attempt suicide will be treated for the acute exacerbation of their symptoms. If the event can be treated with an acute intervention (less than 7 days) then the patient should resume participation in the trial and not be unblinded as to treatment.
- After the acute intervention, the patient must have a MADRS item 10 score of less than 5 to resume participation in the trial.
- After the acute intervention, the patient must resume their previous medication regimen if medications were changed.
- Patient's medications must be stable for a minimum of 7 days prior to an effectiveness visit
- If the patient attempts suicide, or requires a long-term medication change he/she will be considered and followed as a treatment failure.

Patients who were in either the control group or received active stimulation should enter a separate open-label protocol for long-term follow-up.

At any time during the study the patient feels suicidal or in any danger from worsening depressive symptoms, they, or their caretaker should call their study psychiatrist immediately.

7.5 Postoperative Visits

[redacted]

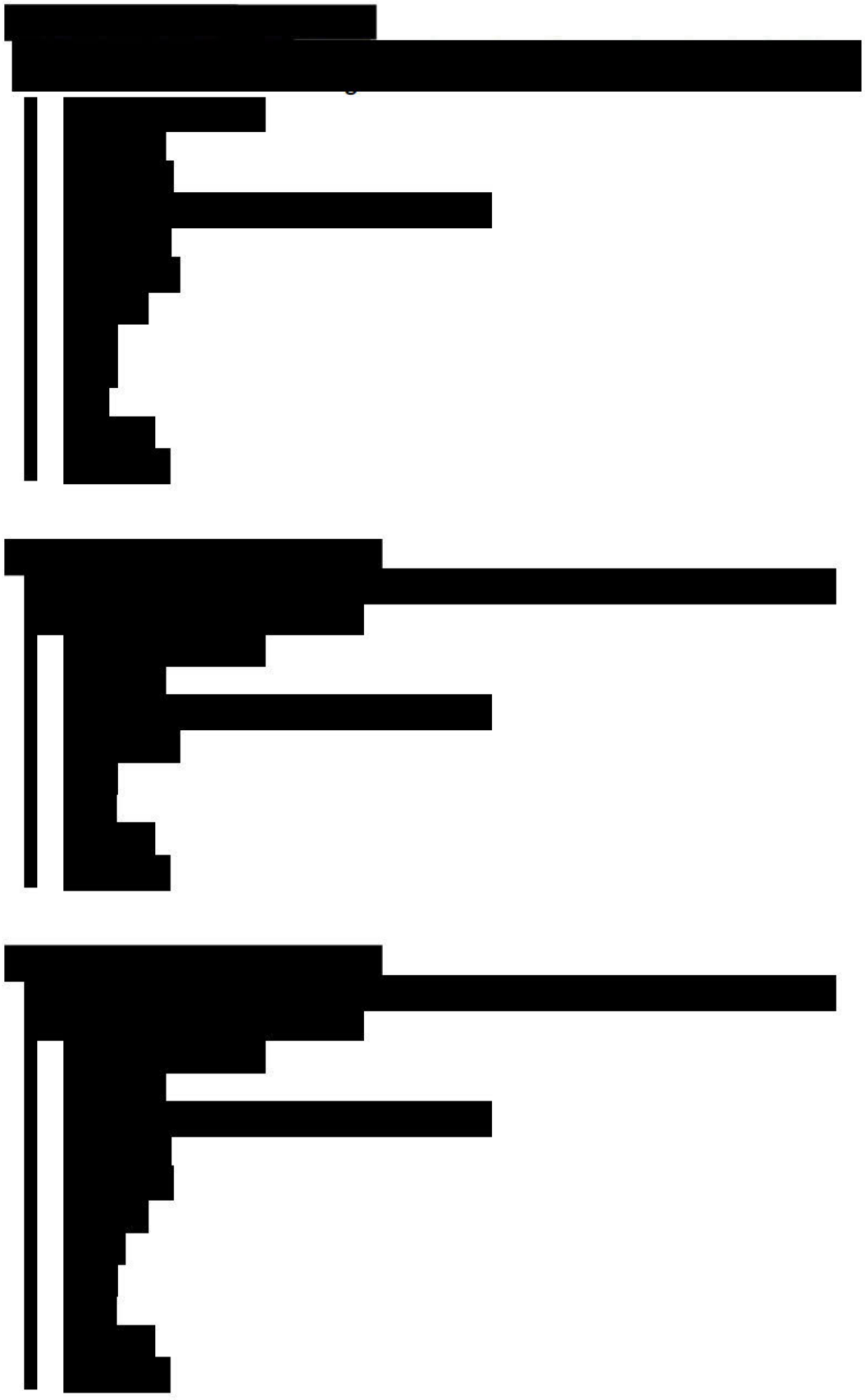
[redacted]

