

12. Substantial Equivalence

12.1. Statement of Substantial Equivalence

In accordance with 21 CFR 807.87 which states the requirements for a pre-market 510(k) notification, including evidence of substantial equivalence of the premarket device to a marketed predicate device, this application demonstrates that the Neuronetics Callisto TMS System, which delivers transcranial magnetic stimulation (TMS), is *substantially equivalent* to Electroconvulsive Therapy (ECT) devices, the predicate devices, for the intended use of “treatment of major depressive disorder”.

The NeuroStar™ System and ECT devices have the *same intended use*. Although the NeuroStar System and ECT devices have technological differences that include modifications in design, materials, and in energy source (magnetic vs. electrical stimulation, respectively) as discussed in more detail in Table 12.3, these differences *do not adversely affect safety or effectiveness under the conditions of intended use*. As described in this section;

- The NeuroStar System *poses the same type of questions about safety or effectiveness* as ECT devices, the predicate device;
- *an accepted scientific method* (i.e. randomized, sham-controlled clinical trial) has been used to evaluate whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; and
- bench and clinical performance data are provided in the submission that demonstrate that these *new technological characteristics have not diminished safety or effectiveness*. That is, the NeuroStar System has been shown by clinical performance data (Study No. 44-01101) that it is safe and effective in the treatment of major depressive disorder and provides substantial safety benefits as compared to ECT devices.

Given the above, the NeuroStar System, using ECT devices as predicate devices, meets regulatory requirements for demonstration of substantial equivalence (see Premarket Notification Review Program 6/30/86 (K86-3) FDA blue book memorandum, “Guidance on the CDRH Premarket Notification Review Program”).

12.2. Rationale for Electroconvulsive Therapy (ECT) Devices as Predicate Devices for the NeuroStar™ System

Electroconvulsive Therapy devices (Product Code GXC) are defined according to 21 CFR 882.5940(a): “An electroconvulsive therapy device is a device used for treating severe psychiatric disturbances (e.g., severe depression) by inducing in the patient a major motor seizure by applying a brief intense electrical current to the patient’s head”.

ECT devices are Preamendments devices that are Class III devices in accordance with 21 CFR 882.5940 (b). As stated in 21 CFR 882.5940 (c), “No effective date has been established for the requirement of premarket approval.” Therefore, ECT devices are cleared to market via premarket notification using prior ECT devices as predicates.

ECT devices cited in this application as predicate devices are listed in Table 12.1 “Electroconvulsive Therapy (ECT) Predicate Devices” below. These devices were cleared by FDA via premarket notifications under the 510(k) numbers shown. The product labeling and premarket 510(k) notification clearance letters from FDA for these devices are provided in the Appendices cited in the table.

Table 12.1. Electroconvulsive Therapy (ECT) Predicate Devices

ECT Device	License Holder	Model No.(s)	510(k) No.(s)	Reference Location in this
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
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The rationale for this premarket notification with ECT devices serving as predicate devices for the NeuroStar System is as follows:

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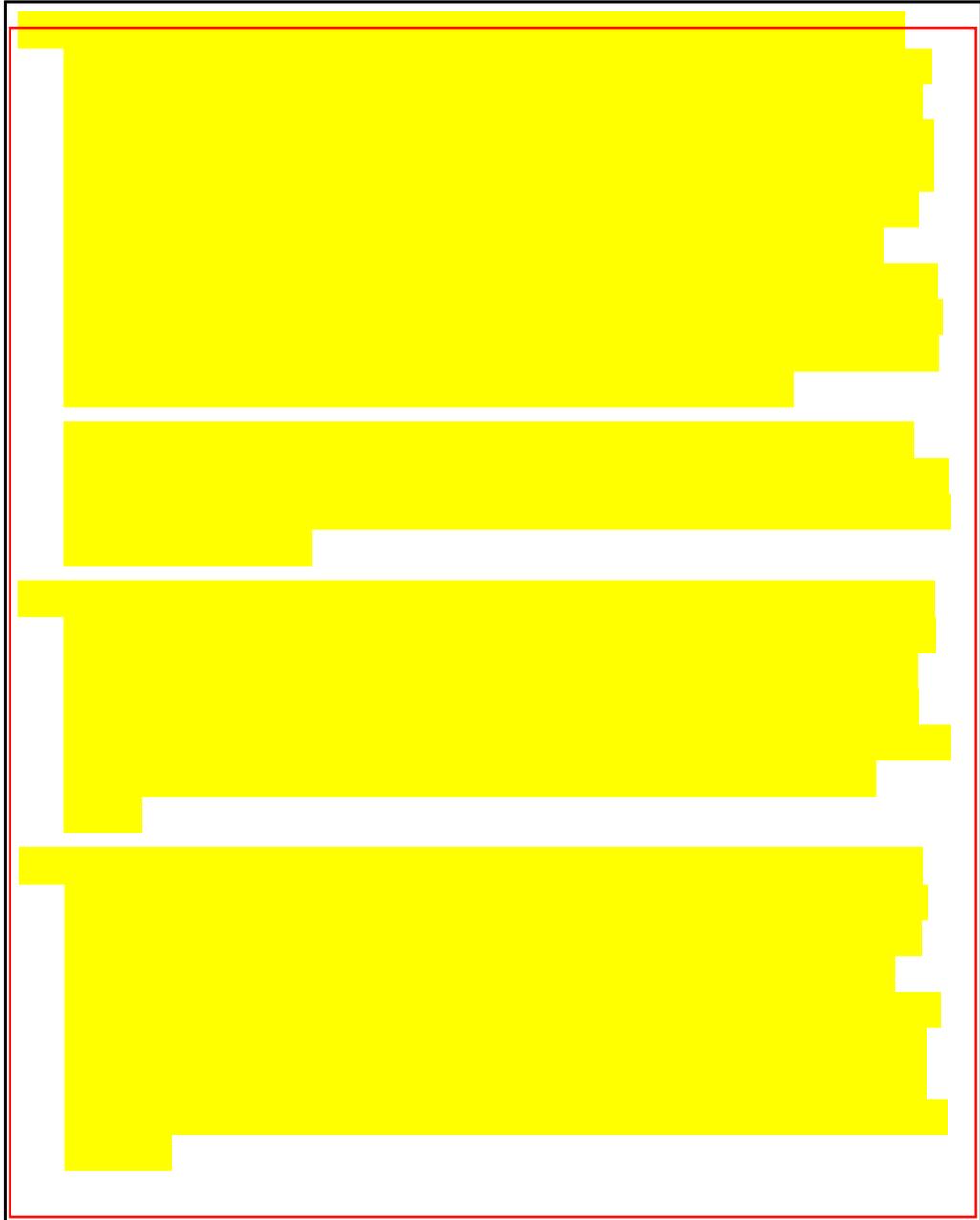


Table 12.2. Magnetic Stimulators Cleared by Premarket Notification for Substantial Equivalence to Electrical Stimulators

K Number / Regulation Number	Device	Classification Advisory Committee / Review Advisory	Cleared Intended Use	Classification Product Code / Subsequent Product Code
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
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12.3. Data Requirements of the Premarket 510(k) Notification for Substantial Equivalence to ECT Devices

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In accordance with these discussions, the clinical data presented in this application to demonstrate safety and effectiveness of the NeuroStar System to treat major depressive disorder are the result of:

- A randomized, sham-controlled acute efficacy trial (Study No. 44-01101) using
 - MADRS mean value of active TMS vs. sham control at 4 weeks of treatment as the primary efficacy endpoint
 - MADRS and HAMD measurements at 2, 4 and 6 weeks as secondary endpoints of active TMS vs. sham control presented as mean values and categorical values for response (>50% reduction in score) and remission (score <11, 10 or 8).
 - Additional physician and patient rated scales for depression, general health and quality of life.
- Weekly MADRS and HAMD data for the 3 weeks of taper from treatment with the Neuronetics TMS System with concomitant transition to oral antidepressant medications for evaluation of immediate durability outcomes.
- Durability data from an uncontrolled follow-up study (Study No. 44-01103) that evaluates these randomized patients after 4 weeks post-taper.
- Safety and efficacy descriptive data that is presently available for patients who completed 3 and 6 months post-taper in Study 44-01103.

Additional supportive data provided in this premarket notification includes safety and efficacy data available for patients completing open-label Study 44-01102 which was conducted under the same protocol conditions as Study 44-01101. Descriptive analysis of the same clinical endpoints as collected in Study 44-01101 is provided for this study.

12.4. Substantial Equivalence Comparison Table

Table 12.3 provides a summary of the use/class, technical and safety characteristics that are compared between the NeuroStar™ System and ECT devices in the Substantial Equivalence Comparison Table 12.4 and includes those comparative characteristics recommended in FDA's 510(k) Device Advice guidance entitled "Content of a 510(k)". Several characteristics were added to the table to address the safety issues for ECT that are cited in the Task Force Report of the American Psychiatric Association (APA, 2001), which is recognized as the authority publication regarding the clinical use of ECT. Table 12.4 provides key information regarding each of these characteristics for the NeuroStar System and ECT devices and identifies the relevant similarities and differences.

The last column of Table 12.4 provides the rationale for claiming that the NeuroStar System and ECT devices are *substantially equivalent*. In those cases where differences exist between the NeuroStar System and ECT devices, the data or other information, such as product labeling, that mitigate these differences, is stated as a rationale for why this characteristic *meets the requirements of substantial equivalence*.

Table 12.3. Contents of the Substantial Equivalence Comparison Table 12.4

Use/Class	Technical	Safety
<ul style="list-style-type: none"> • Indications for use¹ • Target population¹ • Classification • CFR reference and identification • Clinical setting • Additional treatment requirements • Anatomical sites 	<ul style="list-style-type: none"> • Design • Materials • Energy used and/or delivered • Key product specifications • Standards met • Biocompatibility • Performance • Human factors • Compatibility with the environment and other devices • Sterility 	<ul style="list-style-type: none"> • Contraindications and Warnings • Adverse clinical effects¹ • Requirement for informed consent¹ • Evaluation of cognitive changes¹ • Electrical safety • Mechanical safety • Chemical safety • Thermal safety • Radiation safety

¹ From the Task Force Report of the American Psychiatric Association (APA, 2001)

Table 12.4 refers to Section 12.5 of this submission that provides a more detailed description of the basic physics of neuronal depolarization as achieved by ECT devices or TMS devices.

Table 12.4 also refers to Section 12.6 that provides a detailed review of relevant ECT literature regarding safety and efficacy data and compares this data to the results obtained from Neuronetics' clinical studies using the Neuronetics TMS System. Section 12.6 contains the summary basis of the data demonstrating that *the NeuroStar System is safe and effective for the intended use of treatment of major depressive disorder and that it is substantially equivalent to ECT devices within the requirements of 21 CFR 807.87*.



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1. Indications for ECT devices are defined in the The APA Task Force Report; Section 2.3. Principal Diagnostic Indications. 2.3.1, Major Depression. (a) ECT is an efficacious treatment for unipolar major depression, including major depression, single episode (296.2x) and major depression (296.3x) (DSM-IV; American Psychiatric Association 1994a), (b), ECT is an efficacious treatment for bipolar major depression, including bipolar

[REDACTED]

12.5. Biophysical Considerations of ECT Devices and the NeuroStar™ System with Regard to Cortical Neuron Stimulation

12.5.1. General Considerations

Electroconvulsive Therapy (ECT) has been used as a therapeutic antidepressant since its introduction to clinical practice in 1938. The ECT procedure involves the direct application of electrical current to the brain through the placement of electrodes on the surface of the head. It is generally accepted by the scientific community that upon exposure of the brain to a sufficient amount of electrical energy, clinically meaningful antidepressant activity can be achieved in patients with major depression and in other clinical conditions, including some psychotic illnesses. For the first few decades after the introduction of ECT in the U.S., alternating-current ECT devices were used to produce both subconvulsant stimulation and epileptic convulsive seizures (Androp, S., 1941; Gottesfeld, B.H., et al., 1944) that showed effectiveness as depression treatments.

