DE NOVO CLASSIFICATION REQUEST FOR
BRAINSWAY DEEP TRANSCRANIAL MAGNETIC STIMULATION SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Transcranial magnetic stimulation system for neurological and psychiatric disorders and conditions. A transcranial magnetic stimulation system for neurological and psychiatric disorders and conditions is a prescription, non-implantable device that uses brief duration, rapidly alternating, or pulsed, magnetic fields to induce neural activity in the cerebral cortex. It is not intended for applying or focusing magnetic fields towards brain areas outside the cerebral cortex (e.g., cerebellum). A repetitive transcranial magnetic stimulation system that is intended to treat major depressive disorder is classified in § 882.5805. A transcranial magnetic stimulation system for headache is classified in § 882.5808.

NEW REGULATION NUMBER: 21 CFR 882.5802

CLASSIFICATION: Class II

PRODUCT CODE: QCI

BACKGROUND

DEVICE NAME: Brainsway Deep Transcranial Magnetic Stimulation System

SUBMISSION NUMBER: DEN170078

DATE OF DE NOVO: September 29, 2017

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INDICATIONS FOR USE

The Brainsway Deep Transcranial Magnetic Stimulation System is intended to be used as an adjunct for the treatment of adult patients suffering from Obsessive-Compulsive Disorder.

LIMITATIONS

For prescription use only.

Patients already on Obsessive-Compulsive Disorder (OCD) treatments (psychotropic medications and/or psychotherapy) should be maintained at their current dosages during the Deep Transcranial Magnetic Stimulation (DTMS) treatment.

The Brainsway DTMS System is contraindicated in patients with the following conditions:

- Metallic Objects in or near the Head - rTMS devices are contraindicated for use in patients who have conductive, ferromagnetic or other magnetic-sensitive metals implanted in their head or within 30 cm of the treatment coil. Examples include cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair barrettes. Failure to follow this restriction could result in serious injury or death.

- Implanted Stimulator Devices in or near the Head - rTMS devices are contraindicated for use in patients who have active or inactive implants (including device leads), deep brain stimulators, cochlear implants, and vagus nerve stimulators. Contraindicated use could result in serious injury or death.

During treatment with the device, the patient must use earplugs with a rating of at least 30 dB of noise reduction. Verify proper use of earplugs. Ask users to immediately report any loosening or detachment of an earplug. and stop rTMS if a user reports, or if a treater observes, that an earplug has loosened or has fallen out.

The Brainsway DTMS system should be used with caution in patients who have a history of seizures, or a potential for alteration in seizure threshold. Stimulation parameters outside of those studied in the clinical study and recommended for use in the Instructions for Use have not been tested for safety during brain stimulation, particularly for seizure induction.

Long-term effects of exposure to rTMS are unknown.

The safety and effectiveness of the Brainsway DTMS System has not been established in the following patient populations or clinical conditions:

- Age less than 22 and greater than 68;

- Severe Personality Disorder (excluding Obsessive Compulsive Personality Disorder) or severe borderline personality disorder;

- Suicide plan or recent suicide attempt;

- Neurological disorders including a history of seizures, cerebrovascular disease, primary or secondary tumors in CNS, cerebral aneurysm, dementia, or movement disorders;

- History of increased intracranial pressure or head trauma;

- Cardiac pacemakers, implantable cardioverter defibrillators, ocular implants, deep brain stimulators, vagus nerve stimulators, implanted medication pumps, intracardiac lines, or significant cardiac disease;

- History of substance abuse in the past six months prior to treatment;

- Prescribed high doses of antidepressant or psychotropic medications, which are known to lower the seizure threshold or patients on Clomipramine; or

- Pregnant or nursing.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Brainsway DTMS System enables direct non-invasive activation of brain structures. TMS is a non-invasive technique used to apply brief magnetic pulses to the brain. The pulses are administered by passing high currents through an electromagnetic coil placed adjacent to a patient's scalp. The pulses induce an electric field in the underlying brain tissue. When the induced field is above a certain threshold, and is directed in an appropriate orientation relative to the brain's neuronal pathways, localized axonal depolarizations are produced, thus activating neurons in the targeted brain structure.