7.5.1 Study Visits:

[redacted]

[redacted]

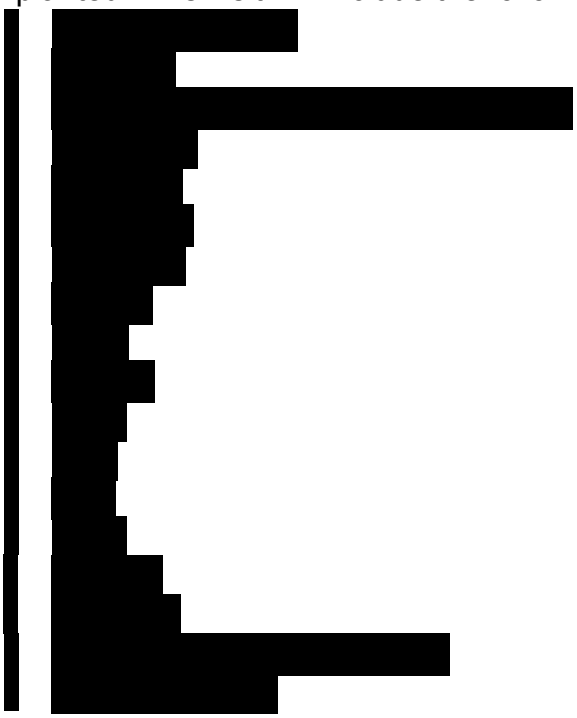
[redacted]



[redacted]

[redacted]

Patient evaluation will take place 52 weeks after the system is implanted. This visit will include the following:



7.5.2 Control Group (Non-Active Stimulation):

At the end of the 6 month visit, patients will be given the option to have device programmed and activated for DBS. Patient will then be followed monthly, until the end of the 52 week study.

7.6 Long-Term Follow-Up

All patients will be encouraged to enroll in a long-term follow-up study under a separate protocol sponsored by ANS to monitor the continued efficacy and safety of this system. Efficacy assessments and device related adverse events will be collected on all willing participants at specific intervals after they exit the currently proposed study. A separate study protocol and patient informed consent will be signed for this long term follow up study.

All study patients may have access to the device at no cost for battery replacement and or revision(s) until the device is commercially available in the United States. The patients/physicians must make a request to the study sponsor to have the device shipped to the appropriate location.

8 Adverse Events (AEs)

8.1 AE Definitions

An ADVERSE EVENT is "Any change, undesired, noxious or pathological in a patient or subject illustrated by signs, symptoms and /or laboratory changes that occur during a clinical trial, whether or not considered drug/treatment related."

A SERIOUS/SEVERE AE is where the event is/causes:
Life threatening or fatal
Requires or prolongs hospitalization
The patient to be disabled

A DEVICE RELATED AE is an anticipated (those events listed in section 8.4) or unanticipated (those events that occur that are not listed in section 8.4) event that occurs that is considered device related. A device-related event is one that the Investigator feels that the device (i.e. IPG, extension or lead) contributed in any way to the adverse event occurring. A stimulation-related event is one that resolves when stimulation is turned off or turned down.

A NON SERIOUS AE is an event other than one described above.

8.2 AE Recording

All Adverse Events volunteered by the Subjects/Patients or elicited by the Investigator must be recorded on the AE forms provided. All serious/severe AEs must be recorded whether or not considered device/treatment related. All device related complications that occur during the study duration and/or malfunctions of study device should be recorded on the AE forms provided. Device complications are defined as those complications relating directly to the functioning of the stimulation system (i.e. IPG, extension or lead).