Practitioners now recognize that production of a seizure is more effective in ECT treatment than subconvulsive therapy. However, *the production of the seizure is not in and of itself sufficient for antidepressant effect.* The magnitude of clinical efficacy produced by ECT appears to be related to the magnitude of the electrical energy applied above the amount needed to induce a seizure (Sackeim, H.A., et al., 1993). Thus, the use of commercial devices for direct application of alternating electric current to treat depression in the U.S. spanned the range from subconvulsant to barely convulsant to supraconvulsant prior to 1978.

Since its introduction, a number of important modifications in ECT treatment technique have been established, including the use of general anesthesia, muscle paralysis, and improvements in cardiovascular monitoring. In addition, improvements in the design of ECT devices have permitted the administration of shorter duration electrical pulses. Overall, these modifications have led to significant changes in the practice of ECT, with accompanying reductions in the morbidity of the procedure. Nevertheless, few practitioners would dispute the fact that ECT remains the most complex and poorly tolerated of all contemporary antidepressant treatments.

From a biophysical point of view, the mechanism of effect of both ECT and TMS are similar, in that with both methods, an electrical current is produced within cortical neurons, resulting in neuronal depolarization. During an ECT procedure, the current is applied directly to the head via electrodes on the scalp. In a TMS session, the electrical current is produced in tissue by magnetic induction as delivered by a ferromagnetic coil

that is applied externally to the surface of the head in the desired region of stimulation, the left dorsolateral prefrontal cortex.

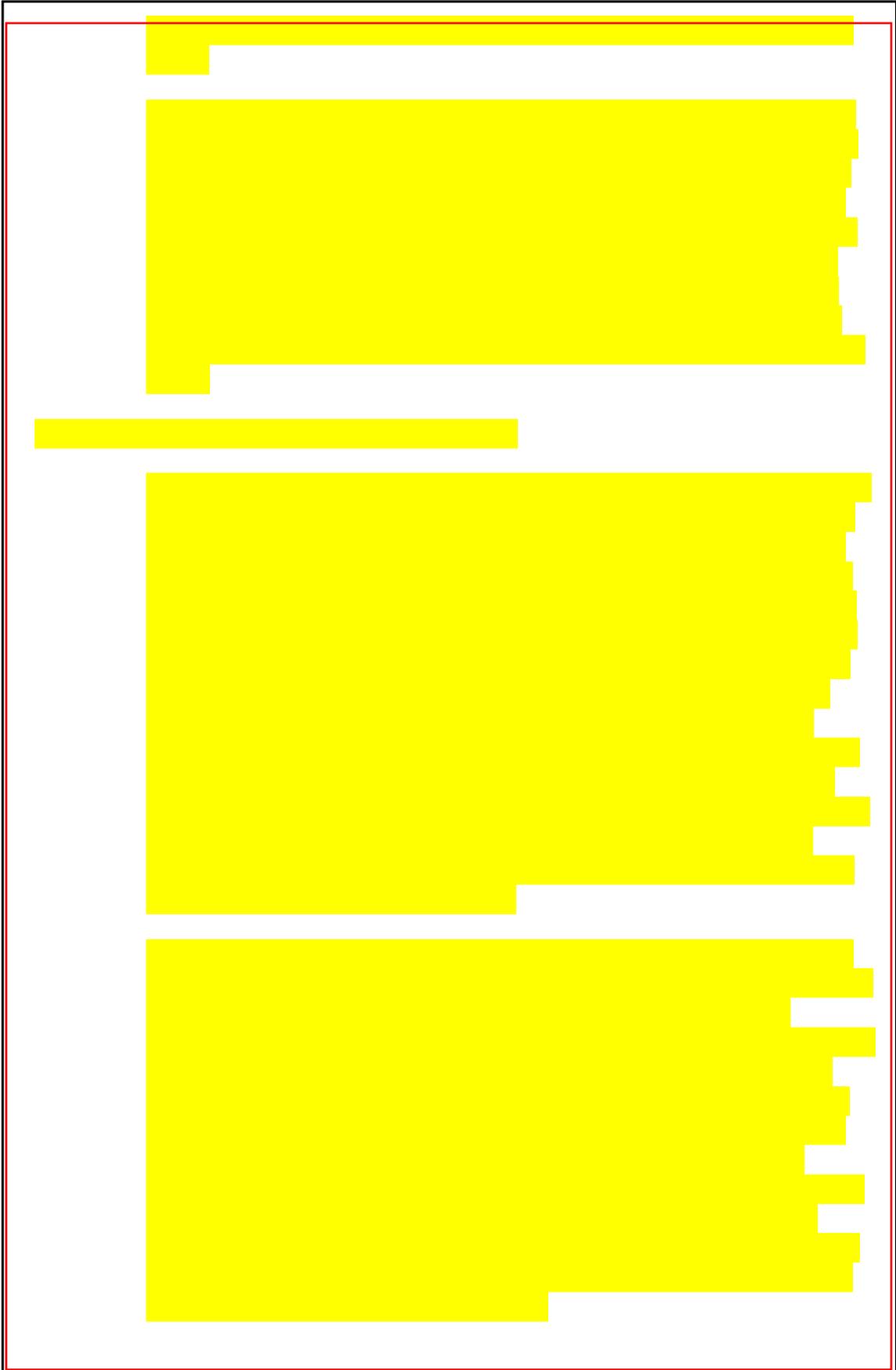
In the case of ECT, the electrical current has a much wider spatial distribution in the brain, the specific pattern of which is dependent upon the impedance of electrodes, and the shunting of electrical current produced by the individual's bone and soft tissue structures that lay in the path of the current flow. In the case of TMS, the electrical current is focused to the volume of tissue beneath the coil. Therefore, although ECT and TMS share fundamental mechanistic similarities in neuronal depolarization, the variation in total current exposure, and the pattern of spatial distribution of the current flow are thought to play a role in the substantial apparent clinical advantages of TMS especially with regard to adverse cognitive effects.

A detailed comparison of the biophysical characteristics of these two techniques in comparable brain volumes of exposure is discussed in the following sections. The differences noted between ECT and TMS biophysical effects on tissue are apparently not essential to efficacy because both methods are efficacious in the treatment of depression (see Section 20 for a summary of the results of Neuronetics clinical studies). However, as stated above, these effects likely play an important role in clinical safety given the superior safety profile of TMS.

12.5.2.



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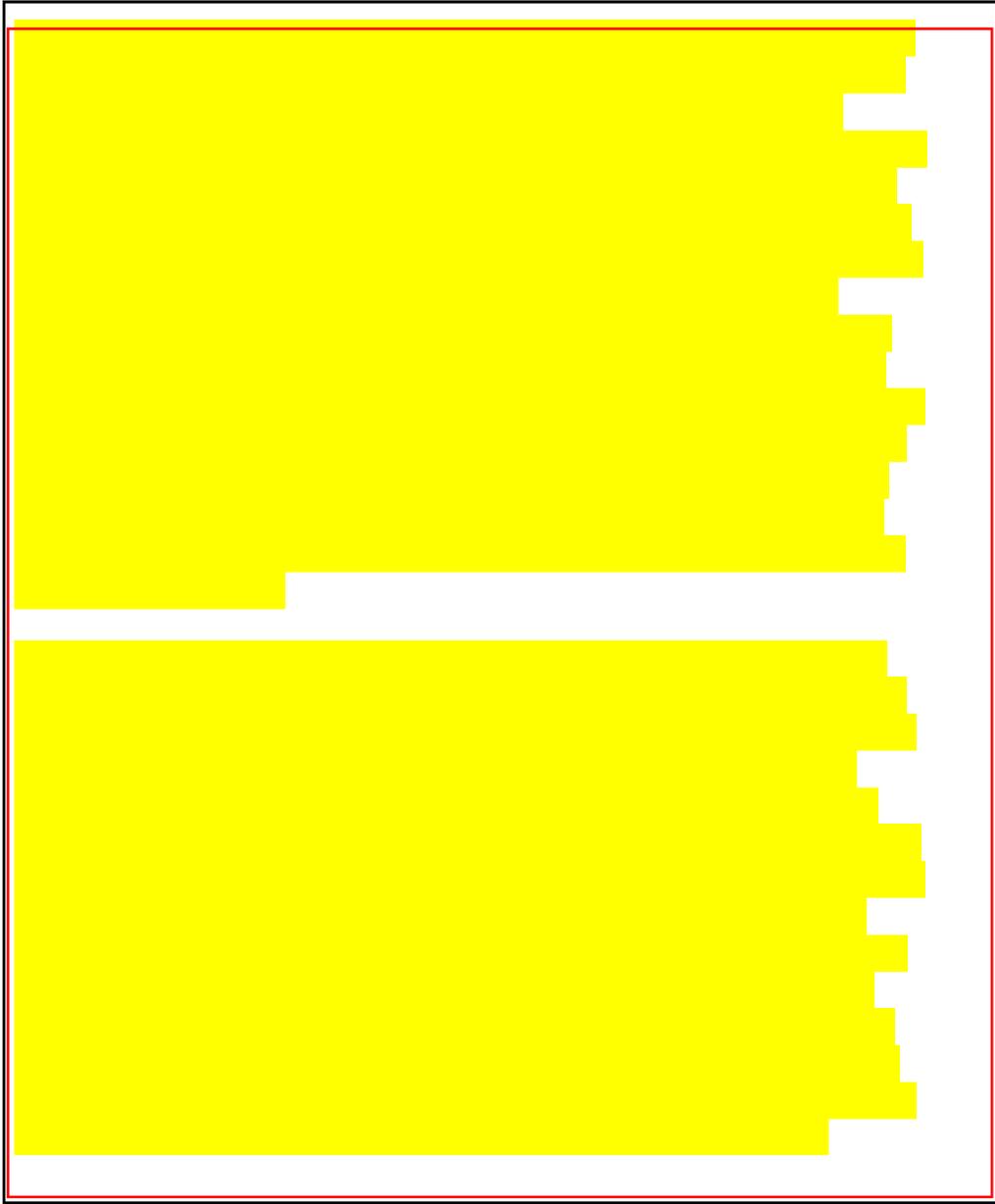
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12.6. Clinical Safety and Efficacy Data: Substantial Equivalence of the NeuroStar™ System to Predicate ECT Devices in the Treatment of Major Depressive Disorder

As stated in Section 12.1, Electroconvulsive Therapy (ECT) devices serve as the predicate devices for the NeuroStar System for this premarket 510(k) clearance for the intended use of “*treatment of major depressive disorder*”.

This section of the premarket 510(k) notification provides a comparison of clinical safety and efficacy data that is available from the medical literature for ECT devices with safety a [redacted] obtained from the clinical studies conducted by Neuronetics [redacted] in depression using Neuronetics’ TMS System. This comparison demonstrate that TMS therapy delivered by the Neuronetics NeuroStar System:

- is *clinically effective* in treating the *same patient population* with major depressive disorder as for predicate ECT devices,
- has an *expected effect size* for this treatment-resistant population as compared to current therapies,
- has a *superior safety profile* as compared with predicate ECT devices, and
- has a *superior risk-to-benefit* as compared to ECT predicate devices due to its proven efficacy and superior safety for patients with MDD.

This section provides:

- An introduction to major depressive disorder, its incidence and biology and a discussion of the unmet medical needs in the treatment of patients who fail to receive adequate benefit from antidepressant pharmacotherapy alone.
- A further description of the patient with treatment-resistant depression and their therapeutic options and outcomes.
- A summary of the current approaches to the physician’s treatment options for major depression and where treatment with the Neuronetics NeuroStar System may fit in their treatment plan.

This section provides a Clinical Substantial Equivalence Assessment that contains the following information and data that substantiates and supports a determination of substantial equivalence for the NeuroStar System and predicate ECT devices:

- A listing and discussion of the principal sources of data used for the substantial equivalence comparison regarding clinical use of these devices.
- Comparison of the indications for use and clinical populations.