The Brainsway DTMS System is composed of the following five main components:

- Electromagnetic Coil (HAC-Coil)
- TMS Neurostimulator
- Cooling System
- Positioning Device
- Personal Head Cap

The Brainsway DTMS System is illustrated in Figure 1. Except for a different Electromagnetic Coil and updated cooling system, the components of this new DTMS system are identical to the Brainsway DTMS System currently marketed in the United States to treat Major Depressive Disorder (K122288).
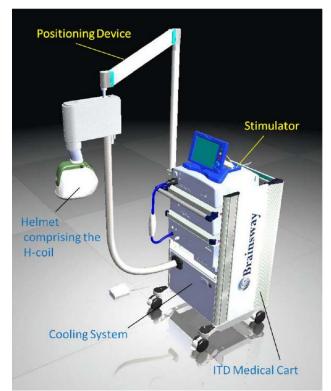

Figure 1: Illustration of the Brainsway DTMS System

A description of each component is provided below:

- HAC-Coil: The HAC-Coil is made of insulated copper wires. The total length is about 500 cm, winded into 16 windings and connected in series. The coil is flexible in order to fit the variability in human skull shape. The electromagnetic coil is contained in a helmet, which is connected by an adaptor to a positioning device. The coil is connected to the neurostimulator cable and a connector. This connector can be connected to the Magstim Rapid, Rapid^2 or Super Rapid^2 neurostimulator. In addition, a temperature sensor is included with an appropriate cable.

- TMS Neurostimulator: The Magstim Rapid, Rapid^2 or Super Rapid^2 neurostimulators are used to deliver the electrical stimulus to the HAC-Coil. These commercial TMS neurostimulators provide a controlled output, frequency, pulse duration, and indication of coil temperature. The Magstim software provided with the neurostimulators allows the user direct control over power level, frequency, train duration, and the interval between trains.

- Cooling System: The Cooling System is designed to maintain ambient temperature in the coils during repetitive and prolonged operation. The cooling system consists of an external unit and an air hose streaming the cooled air into the helmet. The air flow cools the coils while repetitive electrical stimuli are pulsed through the HAC-Coil.

- Positioning Device: The positioning system includes a helmet that comprises the Electromagnetic Coils (one for each side of the head), an adjustable arm connected to the helmet and a device enabling rotation of the helmet around three orthogonal rotation axes. The positioning device enables accurate and comfortable displacement and positioning of the coil over the patient's head.

- Personal Head Cap: A personal cap is provided for each patient. The cap is made of (b) (4)   A flexible ruler is attached along the cap midline, with the 0 mark positioned at the patient's nasion. The cap is used for accurate positioning of the coil on the patient's head during each treatment session, by moving the coil from the area above the motor cortex to the treatment location at the prefrontal cortex. In addition, the cap guarantees hygienic treatment conditions.

Procedural Information

The detailed procedures are described in the Instructions for Use. The following is a brief summary.

The Brainsway Deep TMS device is intended to safely deliver high-frequency (20Hz) repetitive transcranial magnetic pulses (2 second trains) to induce electric field of sufficient magnitude, i.e., 100% of resting Motor Threshold of the foot, for the treatment of OCD, using a flexible coil conforming to the shape of the head.

Before starting each treatment, subjects are instructed to insert earplugs to lessen any possible adverse effect on hearing. Prior to treatment, the treatment administrator must determine the position of the tibialis motor cortex and the subject's individual motor threshold. The minimal stimulator power output required for activation of the tibialis is determined. After finding the position on the patient's head, which requires the minimal stimulator output for reaching the motor threshold for activation of the tibialis, the treatment administrator moves the HAC-coil to the marked treatment location and secures it to the patient's head. The treatment administrator then programs the treatment parameters as defined in the Instructions Manual for safe and effective OCD treatment. The power output for the DTMS treatment is determined relative to the individual motor threshold found for the patient.

The magnetic field characteristics as well as other specifications of the Brainsway DTMS System are summarized in Table 1 below.

Table 1: Specifications for the Brainsway TMS System

DTMS System	Specifications
Output Stimulation Parameters:	
Amplitude in Standard Motor Threshold (SMT) units	0.6-1.4
Pulse width (usec)	324
Frequency range (Hz)	0.02-30
Pulse train duration range (sec)	1-20
Inter-train interval range (sec)	10-60
Maximum trains per session	~140
Maximum # of pulses per session (cumulative exposure)	5000
Physical unit of amplitude setting (e.g., coil current, peak magnetic field) at coil & its relation to SMT unit: Electric field at 1.5cm from coil (equivalent to 1.0 SMT [V/m])	100
Magnetic Field:	
Peak magnetic field strength at coil edge [T] Peak magnetic field strength at 2 cm from coil [T] Maximal dB/dt at coil edge (Gauss/usec) Maximum dB/dt at 2 cm from coil (Gauss/usec) dB/dt ratio	(b) (4)
Temperature on coil surface at maximum output	34° C

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The personal head cap is the only patient contacting material and it is intended for limited duration contact (< 24 hours). The cap is made of (b) (4)   The cap is identical to the one currently marketed by Brainsway in their DTMS system intended to treat major depressive disorder (K122288). In K122288, per ISO 10993-1 (Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing), cytotoxicity, sensitization, and irritation testing were performed for the personal head cap. The testing and results were considered to be adequate.