8.3 Reporting AEs

Throughout the course of the proposed study, all serious/severe adverse events and device related adverse events would be recorded and monitored by the Sponsor and the Investigator. Every effort will be made to remain alert to possible adverse experiences and unexpected findings. If adverse experiences occur, the first concern will be the safety of the subject. Appropriate medical intervention will be made. All completed suicides and suicide attempts (defined by the Columbia Suicide Severity Rating Scale (CSSRS) $\geq$ 3) must be reported to the Sponsor immediately **(less than 10 days)** upon discovery. Once the Sponsor is notified of these events, the Sponsor will report these events to the FDA within 10 days.

Individual reports of device related complications will be documented and reported appropriately. The investigator must report all serious AEs to the Sponsor immediately upon discovery by telephone and forward the completed AE form as soon as it is available. The Investigator must also promptly report the resolution to all reported serious or device related AEs.

8.4 Anticipated Adverse Events and Complications

Implantation of a deep brain stimulation lead is a surgical procedure that may expose the patient to the risks of post-operative pain, stress, or discomfort, intracranial hemorrhage, subcutaneous hemorrhage, intracranial infarctions, venous air embolism (air entering the veins), venous infarctions, symptomatic neumocephalus (intracranial air causing confusion requiring an extra day stay in the hospital), seizure or convulsions, seroma, infection, aphasia, paralysis, stroke, death, cerebrospinal fluid leakage or abnormality. An additional neurosurgical procedure may be necessary to manage one of the above complications or to replace a fractured lead or to replace the pulse generator

The anticipated adverse events associated with the use of this device may include the following:

- Neuropathy;
- Neuralgia;
- Headache;
- Asthenia, hemiplegia or hemiparesis;
- Cognitive impairment, including confusion, abnormal thinking, hallucinations, alteration of mentation, amnesia, delusions, or dementia;
- Infection;
- Fever;
- Disequilibrium;
- Ataxia;
- Myoclonus;
- Hearing and visual disturbance;
- Paresis;
- Dystonia;
- Attention deficit;
- Dysarthria;
- Sleep disturbance;
- Suicide or Suicide attempt;
- Increase in drug side effects;
- Autonomic instability (change in vital signs);
- Urinary incontinence;
- Worsening depression symptoms (will not be considered an AE);
- Anxiety;
- Ruminativeness;
- Hypomania;

- Mania;
- Panic attacks;
- Obsessive compulsive disorder (OCD) symptoms;
- Psychosis;
- Seizure;
- Apathy;
- Eye disorder;
- Sweating;
- Diarrhea;
- Sensory deficit;
- Drowsiness;
- Difficulty breathing;
- Increased salivation;
- Nausea and/or vomiting;
- Rapid heart rate;
- Pneumonia;
- Skin disorder;
- Edema including periorbital;
- Syncope;
- Persistent pain or redness at the IPG site or the surgery site/extension;
- Pulling sensation along extension site;
- Allergic or rejection response to implanted materials;
- General erosion or local skin erosion over the pulse generator (IPG), burr hole cap, and/or extension;
- Undesirable changes in stimulation possibly related to cellular changes in tissue around the electrodes, changes in the electrode position, or loose electrical connections and/or lead fracture;
- Initial jolt or tingling during stimulation;
- Paresthesia;
- Loss of therapeutic benefit as a result of change in electrode positions, lead fracture, loose electrical connections, DBS system battery failure, DBS system malfunction, or inadvertent turning off of device;
- Lead fracture;
- Lead migration;
- System dislodgement;
- DBS battery failure;
- DBS system malfunction.

8.5 AE Classification

Each adverse event will be classified by the Investigator and reported to the Sponsor using the Adverse Event Form of the patient's Case Report Form.

9 Data Analysis and Statistical Plan

9.1 Statistical Plan

The study design for this investigation is a prospective, double-blind, randomized, and controlled study. The primary objective is to demonstrate the safety and efficacy of using subgenual white matter (Brodmann Area 25WM) deep brain stimulation as an adjunctive treatment for Major Depressive Disorder, single or recurrent episode.

9.2 Sample Size

[redacted]

9.3 Datasets

[redacted]

9.4 Primary Effectiveness Analysis

[redacted]

[redacted]

9.5 Secondary Effectiveness Analyses

[redacted]

[redacted]

9.6 Other Analyses

[redacted]

9.7 Safety Analyses

9.7.1 Primary Safety Analysis

[redacted]

[redacted]

9.7.2 Other Analyses of Safety

[redacted]

[redacted]

9.8 Stopping Rule for Futility

The futility analysis will be done when 75 to 100 patients have achieved the primary endpoint by either completing their Month-6 visit or have terminated from the trial prior to their Month 4 visit. No more than 125 patients will be enrolled into the trial until the results of the futility analysis have been completed and reviewed by FDA.