- Comparison of acute efficacy as compared to the relevant control populations.
- Comparison of durability of the acute response.
- Comparison of adverse event profiles, cognitive function outcomes and other relevant safety issues.
- A summary of safety and efficacy of the NeuroStar System as it compares to ECT treatment using predicate devices.

This section concludes with a discussion of the risk-benefit profile of the NeuroStar System vs. current treatment paradigms including pharmacotherapy and ECT treatment.

12.6.1. Overview of Major Depressive Disorder and Treatment Options

12.6.1.1. Disease Epidemiology and Accepted Clinical Definitions

Major depression is a common, disabling and potentially lethal condition. In a recent report (Murray, CJL, et al., 1996), it is estimated that by the year 2020, depression will be second only to heart disease in magnitude of disease burden as determined by disability-adjusted life years. In the most recent epidemiologic estimate in the United States, the National Comorbidity Survey replication study, it was estimated that the lifetime prevalence of formally diagnosed major depression was 16.2% (Kessler, RC, et al., 2003). Over a twelve month interval, in over half of all cases, the clinical significance was independently classified as either severe (38.0%) or very severe (12.9%) (Kessler, RC, et al., 2003). Notably, only about 10% of the cases were seen as mild.

In addition to its sheer prevalence, major depression rarely occurs as an isolated disease state, but frequently occurs in a comorbid manner with both psychiatric (Kessler, RC, et al., 2003) and medical illnesses. A somewhat underappreciated observation is that it has been demonstrated that the presence of major depression also has an aggravating impact on the morbidity and mortality of a range of other medical conditions, including heart disease, cancer, HIV infection, and diabetes mellitus (Katon, WJ., 2003; Eaton, W., et al., 1996; Rugulies, R., 2002; Cook, JA, et al., 2002). Indeed, there is essentially no health condition whose course is not adversely affected by untreated major depression. The impact of this illness is also seen when examining patterns of health resource use and their resulting financial costs, both direct and indirect (Simon, GE, et al., 1995). The concurrence of untreated or unrecognized major depression results in an excess utilization of health care resources among affected individuals, along with a

substantial disruption in their productive work life (Kessler, RC, et al, 1999). In many instances, these health care visits are for the evaluation or treatment of presumed medical conditions that in fact represent untreated symptoms of the underlying major depression.

The most commonly used diagnostic definition of depression in the United States is articulated in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, now in its fourth edition (DSM-IV). In that document, patients suffering from a major depressive episode (for a formal description of the DSM-IV case definition, see Table 12.6) experience a profound disruption in mood or a loss of pleasure in usual activities, termed anhedonia. These two subjective feelings are considered to be hallmark experiences of this disease. A range of other associated symptoms are also required to be present in order to formalize a diagnosis. These associated symptoms can include anxiety, hopelessness and suicidal ideation, excessive feelings of guilt, disturbances in cognition, disruptions in sleep, alterations in sexual function and appetite, either agitation or psychomotor retardation and fatigue. It is generally thought that the diagnostic term 'major depressive episode', actually encompasses a broader phenomenological description of an array of related clinical conditions.

Table 12.6. DSM-IV Case Definition for a Major Depressive Episode

<p>Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.</p>
<p>(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful),</p> <p>(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others),</p> <p>(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day,</p> <p>(4) insomnia or hypersomnia nearly every day,</p> <p>(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down),</p> <p>(6) fatigue or loss of energy nearly every day,</p> <p>(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick),</p> <p>(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or observed by others),</p> <p>(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide</p>

12.6.1.2. **Biological Considerations in the Pathophysiology of Depression**

Although the pathophysiology of major depression is incompletely understood, it is thought to represent a final common pathway condition resulting from a complex interplay of biological, genetic and environmental events. The dominant conceptual model to explain the underlying neurobiology of depression for over three decades has been the so-called “monoamine hypothesis”. A central assumption of this model is the hypothesis that functional changes in the regulation of the classical neurotransmitters serotonin, norepinephrine and dopamine result in a reduced availability of these chemicals in the brain, leading to the clinical experience of depression. The empirical power of this biological framework is compelling. Indeed, virtually all contemporary antidepressant pharmacotherapies have been developed based on this theoretical model, with the presumption that increasing the availability of these neurotransmitters, or altering the pre- or post-synaptic signaling pathways that mediate their effects, will relieve the symptoms of depression.

In recent years, increasing attention has been paid to the downstream cellular and genetic consequences of these changes in monoamine neurotransmission, since these cellular events follow a time course of action that more closely mimics the time course of clinical changes in response to these chemically-based therapeutic interventions (i.e., spanning at least 2-4 weeks). This research has yielded several candidate genes and proteins that may serve to increase an individual’s vulnerable risk for depression. One of the best studied targets has been the cellular protein, brain-derived neurotrophic factor, or BDNF. Unfortunately, advances in specific treatment approaches based on this research have not yet emerged.

Accompanying these observations in the neurobiology and cellular neurochemistry of major depression has been an equally impressive growth in our understanding of the functional integrity of the neuro-circuitry of depression. An extensive, replicated body of research using various neuroimaging approaches appears to converge on a common brain circuitry for depression, which includes regions of the prefrontal cortex, the anterior and subgenual cingulate gyrus, the basal ganglia and thalamus, and limbic structures including the amygdala and hippocampus. Simultaneous with these observations has been the development of novel approaches to modulate these brain circuits. For example, Mayberg and colleagues recently used chronic deep brain stimulation (DBS) to suppress the activity of the subgenual cortex, leading to sustained relief of depression in humans (Mayberg, HS, et al., 2005).

12.6.1.3. **Current Approaches to Treatment Planning for Major Depression**

Treatments for major depression are generally grouped into the biological therapies and the psychological therapies, with the most common approach to treatment combining these two modalities as clinically indicated in the individual patient. Regardless of the approach pursued, clinical outcomes to first line treatment for major depression remain modest at best. For instance, in randomized, controlled clinical trials of antidepressants used in a treatment-naïve or non-refractory patient population, approximately 50-60% of patients may be expected to achieve symptomatic criterion for response at the end of 4-6 weeks of acute treatment (i.e., a reduction of >50% in total symptom score on a standardized rating scale, compared to the level seen on that scale at baseline). Furthermore, only one-third of such treatment-responsive patients will experience complete relief of illness, typically expressed as achieving an *a priori*-defined remission score on a standardized symptom rating scale. Despite continued attempts with available antidepressant treatments, approximately 15-20% of patients will fail to receive clinical benefit from any currently available intervention, including ECT. This latter population is sometimes referred to as the treatment-refractory depressed patient population. The implications of this observation regarding the expectations of treatment benefit from antidepressant treatment are discussed further in Section 12.6.1.4.

Among the biological interventions, antidepressant medication treatment typically serves as the initial step in treatment planning. Selective serotonin reuptake inhibitors such as fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil) or citalopram (Celexa) have largely replaced the older tricyclic antidepressants and monoamine oxidase inhibitors as drugs of first choice in most clinical settings in contemporary practice. In the event that a patient remains symptomatically ill after at least 4-8 weeks of exposure to appropriate doses of their starting antidepressant, the clinician may consider several more options. Changing medications to one of the same or a different chemical class may be considered first. If pursuit of monotherapy is ultimately ineffective, then more complex medication regimens consisting of combination treatment or augmentation approaches is considered in the later stage of medication intervention. Each individual treatment trial may take at least 4-8 weeks or more to determine its outcome, where a sequential course of empirical treatment trials may take several months. During this time, the progressively more complex pharmacotherapeutic regimens are also associated with increasing burdens of adverse effects that add to patient distress.

Shortly after these more complicated treatment approaches enter the therapeutic planning process, interventions beyond pharmacotherapy alone are ordinarily considered by practitioner and patient. In current practice, the most commonly considered alternative approach is ECT. Aside from clinical situations where suicidal ideation is emergent and immediately life-threatening, or in the setting of catatonic stupor that creates a medical crisis, ECT is often approached with apprehension, if at all. The details of the ECT procedure are discussed in more detail in the following sections.

Vagal Nerve Stimulation (VNS) has recently become another approved treatment option for patients with MDD. This treatment requires surgical implantation of a vagal nerve stimulator in the patient's neck which, when activated, stimulates the vagal nerve which, in turn, results in an antidepressant effect. VNS therapy is indicated for the treatment of major depressive disorder for those patients who have failed to receive benefit from at least 4 failed antidepressant medication trials. Therefore, VNS provides another, albeit invasive, treatment option for the treatment refractory MDD patient.

In summary, the patient with major depressive disorder who has failed to receive benefit from pharmacologic monotherapy is a candidate for treatment with combination pharmacotherapy, ECT or VNS therapy. As described above, the invasiveness and/or poor side effect profile associated with these therapies are significant and many patients and physicians choose not to pursue these treatment options.

12.6.1.4. The Impact of Progressive Resistance to Antidepressant Treatment on the Response to Subsequent Treatment Interventions

As discussed in the previous section, despite the availability of current antidepressants, inadequate or non-response to initial treatment with antidepressants is the norm for patients with major depression. In the extreme, it is generally accepted that at least 15-25% of patients fail to receive meaningful clinical benefit from sequential treatment trials with any antidepressant intervention, typically referred to as treatment-resistant depression. The available evidence regarding the impact of progressively more serious degrees of treatment resistance on the likelihood of response to subsequent intervention is reviewed below.

Among the most powerful predictors of subsequent response to treatment are the duration and/or the chronicity of the course of the illness, however, probably most important, is *prior history of treatment non-response* (Thase, ME, et al., 1997; Sackeim, HA, 2001).

Based on these considerations, it is expected that the greatest likelihood of benefit should be seen in patients who, at first clinical presentation, have had a relatively short duration of illness (usually less than 2-3 years) and those who have no or little prior evidence of failing to receive benefit from antidepressant treatment, i.e., those with a so-called uncomplicated, or treatment responsive depression. This is the typical patient population studied in standard antidepressant drug development programs, where those individuals who have a prior history of non-response to at least one antidepressant are typically excluded from study.

In a recent report, Khan and colleagues (Khan, A., et al, 2000) obtained the summary basis of approvals for all recently approved antidepressant medications, and described the magnitude of symptom reduction across these studies. The sample included 19,639 patients studied in multiple registration trials for the antidepressants fluoxetine, sertraline, paroxetine, venlafaxine, nefazodone, mirtazapine, and bupropion. The primary outcome measure in all studies was the Hamilton Depression Rating Scale (HAMD, usually the 17-item version, although some studies used the 21-item version), and the duration of treatment extended from 4 to 8 weeks. They observed that the overall magnitude of symptom reduction on the HAMD was modest, especially when considered against the magnitude of response observed on placebo treatment: 40.7% in patients randomized to investigational drug, 41.7% with active comparators, and 30.9% on placebo.

Where it was possible to calculate the standardized effect size of the active treatment compared to placebo, the results were also modest. The average effect size for 4 week studies was 0.5167 (range: 0.01 to 0.98), and for 6 week studies was 0.4914 (range: 0.20 to 0.75). These results, because of their sample size and rigorous trial designs, are reliable anchors for best outcome estimates in current treatment options for patients with uncomplicated major depression. In an additional large reference sample from the published literature, Walsh and colleagues (Walsh, BT., et al, 2002), reported that the average response rate to known active treatment in a group of 75 published randomized controlled trials of antidepressant medication was 50.1%.

Unfortunately, a similarly large reference database of controlled outcome studies in more complicated depression types, including formally-defined treatment resistant depression, does not exist. However, there are several published references that support the general clinical assertion in the field that progressively more severe degrees of treatment resistance are associated with diminished

likelihood of response to acute treatment and also to the durability of acute treatment in shorter-term follow up.

Among the larger outcome studies that provides a basis for outcome expectations of the treatment of major depression in clinical practice is the large NIMH-funded effectiveness trial, The Sequenced Treatment Alternatives to Relieve Depression, or STAR*D, study. This study was developed to provide a semi-naturalistic treatment algorithm to assess outcome as close to clinical practice as possible. The results of Level 1 and Level 2 of that work have recently been published (Trivedi, 2006a, 2006b; Rush, 2006). These two treatment Levels deal with the early continuum of the treatment resistance spectrum, largely patients who have persistent disease (most patients were in a recurrent course of illness), but who have minimal to no evidence of failure to receive benefit to date.