SHELF LIFE/STERILITY

This is a non-sterile, reusable device. It is intended only for external use and the user manual includes appropriate cleaning instructions for the external surface of the device. The device does not have a stated shelf life, which based upon the nature of the device components is acceptable.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The device was tested for and found to be in compliance with the following standards for electromagnetic compatibility, electrical safety, and thermal safety:

Standard	Title
IEC 60601-1	Medical electrical equipment – Part 1: General requirements for safety and essential performance
IEC 60601-1-2	Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests

SOFTWARE

Software for the device consisted of proprietary software marketed by Magstim that controls the user interface and energy delivery to the stimulation coil provided by the Magstim Rapid, Rapid[2] or Super Rapid[2] neurostimulators (K992911, K051864, K162935). The software was reviewed when each 510(k) was submitted, and the provided documentation was found adequate and consistent with a 'MODERATE' level of concern as discussed in the FDA document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," issued May 11, 2005.

PERFORMANCE TESTING – BENCH

Bench testing included verification of the specifications indicated in Table 1. Bench testing also was performed to characterize the electrical and magnetic field spatial distributions, and magnetic field characteristics (e.g., strength gradient) of the system as recommended in the FDA guidance document titled: "Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems" issued July 26, 2011. The following tests were performed:

- Output waveform: The output waveform produced by the system was measured in a human head phantom model (b) (4)   . The probe was located in the head model in a position where the coil's induced field is maximal according to the electric field distribution mapping. The electric field

pulse outputs and waveforms were measured at predefined stimulator outputs.

- Electric Field Spatial Distribution: The field distribution produced by the system was measured in a human head phantom model (b) (4) The probe was moved in three directions inside the phantom model using a displacement system with 1 mm resolution, and the field distribution of the system was measured in the whole head model volume in 1 cm resolution. Axial and coronal field maps were produced. The field maps were superimposed on anatomical T1-weighted MRI coronal slices, to show the induced field in each anatomical brain region.

- Magnetic Field Strength Gradient: The magnetic field strength was also measured in a human head phantom model. The magnetic field strength at the coil surface and at certain points at various distances from the coil was measured. The probe was located in the head model at a distance of 0 and 2 cm from the coil edge, in a position where the coil's induced field is maximal according to the electric field distribution mapping. The stimulator was operated at 50% and at 100% output and the magnetic field output waveform was measured along three orthogonal axes: X- Anterior-posterior, Y- Lateral-medial, and Z- Superior-inferior.

- Sound level – Testing was performed to determine the physical intensity of the sound generated by the device and that patients are exposed to during treatment.

SUMMARY OF CLINICAL INFORMATION

The applicant performed an IDE clinical study to establish a reasonable assurance of safety and effectiveness of the Brainsway DTMS System for treatment of subjects suffering from Obsessive Compulsive Disorder (OCD) who maintained their current dosages of concomitant OCD treatments (psychotropic medications and/or psychotherapy) during DTMS treatment. Data from this clinical study were the basis for the De Novo granting decision. A summary of the clinical study is presented below.

Methods:

The study was conducted at 11 study sites in the United States (9 sites), Israel (1 site) and Canada (1 site), with active enrollment from October 2014 through February 2017. Eligible subjects were outpatients, aged 22-68, with a DSM-IV diagnosis of OCD. Subject must have had at least moderate OCD, rating a Yale-Brown Obsessive Compulsive Scale (YBOCS) score of >20 to be enrolled in the study. Subjects were maintained on SSRI medications (with or without additional antidepressant or psychotropic augmentation for treatment of OCD), at a stable therapeutic dosage for at least 2 months prior to study entry and/or subjects were maintained on psychotherapeutic behavioral intervention therapy. Symptoms stability was required during the 2-3 weeks of screening. Instability was defined as a change of ±30% in the patient's total YBOCS score between the screening assessment and baseline assessment.