[redacted]

[redacted]

10 Withdrawal of Subjects from Study

Subjects may be discontinued from the study for non treatment-related reasons only when no other option is possible. Reasons for discontinuation include, but are not necessarily limited to:

- Voluntary withdrawal from the study by the subject;
- Subject has moved from the area and is determined to be lost-to-follow-up;
- Investigator may discontinue the Subject's participation in the study for reasons including, but not limited to: subject noncompliance, unwillingness or inability to cooperate with study requirements (therapy regimen, follow-up visits, study determination, etc...).

The reason for discontinuation will be recorded on the appropriate case report form.

Prior to discontinuing a subject, every effort should be made to contact the subject in an effort either to get the subject back into compliance with the protocol, or to obtain as much follow-up data as possible. If a subject decides to discontinue from the study, the subject shall have the option of having the system surgically removed followed by normal psychiatric care. Once the patient exits the study, the device will be turned off (no matter what the randomized treatment was assigned). The device can only be reactivated by the study psychiatrist after the patient enters a separate open-label protocol for long-term follow-up. The patient must sign a separate informed consent and must satisfy the inclusion criteria of the long-term follow up study prior to being enrolled. The study psychiatrist must also deem the subject fit to begin or continue with stimulation.

11 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be appointed to review all SAE data and ensure the appropriate follow up actions necessary. Keeping in mind the safety of patients the status of the study will be evaluated based on a risk to benefit ratio. The Board will create a guidance document prior to the first patient being implanted. This guidance document will indicate the frequency of DSMB meeting, stopping rules and other pertinent information to guide study review.

12 Modification of Protocol

Any amendments to this protocol must be prepared by the study monitor and approved by ANS, the Investigator and the local authority (FDA/IRB/IEC) before implementation.

13 Discontinuation of Study

ANS reserves the right to discontinue any study for administrative reasons at any time, such as but not limited to, a decision to discontinue further clinical investigations with the test article, improper conduct of the study by the Investigator, inability to obtain the number of patients required by the protocol, etc. Reimbursements for reasonable expenses will be made if such action is necessary.

This study may be terminated by the DSMB if an unacceptable number of intracranial hemorrhages or an unacceptable number of completed suicides or suicide attempts is reached without an appropriate explanation. Guidance regarding event evaluation is provided in the DSMB Plan

Study enrollment will be suspended if the following criterion is met until the Data Safety Monitoring Board and FDA can review the safety and effectiveness data to determine whether the study should be halted, modified, or continued.

- If the lower bound of the two-sided 95% confidence interval (based on the normal approximation) for the rate of completed suicides in the combined patient population exceeds 2% at any point during the study.

This study may be terminated if the number of the following events is reached without an appropriate explanation by the 6 month primary endpoint:

- If greater than 24 patients experience an intracranial hemorrhage. This would assume that during the study at the specified interval the rate of intracranial hemorrhage would exceed 12% then the study would be terminated.

14 Administrative Requirements and Quality Assurance

14.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Before the study can begin the Investigator must provide the Sponsor with a copy of the approval notice for the protocol and informed consent forms, signed by the appropriate committee chairperson.

14.2 Clinical Supplies

The Investigator agrees to keep all test articles in a secure location with restricted access. The Investigator will maintain an inventory of test article receipt and distribution. The Sponsor will provide an itemized inventory of all supplies dispatched. The Investigator or appropriate designee will provide written confirmation of receipt. Investigational devices and device accessories required for maintenance of the implanted devices will be made available to all patients enrolled in this study, at the request of the study Investigator, during the period the patient has completed study participation and prior to PMA approval.

14.3 Reporting and Recording of Data

All study data will be recorded on electronic Case Record Forms (eCRF). Electronic data capture (EDC) will also be utilized to monitor, correct, and store the collected data.