It should be noted that the treatment history criteria defining entry into Level 1 of STAR*D was having *no evidence of having failed to receive benefit* from any of the various treatment options offered in the first two Levels of the study, as described below. In other words, most of the patients entering this study in Level 1 would not have qualified for entry into the Neuronetics studies because of insufficient evidence of resistance to treatment. On the other hand, many of the patients in the Level 2 to Level 3 continuum showed a prospectively demonstrated pattern of resistance to treatment consistent with the range of the treatment resistance history required for entry into the Neuronetics clinical development program. The primary outcome in the STAR*D study was remission, measured using the 17-Item HAMD, with an endpoint total score of less than 8, similar to the 17-Item HAMD remission endpoint used in the Neuronetics studies.

During Level 1, patients presenting with a clinically diagnosed major depression (N=2,876), and had not shown non-response or intolerance to any of the antidepressants to be used in the first two Steps of the STAR*D algorithm were eligible for entry. At entry to Level 1, the majority of the patients were relatively young (mean age = 40.8 years), however, the majority (~75%) had recurrent major depression. Their presenting HAMD17 total score was 21.8 (SD=5.2).

In comparison, over 90% of the patients entering the Neuronetics clinical program had a history of recurrent depression, their average age was nearly a decade greater (48 years of age), and their mean HAMD17 score at study screening was about 1-2 points greater (active TMS mean score of 22.7, SD = 2.37, and sham group mean score of 22.9, SD=3.13) than in the STAR*D cohort. This data

points to a less severely ill population in the Level 1 STAR*D cohort than in the Neuronetics studies.

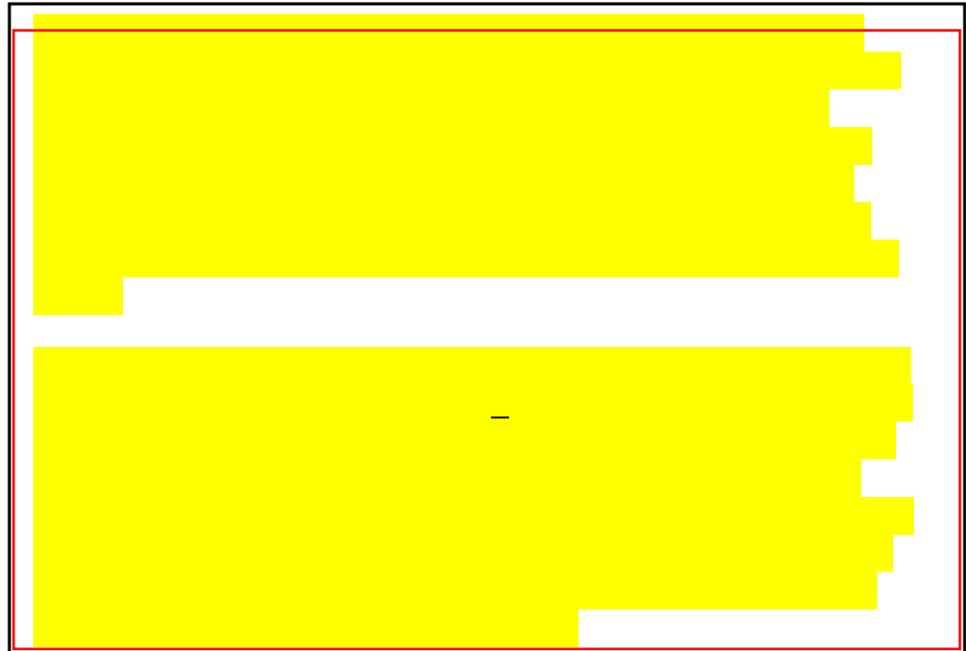
For the STAR*D population, after flexible-dose, open-label treatment with citalopram for up to 14 weeks, the overall remission rate was 27.5% by HAMD17 criterion.

Those patients who did not respond to treatment in Level 1, were offered the opportunity to proceed to Level 2 (N=1292), where two additional options were offered in an equipoise statistical design. These included either switching medication (3 different choices: sertraline, bupropion-SR, or venlafaxine-XR), or antidepressant augmentation (2 choices: add-on bupropion-SR, or add-on buspirone). Outcomes in Level 2 revealed a slight decline in the rate of remission with the two treatment options: for the switching strategy, the average rate of remission across the 3 options was 21.2 % (range: 17.6% to 24.8%), while for the two augmentation options, the average remission rate was 29.9% (range: 29.7% and 30.1%).

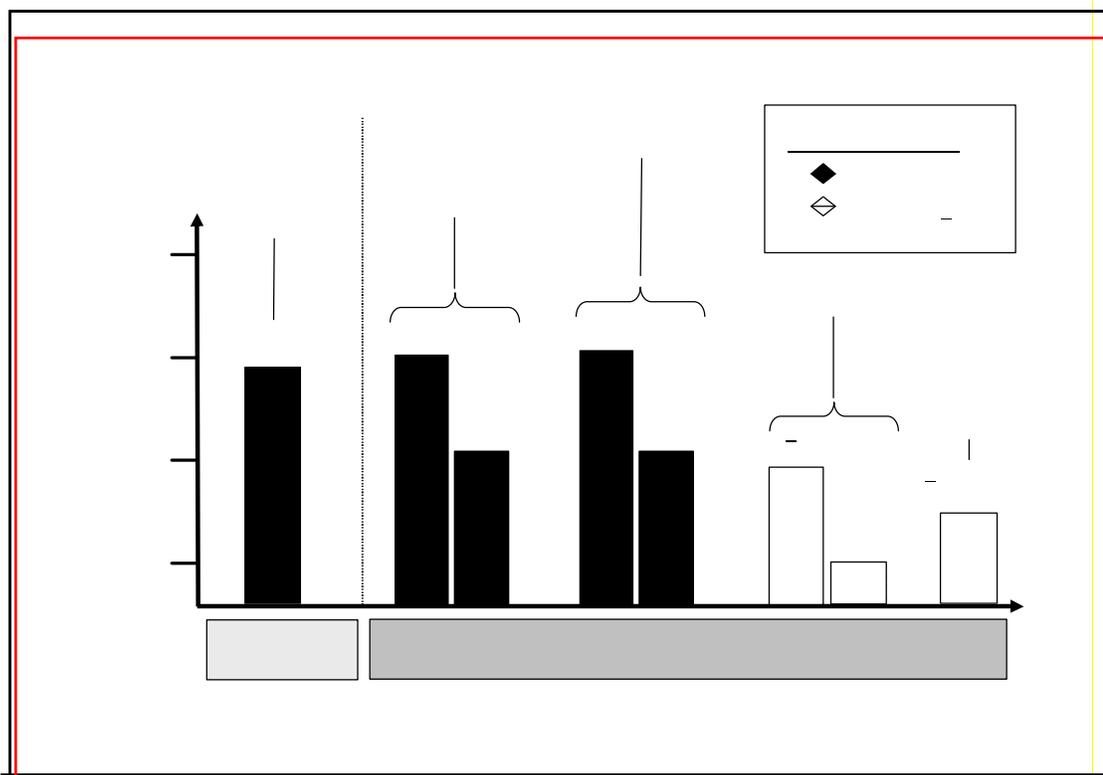
It is worth noting that in Level 2, the average HAMD17 total score at entry for the switching cohort was 18.9 (SD=7.3) and for the augmentation cohort was 15.8 (SD=7.1). While response rates for the HAMD17 were not reported in the study, based on the entry HAMD17 total scores, it may be concluded that these results are consistent with the range of outcomes expected based on the data from Khan and Walsh described above, and are consistent with a gradually diminishing rate of response with progressive treatment resistance.

It should be noted that the baseline HAMD17 total scores in Level 2 are at or below the values observed for patients entering the Neuronetics studies, indicating that a proportion of these patients still precede the clinical severity of the population studied in the Neuronetics sample in terms of symptom severity and treatment resistance.





The most appropriate data from the Neuronetics studies to compare with the STAR*D results are the results from Neuronetics open-label TMS study 44-01102. The most relevant population in this study is Group B, those individuals who were exposed only to sham TMS treatment in protocol 44-01101 and had their first exposure to TMS in the open-label study 44-01102 (n=85). In that study, the HAM-D17 was among the key outcome measures that was collected and evaluated. The data for the STAR*D Levels and the Neuronetics 44-01102 Group B cohort (HAM-D17 <8 = 11% at week 4 and 21.2% at week 6) is shown in Figure 12.1. It is worth noting that the duration of exposure in the Neuronetics protocols (6-9 weeks) was substantially reduced in comparison to the average duration of treatment exposure in the STAR*D Levels (~9-11 weeks).



A smaller amount of data exists in even more treatment resistant forms of depression, and are consistent with the data supplied by the STAR*D literature. For example, Nierenberg and colleagues (Nierenberg, AA, et al., 1994) reported on an open-label case series of 84 consecutive outpatients and inpatients with rigorously defined treatment resistant major depression, who were then treated with the antidepressant venlafaxine. These patients, by clinical history, had failed to receive benefit from at least 3 adequate trials of antidepressants from at least two different antidepressant classes or ECT, plus at least one attempt at augmentation therapy. Outcome was assessed using both the HAMD (21-item), and the MADRS. The mean dose of venlafaxine treatment was 245.2 mg (SD = 99.3 mg). Response was classified as either full (HAMD \leq 8, or MADRS \leq 12) or partial (50% decrease for either HAMD or MADRS, with final scores $>$ 8 or $>$ 12, respectively).

In a final analyzable sample of 70 patients, Nierenberg and colleagues reported that after 4 weeks of treatment, by HAMD criteria, 11.4%

and 2.9% of patients were partial or full responders, respectively, and by MADRS criteria, 10% and 5.7% of patients were similarly partial or full responders. Interestingly, those patients who had previously failed to receive benefit from ECT had the poorest outcome to venlafaxine. They also noted that of those patients who received benefit, only 46% had sustained the benefit after 3 months of follow-up treatment.

The predictive relevance of treatment resistance has also been described in the ECT literature. For instance, Prudic and colleagues (Prudic, J, et al., 1996) reported the acute antidepressant outcome to open-label ECT treatment in a cohort of 100 patients who met Research Diagnostic Criteria for unipolar major depression. In this study, patients were rigorously staged in terms of their antidepressant resistance using the Antidepressant Treatment History Form (ATHF), the same methodology used in the Neuronetics clinical studies. The HAMD (24-item version) was used to assess outcome to acute treatment immediately after the last ECT session and then in follow up one week later. Treatment was *to effect* and was an average of 8.9 (SD=2.8) ECT sessions in patients who had ATHF-confirmed medication resistance, and 9.9 (SD=4.0) ECT sessions in patients who did not have such confirmed resistance. The overall remission rate was reported and was operationally defined as having at least a 60% reduction of HAMD score from baseline, and a maximum total score of no more than 10. Immediately after the last treatment, 73.0% of the overall sample met these remission criteria, while only 63.1% of those patients who had confirmed medication resistance met such criteria. After one week, 57.0% of the overall sample continued to meet remission criteria, while 47.7% of the confirmed medication resistant sample continued to meet these criteria.

The relationship between resistance to antidepressant treatment and acute response has also been explored in studies of vagal nerve stimulation (VNS). An early, open label study of the use of VNS and open-label pharmacotherapy (Sackeim, HA, et al., 2001; Protocol D-01) was conducted in a sample of 60 patients who met DSM-IV criteria for non-psychotic major depression, and who had demonstrated resistance to at least two different antidepressant treatments as assessed using the ATHF. Response was assessed using the HAMD (28-item version), and operationally defined as a $\geq 50\%$ reduction in total score compared to baseline assessment.