Subjects were excluded from the study if they suffered from any other Axis I diagnosis as the primary diagnosis or if they were diagnosed with severe Personality Disorder (excluding Obsessive Compulsive Personality Disorder). Additional exclusion criteria included any significant neurological injury, disorder or insult; increased risk of seizure for any reason, including familial or personal history of epilepsy; prior treatment with rTMS (because they could not be blinded); history of significant hearing loss; history of substance abuse; pregnancy; presence of intracranial implants or any other metal object within or near the head excluding the mouth that cannot be safely removed. Additionally, subjects were excluded if they were assessed with a present risk of suicide or if they had a history of suicide attempt in the last 3 years (because of risk the patient might be assigned to sham).

The study consisted of three phases:

- Screening phase (approximately 2-3 weeks, with no treatment);
- 6-week treatment period (daily treatment with DTMS or sham); and
- 10-week follow-up visit (4 weeks after the last treatment)

At the Baseline visit subjects were randomly assigned to either active DTMS treatment or Sham treatment (1:1 ratio). Subjects were stratified by center. During the treatment phase, TMS sessions were performed daily in a 5-day sequence. Subjects were discontinued from the study at any point if they had elevated risk for suicide as assessed by the investigator; if they missed more than 3 treatments; or if the investigator concluded that for safety reasons (e.g. an adverse event) it was in the best interest of the subject to stop treatment.

Prior to initiation of each treatment, OCD symptoms were provoked for each subject in an individual manner for up to 5 minutes to activate the relevant brain circuits. The symptom provocation had to induce a stress level between 4-7 on a visual analog scale (VAS) in order to proceed with DTMS treatment.

Each DTMS treatment (for active and sham groups) was conducted as follows: Before starting each treatment, the subject was instructed to insert earplugs to lessen any possible adverse effect on hearing. The patient's motor threshold (MT) was measured at the beginning of each week by delivering single stimulations over the leg area of the motor cortex. The anterior cingulate gyrus was chosen as the treatment location which was determined by locating the coil 4 cm anterior to the leg MT location using the ruler on the head cap. The treatment location was recorded in the operator case report forms. Subjects should have received treatment at a power output of 100% of the measured MT. The treatment group received DTMS at 20 Hz and 100% stimulation intensity of the measured MT. Each DTMS repetition included 2 second pulse trains and 20 second inter-train intervals. Subjects received 50 trains in each treatment session, for a total of 2000 pulses per session. Each session lasted about 30 minutes of which the DTMS session lasted approximately 20 minutes. The control group received sham (placebo) treatment with identical parameters. Subjects were told that facial and hand twitching may occur due to either sham or active treatment.

During the treatment session, the operator swiped the subject's treatment card by the card reader in the DTMS System. The card reader activated either active or sham treatment mode according

to the treatment group to which the subject had been randomized. The study personnel did not have any knowledge of whether the active mode or sham mode was activated by the subject's treatment card. Thus, all study personnel, including the operator, the independent rater and study subjects were blinded to the treatment administered. The study subjects were asked whether they believed they had received active or sham stimulation after the first treatment session. Patients were asked not to meet or discuss the study treatment with other subjects before, during and after assessment or treatments in order to maintain study blinding.

The primary outcome measure was the following:

- Compare the change in YBOCS scores from baseline to the 6 week (post-randomization) visit, between the two treatment groups.

The secondary outcome measures were the following:

- Compare the change from baseline to the 6 week visit in the Sheehan Disability Scale (SDS) score and Clinical Global Impression - Severity (CGI-S) and Improvement (CGI-I) scores, between the treatment groups.

- Response rate comparison at the 6 week visit, where response is defined as a reduction of at least 30% in YBOCS score from baseline, between the treatment groups.

- Partial Response rate comparison at the 6 week visit, where response is defined as a reduction of at least 20% in YBOCS score from baseline, between the treatment groups.

- Compare the change from baseline to the 10-week visit in the YBOCS score between the treatment groups.

- Compare the change from baseline to the 10 week visit in the Sheehan Disability Scale (SDS) score and Clinical Global Impression - Severity (CGI-S) and Improvement (CGI-I) scores, between the treatment groups.

- Remission rates comparison at the 6-week visit, where remission is defined as YBOCS score < 10, between the treatment groups.

The safety outcome measures were the following:

- Compare the change in subject physical and neurological status before and after treatment, between the treatment groups.