14.4 Monitoring

The Investigator will permit the Study Monitor to visit the Investigational Site at regular intervals to review all the CRFs, study related adjunctive data, and study management. These reviews are for the purpose of verifying the adherence to the protocol and the completeness and exactness of the data being entered as required by Federal Regulations. The Study Monitor must be kept informed of all issues pertinent to the study. The Study Monitor will be available to discuss by telephone questions regarding adverse events, removal of patients/subjects from the study, conduct of the study or any other questions that should arise. At the final monitoring visit the Study Monitor must resolve any outstanding data deficiencies and retrieve all used and unused test articles.

14.5 On-site Audits

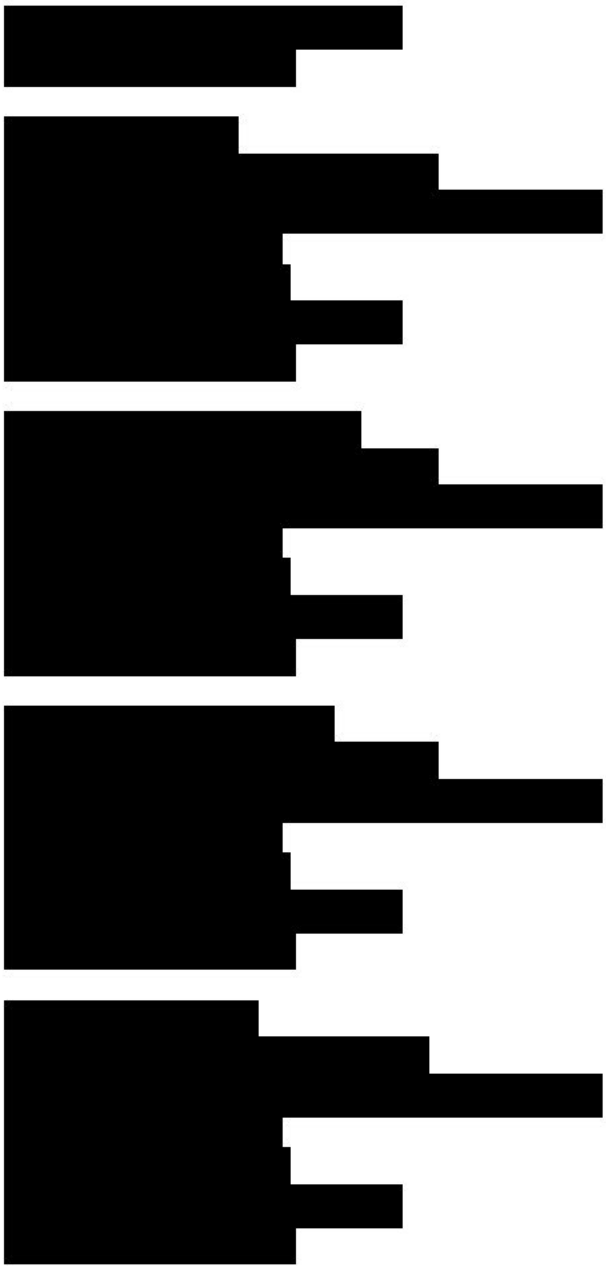
The various National Regulatory Authorities (including the United States Food and Drug Administration) in the person of a scientifically trained and properly authorized employee of the department, may request access to all study records, including source documents, for inspection and copying. Similar auditing procedures may also be conducted by a representative of the Sponsor.

14.6 Record Storage and Retention

Federal law and GCP requires that a copy of all study records (e.g., Informed Consent documents, source documents, study records, etc.) which support CRFs of this study, must be retained in the files of the responsible Investigator for a minimum of two years following notification by ANS that all Investigations (not merely the Investigators portion) are completed, terminated, or discontinued, or that the Food and Drug Administration has approved the submission.

If the Principal Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept responsibility. ANS must be notified in writing of the name and address of the new custodian.

14.7 Clinical Monitors



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16 Appendices

16.1 Appendix A: Product Labeling

16.2 Appendix B: Sample Informed Consent

16.3 Appendix C: Case Report Forms (CRFs)

16.4 Appendix D: Study Visit Schedule

16.1 Appendix A: Product Labeling

16.2 Appendix B: Sample Informed Consent

16.3 Appendix C: Case Report Forms (CRFs)

16.4 Appendix D: Study Visit Schedule