This study showed an inverse relationship between the number of ATHF-rated medication failures and clinical response, with those individuals who had failed more than 7 antidepressant treatments show-

ing *no clinical response* to acute, open-label therapy. Based in part on this preliminary evidence, a 10-week controlled trial of VNS was subsequently conducted (Rush, AJ, et al., 2005; Protocol D-02), using similar diagnostic criteria, however, the entry ATHF criteria had an upper limit of no more than 6 medication failures in the current episode. Response was assessed using the HAMD (24-item version), and operationally defined as a $\geq 50\%$ reduction in total score compared to baseline assessment. After 10 weeks of masked treatment, the response rate to active VNS was reported as 15.2% compared to 10.0% for the sham VNS intervention.

Taken together, these data provide a context in which to compare the magnitude of the clinical effect observed in the Neuronetics IDE clinical studies summarized in this submission with the existing literature for treatment outcomes in progressively more treatment resistant forms of major depression. Based on these considerations, the results of the Neuronetics studies present an *expected outcome* given the clinical severity and treatment resistance profile of the patients studied. Further discussion of the comparison of efficacy of the Neuronetics TMS System in this patient population to efficacy data published for ECT is provided in Section 12.6.1.5 below.

12.6.1.5. Potential Role of TMS Therapy™ in Treatment Planning for Major Depressive Disorder

The theory that TMS would function as a therapeutic intervention for the treatment of depression is derived from the biological and clinical observations pertaining to the current understanding of both the neurocircuitry and the pathobiology of depression as previously discussed in Section 12.6.1.2. Data reported in neuroimaging research highlights the fact that a distributed and definable network of brain circuits is functionally disrupted during the depressed state. These data support the view that there are identifiable, therapeutically accessible areas of the brain, such as the prefrontal cortex, that are theoretically the most plausible sites of therapeutic interest for a focally-applied treatment intervention.

Clinical evidence of studies with DBS suggest that delivery of a focal electrical stimulus to a discrete brain region results in symptomatic relief of the depressed state, *without the induction of a seizure and an accompanying motor convulsion* (Mayberg, HS, et al., 2005). As will be further discussed in Section 12.6.2 below, it is now well-accepted that during the application of ECT, *the seizure is a neces-*

sary but not sufficient condition for therapeutic success with ECT. In other words, the therapeutic effect of ECT is critically dependent upon the exposure of the brain to an electrical current that *exceeds* the amount required for the induction of a seizure (Sackeim, HA, et al., 1993).

Based on these considerations, TMS is predicted to be a therapeutic alternative to ECT for many patients, wherein by magnetically inducing an electric field in an area of the brain associated with mood, i.e., the left prefrontal cortex, depolarization of local neuronal populations occurs, leading to relief of the symptoms of depression. The question in the medical literature regarding TMS therapy has been whether this localized neuronal depolarization is sufficient for significant symptom relief in the absence of seizure, since generation of a seizure is required with ECT.

The data presented in Section 20 of this application and summarized here indicates that TMS Therapy™ as delivered by the Neuronetics NeuroStar™ System is efficacious in the treatment of depression and therefore offers a logical treatment option for patients with major depressive disorder who have failed to receive benefit from initial medication therapy.

Treatment of MDD patients using the Neuronetics TMS System in the multicenter study 44-01101 resulted in a *clinical response* rate (i.e., 50% reduction in depression symptoms) after 4 to 6 weeks of treatment that ranged from ~20-25%. In the open-label study 44-01102, a clinical response rate after 4 to 6 weeks of treatment ranged from ~20-40%. *These response rates from both of these studies are equivalent to or greater than the response rates reported in the available literature for this patient population who has shown poor to no clinical benefit using available pharmacotherapeutic interventions.*

The data presented here demonstrate that the efficacy achieved with the Neuronetics TMS System lies within the range of effectiveness expected for currently available treatment options for this treatment-resistant population with MDD. Therefore, the Neuronetics TMS System provides the depressed patient an opportunity for an effective clinical outcome that compares favorably to the likelihood of response to further courses of pharmacotherapy for treatment of their illness. In addition, for those patients who experience intolerable adverse effects with pharmacotherapy, the virtual absence of systemic adverse effects with therapeutic TMS provides an additional rationale for clinical consideration in these patients.

As will be discussed further in the sections to follow, the clinical response to ECT has been shown in single-site clinical studies to be high but variable (i.e., effect size range across studies is -0.91, range of -1.27 to -0.54). ECT is clearly an effective antidepressant, however, it is difficult to compare ECT treatment with other antidepressant therapies given that there are no well-designed and methodologically sound head-to-head comparative studies and given that the design of ECT studies differs considerably from typical antidepressant studies. For example, ECT treatment is given “to effect”, while other antidepressant studies select a standard treatment time for effect (i.e., 1-3 months). Given the difficulty in recruiting patients for ECT studies, it is also likely that ECT studies select a particular patient population (i.e., ECT responders) that may contribute to the high efficacy values reported in some studies. The risk of a large placebo contribution to the clinical effect is considerable with ECT, given the elaborate clinical ritual, inpatient care, and substantial personal attention provided during the course of an ECT treatment sequence. The rapid loss of effect in the early days and weeks after a course of ECT has also been suggested to be due to the placebo contribution to the overall clinical effect of this treatment. Indeed, all of these variables have raised questions regarding the interpretation of the true effect size for ECT. Most likely, the effects seen in the community ECT study (i.e., remission rates ranged from 30.3% to 46.7% across community sites) are more reflective of actual ECT response rates in general practice circumstances of ECT treatment (Prudic, 2004). This will be discussed further in Section 12.6.2.3.

In general clinical practice, the use of ECT as a treatment option requires the *weighing of the potential benefit of ECT against the risks* of ECT treatment for a particular patient. ECT’s substantially unfavorable tolerability profile relative to other therapeutic options as well as the societal stigma associated with its use, places ECT in the later portion of the continuum of treatment choices for the patient with major depression and may not be accessed by many patients.

In summary, the safety and efficacy data presented in this submission support the opportunity for the Neuronetics NeuroStar System to expand the range of potentially effective treatment options for patients with major depressive disorder. As shown in Figure 12.2, patients whose only treatment options are combination pharmacotherapy, ECT, or VNS are faced with the choice of potential wellness versus the troubling invasiveness and side effects of these treatments. ECT is a treatment option for these patients but is not often prescribed or accepted by patients because of its safety and societal issues.

ECT devices serve as an appropriate predicate device for the Neuronetics TMS System for the treatment of this patient population due to the similar mechanism of action of these devices and the demonstrated efficacy of both treatments in the same MDD population.

In addition, the Neuronetics TMS System offers a treatment option that is both *safe and effective* and has neither the adverse effects of ECT treatment nor the societal concerns related to “shock therapy”. Given this, the Neuronetics TMS System provides the psychiatrist with a therapeutic option to ECT for this MDD patient population.

As a treatment option for MDD, TMS therapy as delivered by Neuronetics’ NeuroStar System will therefore appropriately occupy a position in the armamentarium of available antidepressant treatments intermediate between more complex medication regimens on the one hand and ECT on the other.