- Compare the change in subject cognitive status before and after treatment using Mini Mental State Exam (MMSE), Buschke Selective Reminding Test (BSRT) and Autobiographical Memory Interview – Short Form (AMI-S) cognitive tests, between the treatment groups.

- Compare the incidence, severity and frequency of all Adverse Events (AE) during the study, including seizures and suicidality (i.e., suicide attempts and completed suicides), between the treatment groups

Statistical Methods

Sample size calculations were based on results obtained from pilot work. A total of 78 subjects (39 per group), provided a power of approximately 90% at a 5% significance level, to detect a difference between the groups of 3 points in the mean YBOCS score assuming a standard deviation of 4.0 points. The minimum sample size was increased to 49 subjects per arm to account for potential drop-outs, for a total of 98 subjects.

Each of the following analysis sets were defined and prespecified for the statistical analyses:

- Intent-to-treat (ITT) Analysis Set: The ITT analysis set included all patients randomized to the study who had received at least one active/sham treatment.

- Modified Intent-to-treat (mITT) Analysis Set: The modified intent-to-treat (mITT) analysis set included all patients randomized to the study who had received at least one active/sham treatment and met the study Eligibility Criteria. The list of subjects who did not meet the study eligibility criteria was prepared and documented prior to randomization code unblinding.

- Per-Protocol Analysis Set: The per-protocol (PP) analysis set consisted of all subjects included in the mITT analysis set who in addition had no major protocol deviation. Potential protocol deviations were defined and classified as minor or major before opening the randomization codes. The list of protocol deviation was documented prior to randomization code unblinding.

Safety assessments are performed on the ITT analysis set. The mITT analysis set serves as the principal data analysis set for the primary and secondary efficacy statistical inference.

Statistical analyses were performed using SAS V9.4 (SAS Institute, Cary NC, USA). All statistical tests are two-sided. Where confidence limits are appropriate, the confidence level is set to 95%. For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test are used as appropriate. For comparison of proportions (categorical variables), the Chi-square test or Fisher's exact test are used as appropriate.

The principal statistical analysis is a comparison between the treatments groups. The principal statistical analysis is performed using a Repeated Measures Analysis (RMA) of covariance model (SAS® MIXED procedure). The analysis, which aims to compare the YBOCS slopes of change from baseline between study arms, includes the following fixed effects: time from randomization, treatment group, time by treatment interaction, use of SSRIs and any other antidepressant or psychotropic medications, and/or psychotherapeutic behavioral interventions at enrollment, center and baseline YBOCS score. Baseline YBOCS scores are entered as continuous variables so that the potential for co-linearity problems will be minimized. The time

is entered using study visit number as a categorical variable. The individual subject is entered as random subject effect. The unstructured covariance is used for the responses within subjects.

The adjusted mean changes from baseline in YBOCS scores to 6 weeks post randomization are estimated from the model (LS Means) for each group as well as the difference between the adjusted means and presented together with 95% confidence intervals. Other efficacy measures of continuous variables are analyzed with similar models with baseline values as another covariate when relevant. Binary efficacy and other categorical measures are compared between the study groups at the week 6 and week 10 with a chi-squared test or Fisher's exact test.

Patients who drop out after one or more treatments and have data available for the analysis (i.e., at least one post-baseline assessment) of continuous variables are analyzed with a repeated measures analysis of variance model using PROC mixed in SAS which can handle missing data at random. At the 6 week, post-baseline visit, the applicant did not expect a high proportion of drop outs, thus, any missing data at 6 weeks post baseline can be considered missing at random. Therefore, for this evaluation no imputation of missing data is considered beyond the model estimates.

Results:

Subject Accountability

A total number of 100 OCD subjects were enrolled in the study (75 in the United States (US), 25 outside the United States (OUS)). Eligible and consenting subjects were randomized to either the active treatment group (denoted hereafter as **DTMS**) or the sham control group (denoted hereafter as **Sham**).

Table 2 presents subject accountability by study treatment group for each analysis data set. The Intent-to-treat (ITT) analysis set includes 99 randomized patients, as one subject withdrew consent while the motor threshold was being measured. The patient did not tolerate the stimulation used to measure the motor threshold. The subject withdrew consent after randomization, but before receiving even one active/sham treatment. Thus, the subject is not included in the ITT analysis set. 48 subjects were randomized to receive DTMS treatment and 51 to receive Sham treatment.

The mITT analysis set includes 94 subjects. Five (5) subjects in the ITT analysis set were excluded to form the mITT analysis set because even though they received treatments, they did not meet one of the study eligibility criteria and therefore they should not have been included in the study. Four of the five subjects were excluded because they did not meet the inclusion criterion that subjects should be maintained on a stable dose of OCD treatments (medications, psychotherapy) 2 months prior to the trial and during the trial. One subject was excluded because they were diagnosed as having a severe personality disorder that they apparently suffered from prior to commencement of the study, and therefore they should not have been recruited into the study.

One (1) additional subject with a major protocol deviation was excluded from the mITT analysis set to form the Per Protocol analysis set. The study results for the Per-Protocol analysis set are nearly identical to those of the mITT analysis set, and therefore they are not described any further in this summary.

Table 2: Accountability of Enrolled Subjects According to Treatment Group

	Group				Total	
	DTMS		Sham			
	N	%	N	%	N	%
ITT Analysis Set (Subjects who were Randomized & who have received at least one active/sham treatment)	48	48.48%	51	51.52%	99	100.00%
mITT Analysis Set (Subjects who met the Eligibility Criteria)	47	50.00%	47	50.00%	94	100.00%
PP Analysis Set (Subjects without Major Protocol Violations)	46	49.46%	47	50.54%	93	100.00%

Table 3 shows the number and percentage of subjects withdrawn or dropped out up to 6 weeks and 10 weeks. Table 3 indicates that only 10% of the subjects dropped out before the 6-week end-point in both study groups, thus demonstrating a low drop-out rate in this study.

Table 3: Number of Subjects Withdrawn or Dropped Out at 6 Weeks and 10 Weeks (ITT)

	Group			
	DTMS (N=48)		Sham (N=51)	
	N	%	N	%
Subject completed up to visit number - 6 Week Visit	43	89.58%	46	90.20%
Subject completed up to visit number - 10 Week Visit	40	83.33%	44	86.27%

Demographics

The age range of the subjects was between 22 and 68 and 41% (41/99) of subjects were female. The baseline demographic data, general medical and psychiatric history, concomitant medications, baseline assessment scores and physical and neurological examination data were analyzed to assess if there were any basic differences between the treatment groups prior to commencement of the clinical study. The baseline demographic information, including age, gender and the medical and psychiatric history data did not show any significant differences in the data between the treatment groups.

The baseline assessment scores were very similar between the treatment groups (Table 4). This was true of the physical and neurological examination data, as well. The data show that there were no notable differences between the study treatment groups.

Table 4: Baseline Assessment Scale Data (ITT)

		DTMS (N=48)	Sham (N=51)	p-value
YBOCS score	N	48	51	
	Mean (SD)	27.6 (3.87)	26.9 (4.13)	0.3335(*)
	Median [Range]	27.0 [20.0;35.0]	26.0 [20.0;36.0]	
CGI-I score	N	48	51	
	Mean (SD)	5.4 (1.28)	5.5 (1.51)	0.6881(*)
	Median [Range]	5.0 [4.0;10.0]	5.0 [4.0;10.0]	
CGI-S score	N	48	51	
	Mean (SD)	5.1 (0.71)	5.0 (0.89)	0.6102(*)
	Median [Range]	5.0 [4.0;7.0]	5.0 [4.0;7.0]	
SDS score	N	48	51	
	Mean (SD)	19.3 (6.36)	19.0 (5.92)	0.7885(*)
	Median [Range]	20.5 [3.0;30.0]	20.0 [5.0;28.0]	

(*unadjusted p-value for multiplicity) t-test

Safety Results

Safety and tolerability of the DTMS treatment were evaluated during the course of the study, including assessment of vital signs, physical and neurological examinations, Scale for Suicide Ideation (SSI) assessments, cognitive examinations (MMSE, BSRT and AMI-SF) and adverse event (AE) reporting. Audiometric testing to assess the effects of the sound produced by the active and sham device was not performed. No notable differences in vital signs, physical and neurological examination results were observed between the study groups at each of the time points.

AEs were reported by 35 subjects (73%) in the DTMS group and 35 (69%) subjects in the Sham group.

The AEs reported in the study are typical side effects reported previously with the DTMS system and with other marketed TMS devices. The most frequent AE was headache reported by 37.5% (18/48) of the subjects who received the DTMS treatment and by 35.3% (18/51) of the subjects who received the Sham treatment. Most other forms of pain and discomfort (administration/application site pain/discomfort, pain in jaw, facial pain, muscle pain/spasm/twitching, neck pain, dizziness) were reported as either mild or moderate and mostly resolved after treatment. In most of the subjects the discomfort or pain disappeared once the subject became accustomed to the treatment. There were no reports of hypoacusis (hearing loss). Overall, there were no notable differences found between the treatment groups for any of the adverse events reported in the study.