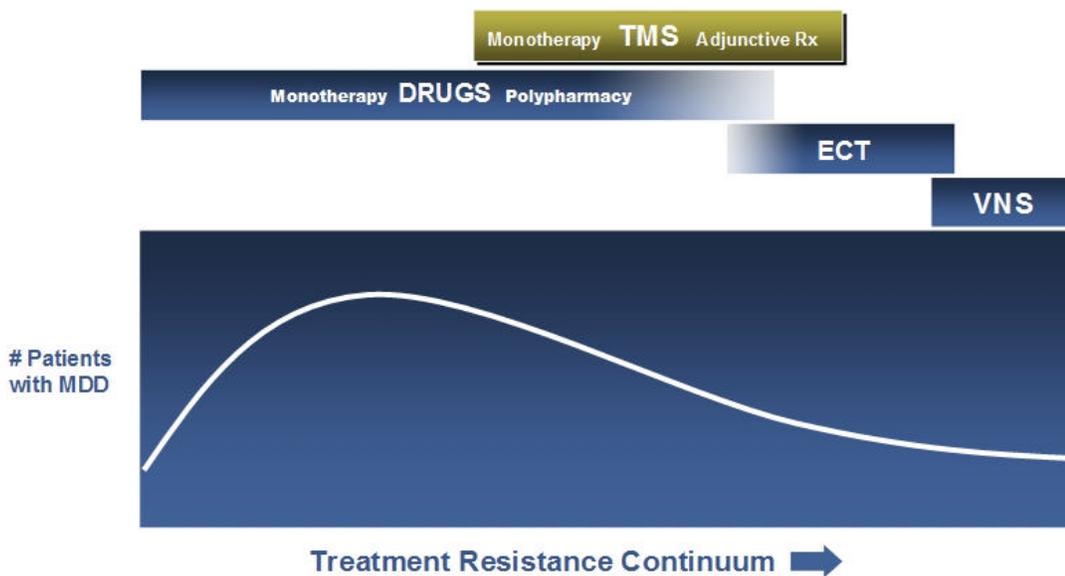
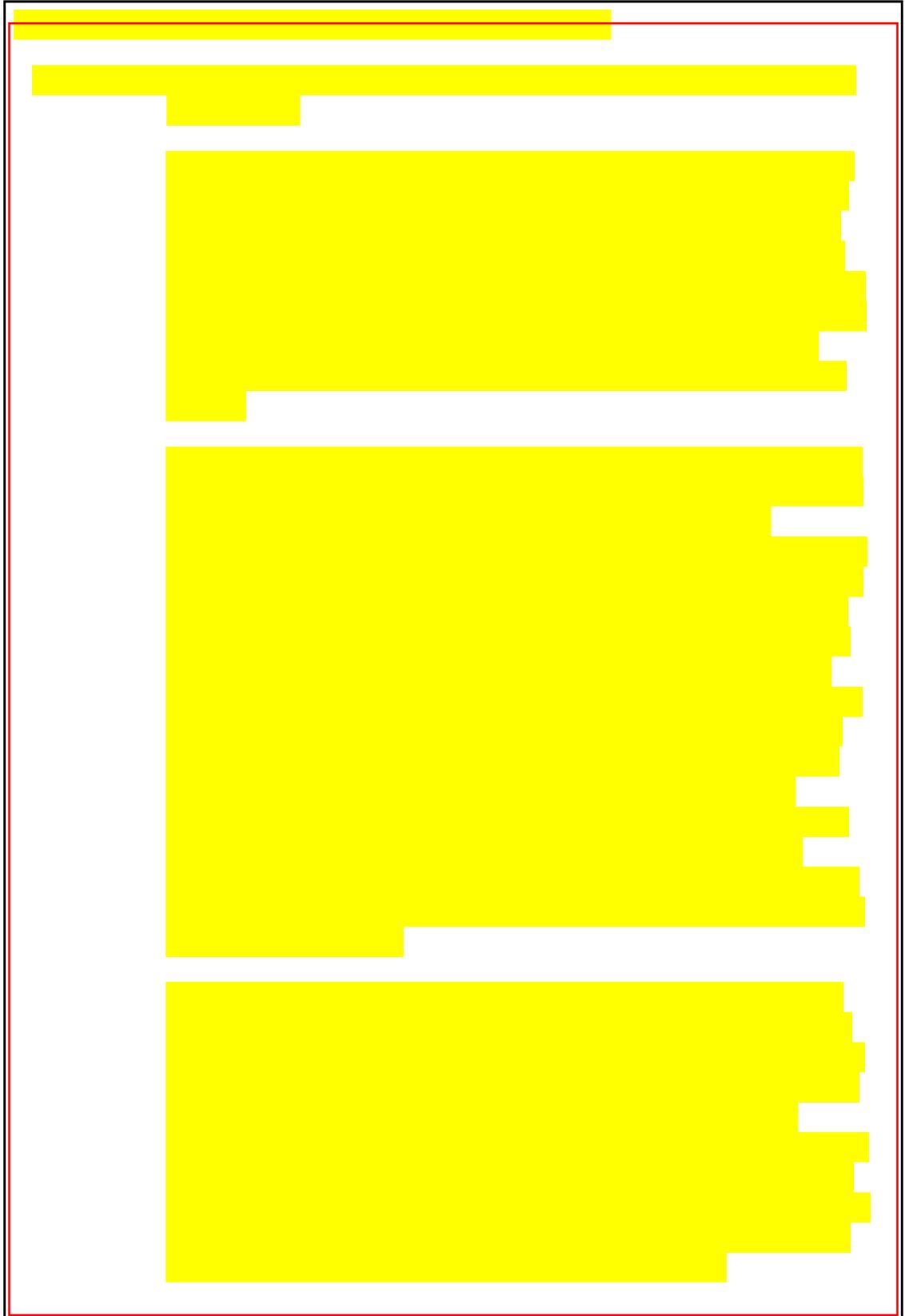
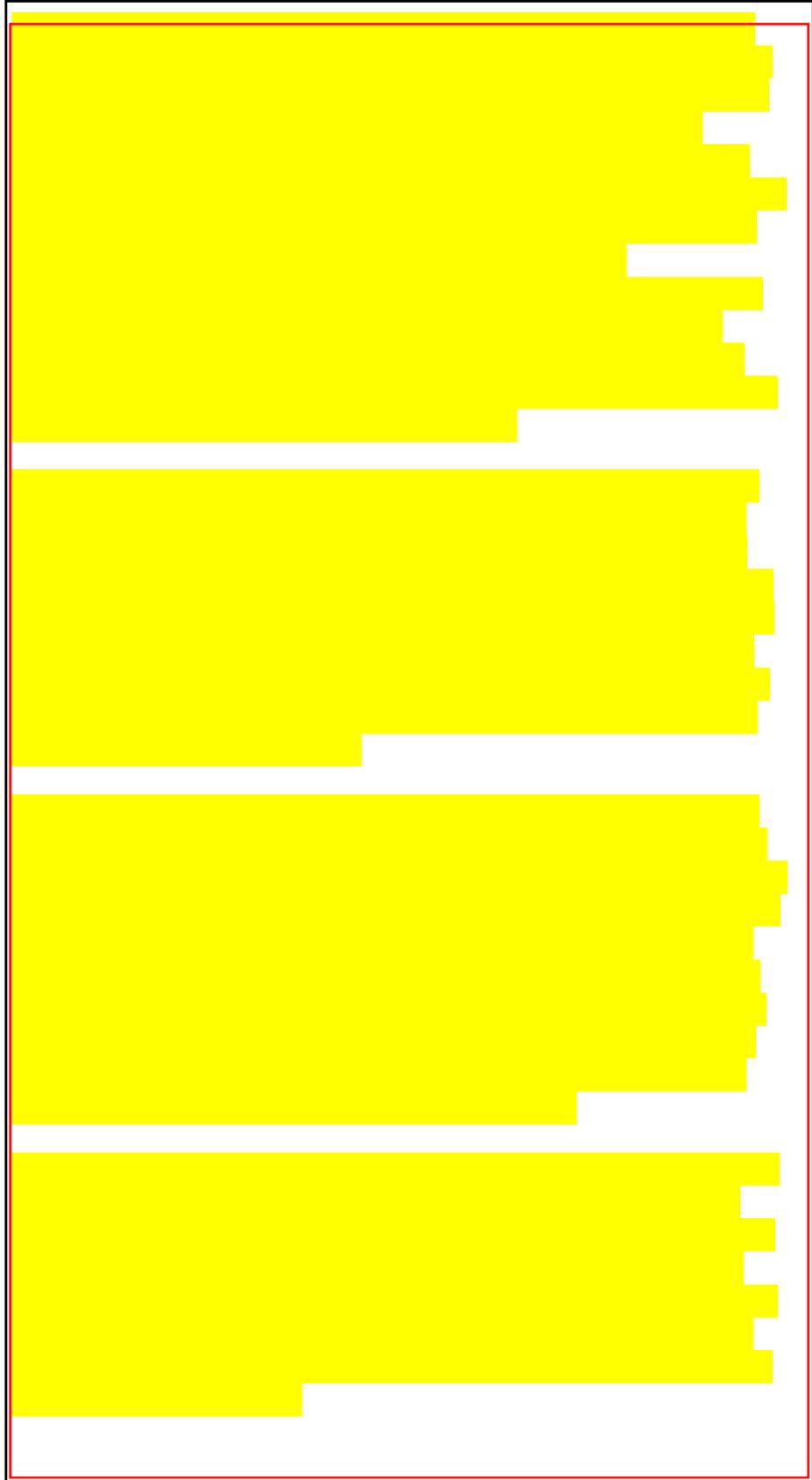
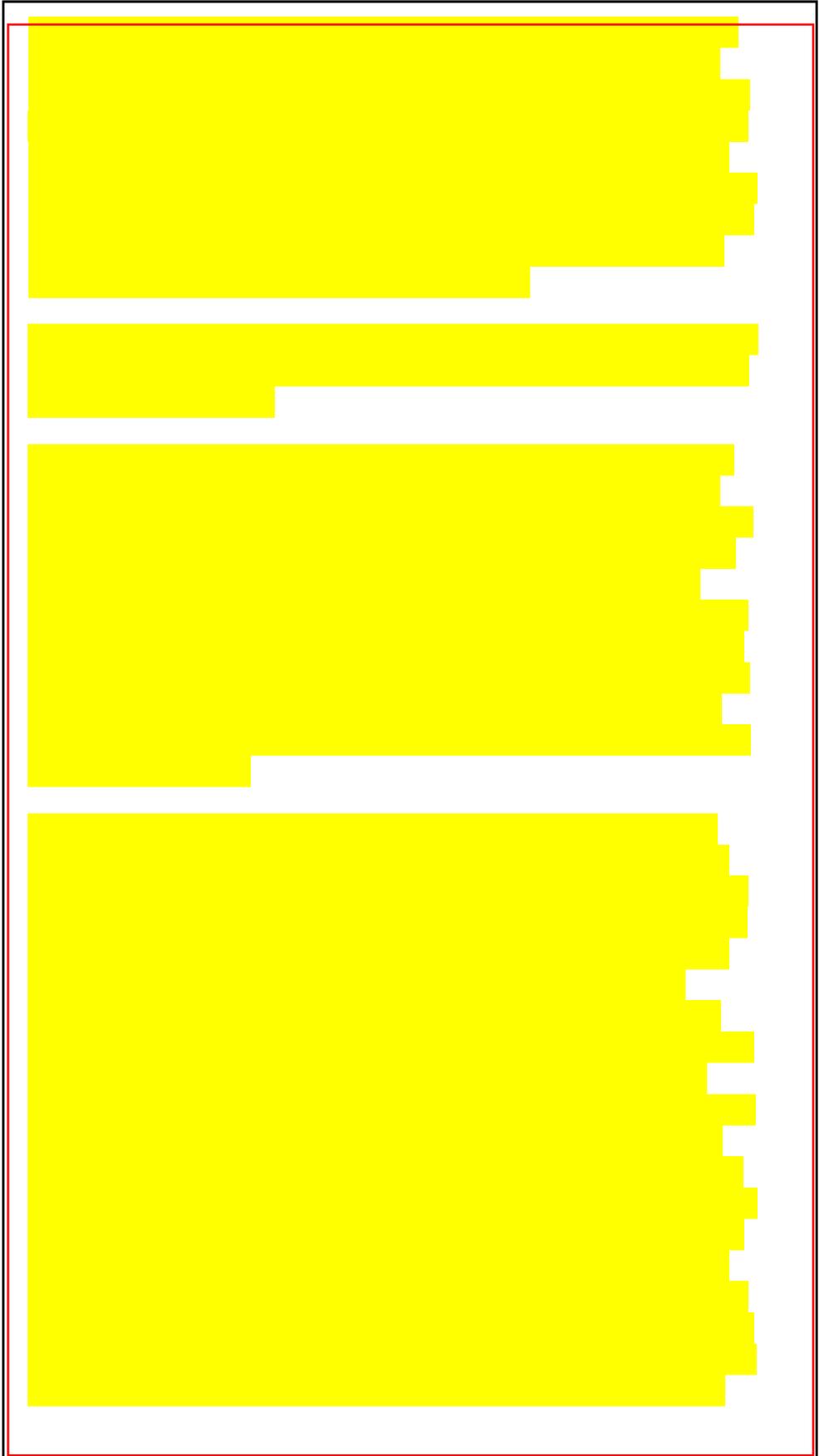
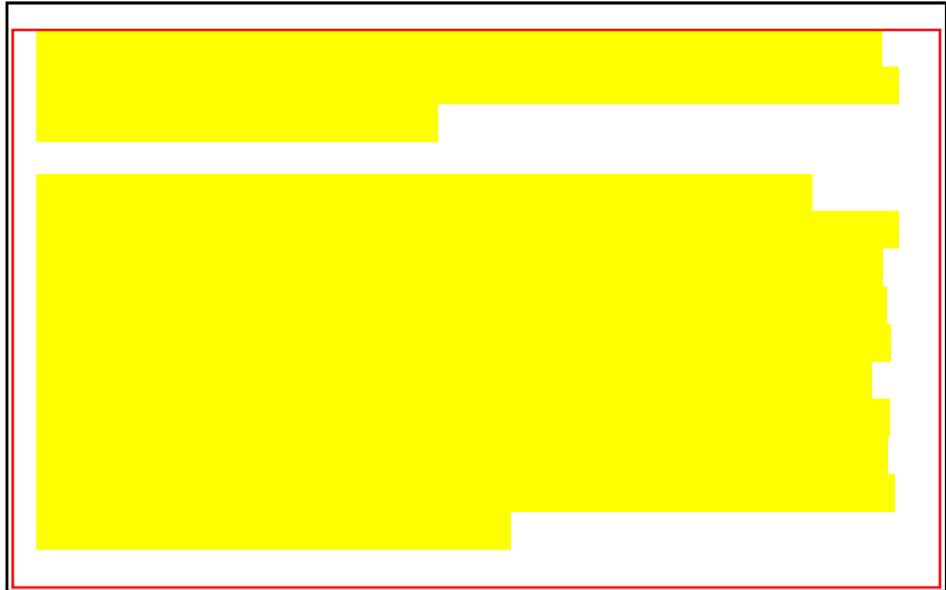


Figure 12.2. Placement of Neuronetics’ TMS Therapy as a Therapeutic Option for Major Depressive Disorder