There was one (1) serious adverse event (SAE) reported in the study, which was assessed by the investigator and the sponsor as not related to the device treatment. After receiving 2 treatments, one subject reported having significant suicidal thoughts that he indicated had preceded the beginning of the treatment sessions, but had neglected to mention prior to study commencement. The investigator and subject decided that hospital admission would be appropriate. The subject claimed his suicidal thoughts/urges were related to escalating problems with his family and not to the study treatments.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change from baseline in YBOCS scores to the 6 week visit. To assess the effect of missing data for the mITT population, a sensitivity analysis was performed using a last observation carried forward imputation for the missing YBOCS scores. This sensitivity analysis demonstrates that missing mITT data does not effect the overall conclusions of the study.

Figure 2 displays the mean (±SE) of the YBOCS change from baseline over time during the study for the two study groups (mITT). In both groups, there was a reduction over time in YBOCS scores but it was larger for the DTMS group. For example, the YBOCS score decreased by 6.7 points in the DTMS group vs. 3.6 points in the Sham group at the 6 week visit.
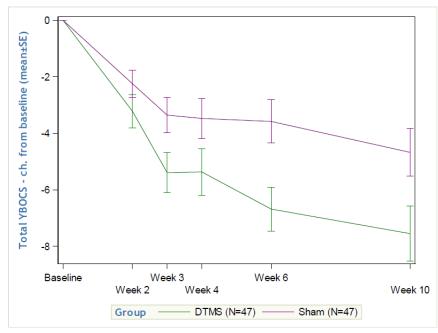

Figure 2: YBOCS Change From Baseline Over Time (mITT)

Table 5 presents the adjusted means extracted from the model at the 6-week visit for the mITT analysis set. The YBOCS score decreased by a clinically meaningful 6.0 points (N=47, 95% CI: [4.0;8.1]) in the DTMS group and by 3.3 points (N=47, 95% CI: [1.2;5.3]) in the Sham control group, these decreases were both statistically significant. The difference between the slopes of 2.8 points across 6 weeks between the treatment arms is also statistically significant (p-value:0.0127).

Table 5: Adjusted Means of the Change from Baseline to 6 Weeks in YBOCS (mITT)

		Estimate	Standard Error	Pr > |t|	95% CI
Adjusted means of the changes	DTMS	-6.044	1.049	<.0001	[-8.126;-3.962]
	Sham	-3.266	1.032	0.0021	[-5.314;-1.218]
Comparison of the adjusted means		-2.778	1.091	0.0127	[-4.948;-0.609]

Table 6 presents the adjusted means extracted from the model at the 6-week visit for the ITT analysis set. The YBOCS score decreased by a clinically meaningful 6.0 points (N=48, 95% CI: [3.8;8.2]) in the DTMS group and by 4.1 points (N=51, 95% CI: [1.9;6.2]) in the Sham control group, these decreases were both statistically significant. However, in contrast to the result for the mITT analysis set, the difference of 1.9 points across 6 weeks between the treatment arms is not statistically significant (p-value: 0.0988). The Sham group in the ITT patient cohort showed a higher reduction in YBOCS score (4.1 points) than in the mITT patient cohort (3.3 points) and therefore, a statistically significant difference between the treatment groups was not found for the ITT cohort.

For the mITT population, the study had a total of 70 US subjects and 24 OUS subjects. It was observed that the Sham group in the US subject cohort (mITT) had a larger reduction in YBOCS score (4.5 points, N=34) than that observed for the OUS subject cohort (1.2 points, N=13), and therefore a statistically significant difference between the treatments was found for OUS subjects (5.6 points) but not for US subjects (1.8). However, for both subject populations (mITT and ITT), and for subjects in both regions (US, OUS), the YBOCS score decreased an average of 6.0 points or more in the DTMS group (N=47 for mITT, N=48 for ITT) across 6 weeks and this is a clinically meaningful reduction in the severity of OCD symptoms.