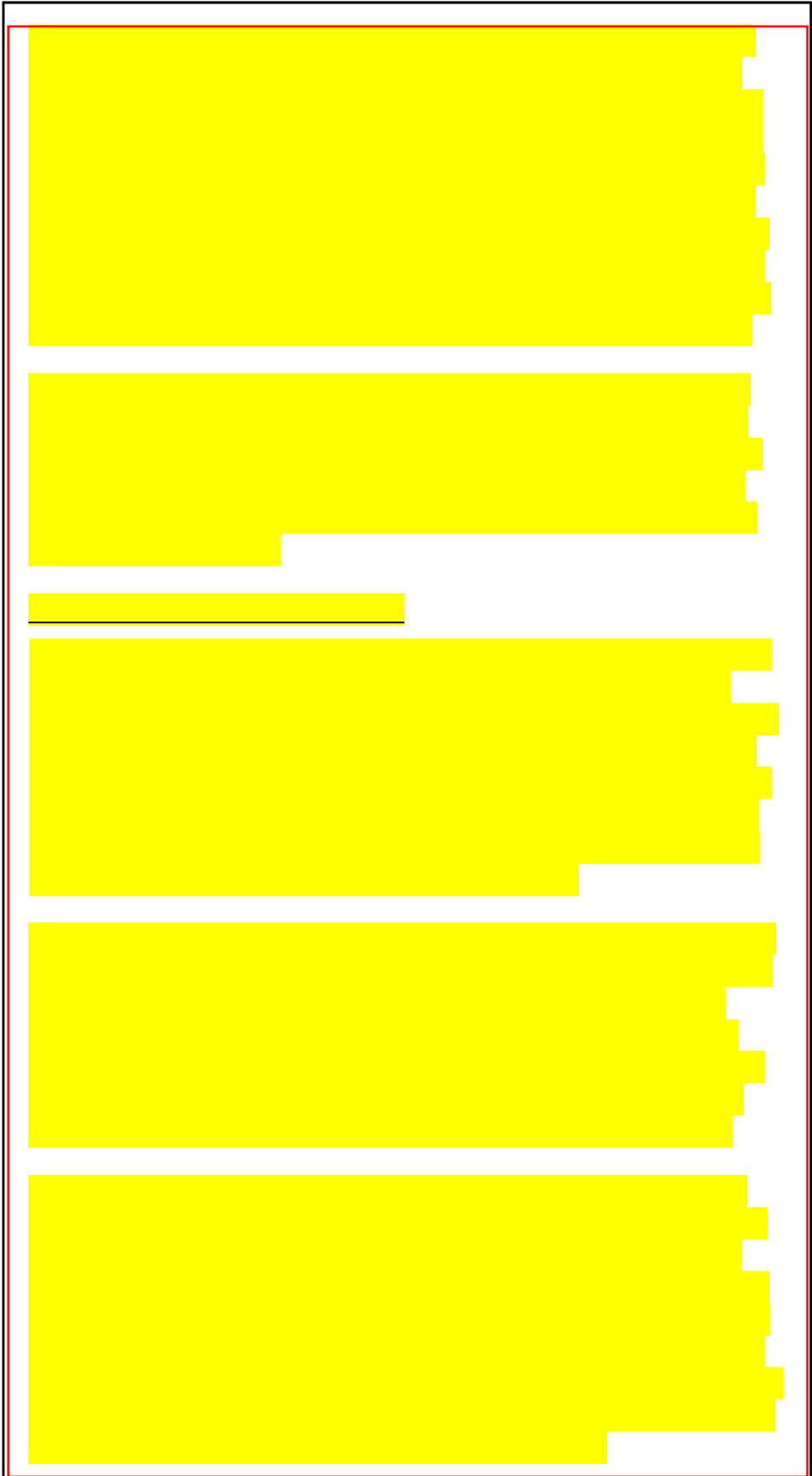






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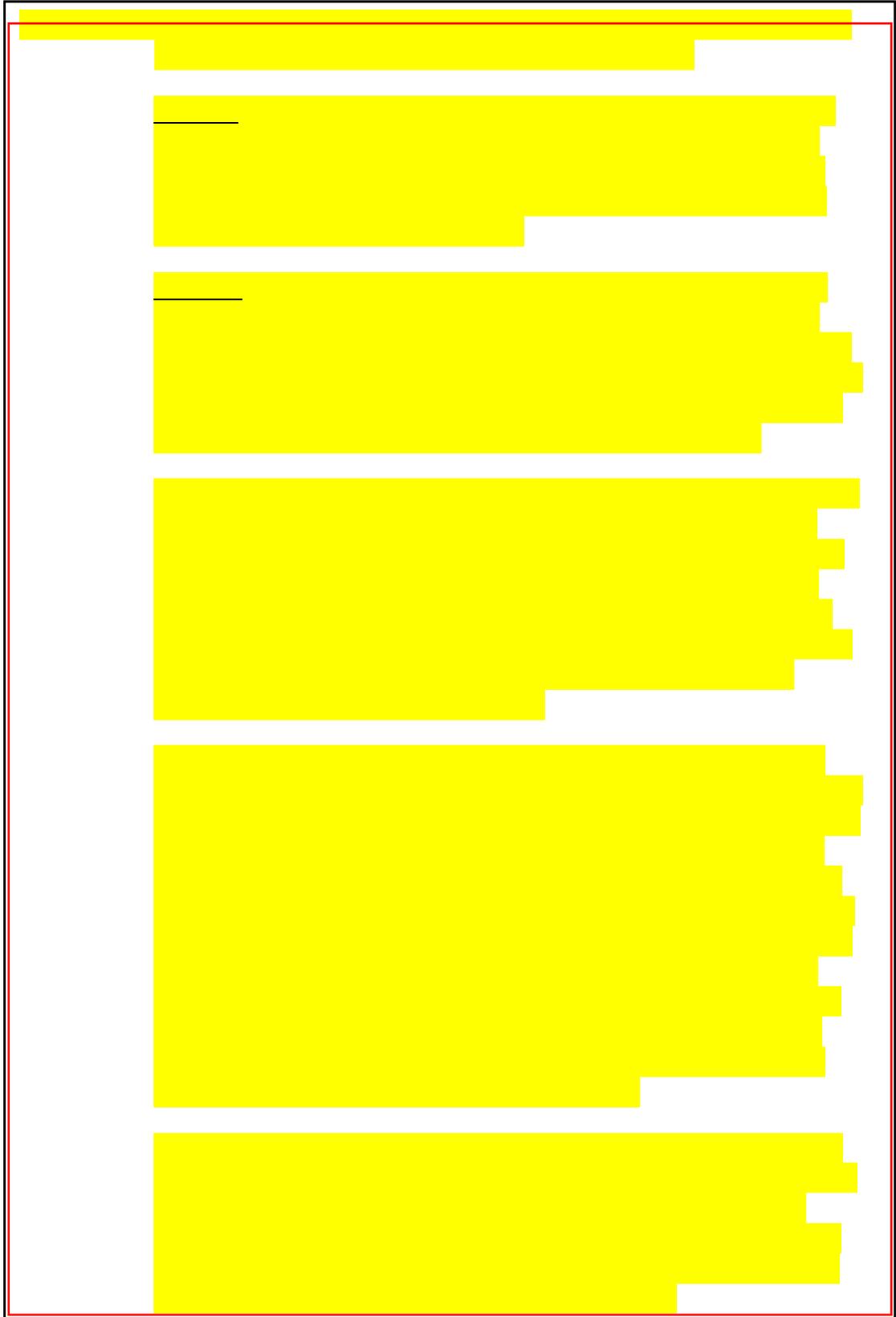
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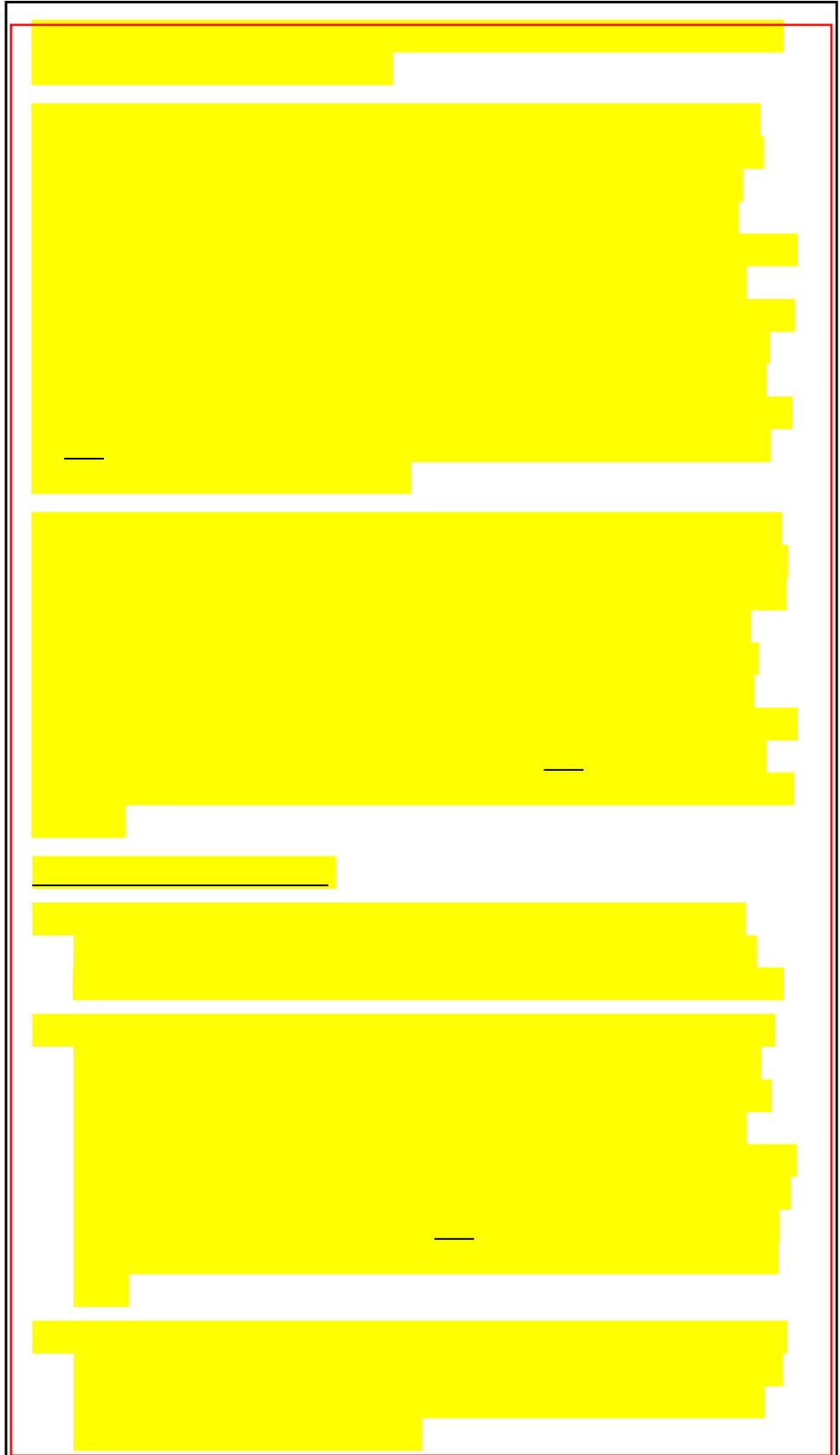
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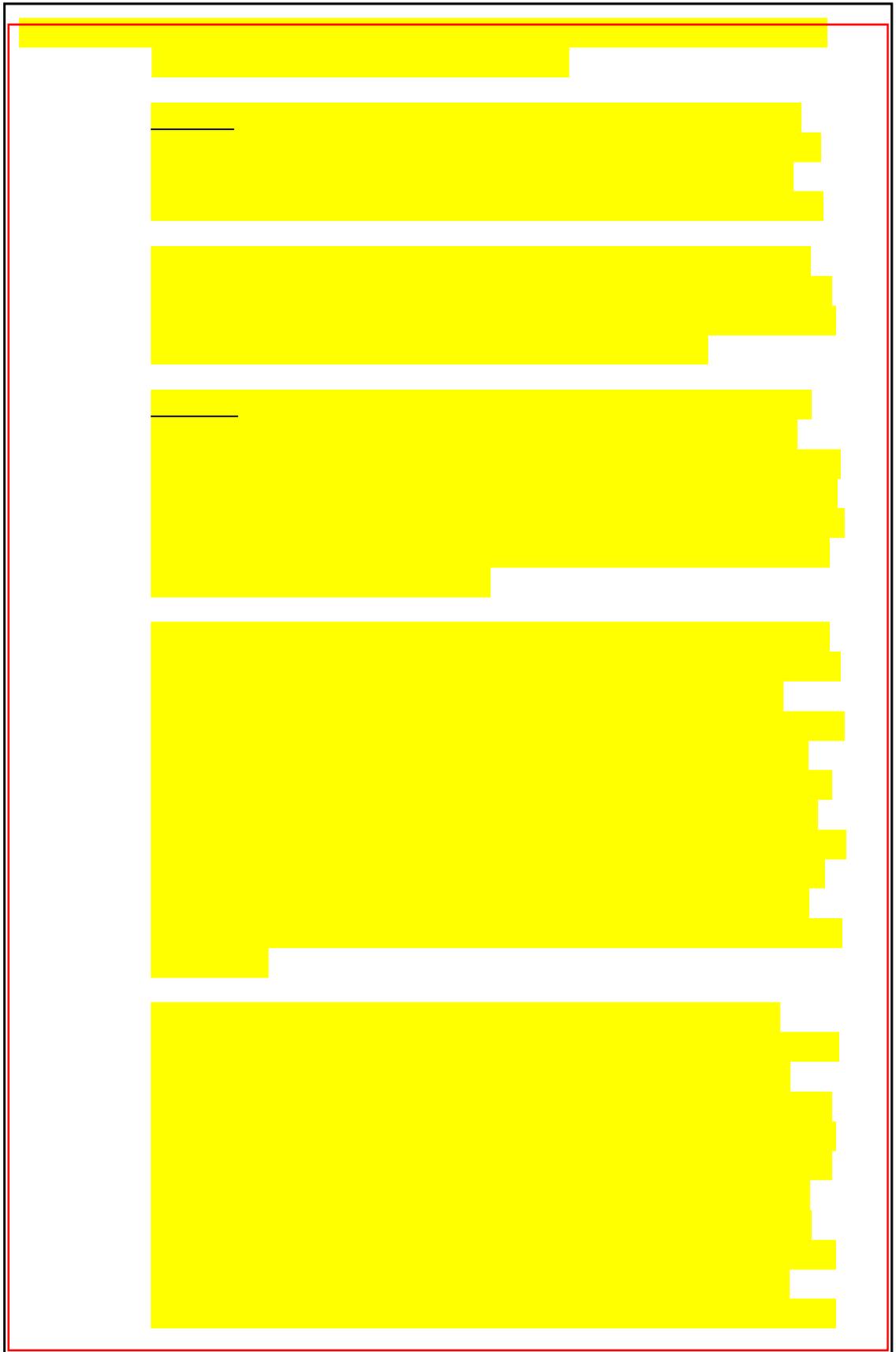
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12.6.3. Discussion of Risk-Benefit Profile of TMS Compared with Other Current Treatment Antidepressant Treatment Paradigms

Transcranial magnetic stimulation (TMS) as delivered by the Neuronetics TMS System (NeuroStar™ System) is an effective, safe and well-tolerated antidepressant for the treatment for patients with major depressive disorder. The acute response to TMS treatment can be effectively maintained in a clinically meaningful manner during a follow up period of up to 24 weeks.

The most important source of support for this claim is derived from the results of the randomized, sham-controlled clinical trial, protocol 44-01101, which provides several important pieces of evidence that offer definitive support for the efficacy of TMS as delivered by the NeuroStar™ System in patients with major depression. Using accepted disease-specific measures of symptom change, active treatment with TMS was *statistically significantly superior to sham* TMS treatment at the primary outcome time point of 4 weeks (HAMD 17 and HAMD 24, MADRS with baseline adjustment). Importantly, the symptom change was also statistically significant for the traditional categorical outcomes of response ($\geq 50\%$ reduction of baseline scores) *for all measures* and for remission (successful resolution of clinical symptoms below accepted thresholds of wellness specific to each rating scale) at 6 weeks (MADRS and HAMD 24 item).

The pattern of symptom change observed in protocol 44-01101 was also accompanied by statistically significant evidence of functional improvement (Medical Outcomes Study SF-36), and by statistically significant evidence of patient-reported symptomatic and functional benefit (Q-LES-Q). These effects were broadly represented across the known symptom domains of the major depression syndrome, and followed a coherent temporal pattern.

What evidence supports the clinical significance of the observed effects?

First, the outcome on the major symptom rating scales achieved statistically significant separation on both the continuous and the categorical outcomes.

All 3 of the measures, the MADRS, the HAMD24 and the HAMD17 achieved statistically significant separation on the categorical outcome of response at both the 4 and 6 week time points, while 2 of the 3 measures achieved the more stringent threshold of remission at the 6 week time point, and the 3rd instrument (HAMD17) showed a strong statistical trend for effect.

A second manner of analysis to support the clinical significance of the observed outcome on these rating scales is provided by the statistically significant changes in key sub-factor scores of the HAMD and in individual item analyses of the HAMD and the MADRS.

The HAMD and MADRS scales, are multidimensional rating scales wherein analysis of the sub-factors (HAMD) and individual item scores (HAMD and MADRS) allows a more detailed understanding of which symptoms among those measured on the scale, are the most important in driving the overall change in total score.

Analyses of sub-factors for the HAMD and the individual items scores for the HAMD and the MADRS showed that the most critical indices of core depression symptom change showed the most powerful separation between active and sham treatment conditions. Statistically significant change was found in both scales for those items that are specific and disease-focused, rather than those items that are associated with non-specific improvement in non-core symptoms. For example, the most significant change on the MADRS was contributed by the items Apparent Sadness, Reported Sadness, Pessimistic Thoughts and Lassitude (see Final Study Report, Study 44-01101, Section 13.2). On the HAMD, the most significant change was contributed by the items Depressed Mood, Feelings of Guilt, Psychic Anxiety and Work/Activities (see Final Study Report, Study 44-01101, Section 13.2, Tables 31-36).

A third source of evidence to support the clinical significance of the observed changes is found in the pattern of statistically significant change in patient-rated outcome measures.

In study 44-01101, the temporal pattern of change in the patient-rated outcomes followed, rather than led, the clinician changes. This is consistent with general clinical observations in both real world and research settings that patient-reported changes are typically reported after clinician observations. Second, on the Medical Outcomes Study SF-36, a measure of functional status, the reported improvement was not non-specific, but was focused and most pronounced in the areas of mental health and emotional role functioning, and was also represented in measures that reflected an improvement in general well being (i.e., General Health and Vitality).

The primary patient-rated outcome measure of disease-specific symptom change was the IDS-SR; this measure showed a strong statistical trend at both the 4 and 6 week time points. Finally, the patient-reported outcome of work and life satisfaction, the Q-LES-Q, showed a statistically significant effect at the 6 week time point, mirroring the statistically significant change seen in the HAMD item Work/Activities.

A fourth source of evidence for the clinical significance of the results observed in protocol 44-01101 comes from the specific pattern of results observed in the accompanying open-label cross-over study, protocol 44-01102.

Patients were permitted to enter that study, without treatment unblinding, and continue on open-label active TMS treatment under an identical treatment schedule as was used in study 44-01101. If treatment with active TMS as applied in protocol 44-01101 was truly exerting a clinically meaningful effect, several outcomes would be expected in patients treated in study 44-01102.

In study 44-01102, the transition of patients from the sham allocation in study 44-01101 compared to the active allocation would be expected to contribute a greater proportion of patients to the study. It would also be expected that, if treatment with active TMS in study 44-01101 were clinically effective, the patients previously allocated to active TMS who were continuing on active TMS would constitute a more treatment resistant population, since active TMS would be removing easier to treat patients at a more effective rate than sham TMS treatment in study 44-01101. On both of these points, the evidence is consistent with and supports the claim of efficacy for active TMS treatment. A slightly greater proportion of sham TMS patients elected to cross-over to study 44-01102 as compared to patients previously allocated to active TMS. In all instances, the clinical outcome observed in the former patients (i.e., Group B in the study analysis), was numerically superior to that observed in the patients previously allocated to active TMS (i.e., Group A in the study analysis).

The final source of evidence to support the clinical significance of the observed effect of active TMS is in the durability of the clinical response during the post-treatment taper phase of studies 44-01101 and 44-01102, and continuing into the first month of TMS-free follow up (See Interim Study Report; Study 44-01103, Appendix 21).

During the post-treatment taper phase of studies 44-01101 and 44-01102, the clinical effect obtained in the acute treatment phase was transitioned in a clinically meaningful manner to antidepressant medication therapy for most patients. Furthermore, this effect was sustained through the first four weeks of medication treatment in the absence of TMS treatment in study 44-01103.

During this transition period in study 44-01101, the pattern of symptom change for those patients who had received active TMS treatment was numerically superior to those who had received sham TMS treatment. Notably, the incidence of remission in the active TMS group exceeded

the incidence of response (a less stringent outcome measure) in the sham TMS group. This general trend was also seen in a confirmatory fashion in both Group A and B in study 44-01102, with a more pronounced effect in Group B, consistent with the overall pattern of efficacy in that study.

How can the magnitude of the observed change in the Neuronetics studies be interpreted relative to the expected outcomes from other available therapies?

A review of the literature was provided in this section to show that a prior history of treatment resistance is probably the most powerful and best replicated predictor of diminished response to subsequent interventions. Therefore, the effectiveness of TMS therapy delivered by the Neuronetics TMS System should be weighed relative to the spectrum of outcomes seen across the known range of clinical severity and treatment resistance in major depression.

As discussed in Section 12.6.1.4, the large experience provided by the STAR*D clinical trial provides the most definitive benchmark with which to measure the relative significance of the Neuronetics results. In that study, the most comparable levels to the patient population recruited for the Neuronetics studies were the patients extending from Level 2 through Level 3. When comparing the remission rates observed in that open-label study to the results observed in the comparable Neuronetics open-label study 44-01102, the remission rates are virtually identical using same the clinical outcome measure (i.e., HAM-D17 total score < 8), and were superior to the results observed in the most treatment resistant group in the STAR*D study, Level 4 (Study 44-01102; 21.2% remission at end of week 6, and 30.6% remission at end of taper week 3, STAR*D; mean remission rates of 29.9%, 21.2%, 13.6% and 14.7% for Level 2 augmentation, Level 2 switch, Level 3, and Level 4, respectively).

While ECT is an effective antidepressant for patients diagnosed with treatment-resistant major depression, it is nevertheless difficult to accurately determine the true response and remission rates for this treatment as compared to other less intensive therapies because of the limitations inherent in conducting well-designed, sham-controlled clinical trials for this intervention in contemporary research. As described above in Section 12.6.1.3, a direct data comparison of the observed efficacy rates for ECT with those obtained in studies of other antidepressants, including the Neuronetics studies, is not appropriate given the differences in study design, the limitations of accurately comparing dose exposures of the different treatments, and the highly invasive nature of ECT treatment itself. Although it can be stated that ECT is indeed acutely effective for this

treatment resistant population, the effectiveness, even in the presence of maintenance pharmacotherapy, is transient for most patients. It is notable, therefore, that in contrast to ECT, the clinical effect obtained during acute treatment with TMS as se

In choosing a treatment option for the patient with major depression, the physician must consider and balance efficacy of treatment, its durability of effect, and the overall safety. *Considering these various aspects in aggregate, TMS treatment using the Neuronetics TMS System shows an equal, if not superior, profile to ECT.*

With regard to safety and tolerability, there is clear evidence of a clinically superior profile with TMS as compared to all treatment options available for these MDD patients. The adherence to treatment in the controlled clinical trial 44-01101 was >90%, and the drop-out rate during the acute treatment phase to the primary endpoint was less than 10%, a result that contrasts sharply with the typical acute treatment dropout rate in excess of 25% in randomized clinical trials of antidepressant medications in non-resistant patients. On the targeted safety measures of cognitive function and auditory threshold, there was no evidence of acute change. The spontaneous adverse event profile was similarly unremarkable, reflecting a pattern of change expected from the earlier exploratory TMS literature. Moreover, these symptoms were generally classified as mild to moderate, and the more common adverse events were transient, largely restricted to incidence during the first week of treatment exposure.

There has been substantial recent interest in the safety of antidepressants with regard to the re-emergence or exacerbation of acute suicidal ideation during the course of treatment. Because of this, a specific exploratory analysis of this potential risk for acute TMS treatment was performed in the randomized trial 44-01101. There was no evidence that treatment with TMS resulted in a re-emergence or exacerbation of acute suicidal ideation. In fact, there was an excess of patients experiencing worsening of suicidal ideation as measured by categorical increases in Item 3 (Suicidal Ideation) scores on the HAMD in those individuals allocated to the sham TMS treatment arm. It is worth noting that this observation also is consistent with the overall evidence summarized above for the clinical efficacy of active TMS treatment.

In summary, TMS is an effective and safe antidepressant for the treatment of patients with major depressive disorder. It compares favorably

in clinical efficacy to the most commonly used options available for patients with major depression of this degree of clinical severity and treatment resistance and provides a safety profile and evidence of clinical tolerability that also compares favorably to these other available options, including ECT.