Table 6: Adjusted Means of the Change from Baseline to 6 Weeks in YBOCS (ITT)

		Estimate	Standard Error	Pr > |t|	95% CI
Adjusted means of the changes	DTMS	-5.967	1.106	<.0001	[-8.158;-3.776]
	Sham	-4.051	1.073	0.0003	[-6.176;-1.925]
Comparison of the adjusted means		-1.917	1.149	0.0988	[-4.200;0.366]

Secondary Effectiveness Endpoints

Results for the secondary outcome measures are summarized in Table 7 for the mITT and ITT analysis sets. The results for the mITT and ITT analysis sets are similar, and therefore only the mITT results are discussed below.

The 6-point reduction in the YBOCS score in DTMS group (N=48 for ITT, N=47 for mITT) observed after 6 weeks of treatment was stable when observed at 10 weeks (4 weeks after

treatment completion). At 10 weeks, the adjusted mean YBOCS score had decreased by 6.5 points (95% CI: [4.3;8.7]) in the DTMS group.

The CGI Improvement (CGI-I) and CGI Severity (CGI-S) results are presented using a categorical analysis. For CGI-I results, subjects were categorized into the following two categories: "Improved" (moderately improved to very much improved) or "minimally improved" (very much worse to minimally improved). The change from baseline in CGI-S scores were categorized into the following three categories: "Improved", "No Change", or "Worsened". The categorical analysis of the CGI-I results at 6 weeks demonstrate that 49% of DTMS subjects (N=41) are in an "Improved" clinical state vs. 21% of Sham subjects (N=43). The categorical analysis of the CGI-S results at 6 weeks demonstrate that 61% of DTMS subjects (N=41) are in an "Improved" clinical state vs. 33% of Sham subjects (N=43). The CGI-I and CGI-S results for the DTMS group are maintained 4 weeks after treatment when observed at 10 weeks (10-week data are not shown).

Table 7: Secondary Effectiveness Endpoint Results for mITT and ITT Analysis Sets

Secondary Endpoint		DTMS		Sham	
		N	Proportion or Adjusted Mean Change	N	Proportion or Adjusted Mean Change
CGI-Improvement at 6 Weeks ["Improved" Category]	mITT	41	48.8% (20/41)**	43	20.9% (9/43)
	ITT	42	47.6% (20/42)**	47	25.5% (12/47)
CGI-Severity at 6 Weeks ["Improved" Category]	mITT	41	61.0% (25/41)**	43	32.6% (14/43)
	ITT	42	59.5% (25/42)	47	36.2% (17/47)
Sheehan Disability Scale at 6 weeks	mITT	47	-3.80 [-6.08;-1.53]	47	-3.01 [-5.25;-0.78]
	ITT	48	-3.94 [-6.22;-1.66]	51	-3.3 [-5.52;-1.07]
Response Rates at 6 Weeks (≥30% reduction in YBOCS)	mITT	42	38.1% (16/42)**	45	11.11% (5/45)
	ITT	43	37.2% (16/43)**	49	18.4% (9/49)
Partial Response Rates at 6 Weeks (≥20% reduction in YBOCS)	mITT	42	54.8% (23/42)**	45	26.7% (12/45)
	ITT	43	53.5% (23/43)**	49	32.7% (16/49)
Change from Baseline to 10 Weeks in YBOCS	mITT	47	-6.53 [-8.73;-4.34]	47	-4.06 [-6.22;-1.89]
	ITT	48	-6.53 [-8.82;-4.25]	51	-4.72 [-6.95;-2.45]
Remission Rate at 6 Weeks (YBOCS score < 10)	mITT	42	4.76% (2/42)	45	4.44% (2/45)

		ITT	43	4.65% (2/43)	49	8.16% (4/49)

**: p-value < 0.05 unadjusted for multiplicity (The formal statistical test was stopped at the 1st secondary endpoint – Sheehan Disability Scale.)

The Response rate, Partial Response rate, and Remission Rate (all defined by Brainsway) at the 6-week visit are presented in Table 7. Response is defined as a reduction from baseline of at least 30% in the YBOCS score. Partial Response is defined as a reduction from baseline of at least 20% in the YBOCS score. Remission rate is defined as a YBOCS score less than 10.

The Response rate at the 6 week visit in the DTMS group is 38.1% (16/42) versus 11.1% (5/45) in the Sham group. The Partial Response rate at the 6 week visit in the DTMS group is 54.8% (23/42) versus 26.7% (12/45) in the Sham group. The percent reduction in the YBOCS score observed at 6 weeks for all individual subjects in the DTMS group is displayed in Figure 3 and for all individual subjects in the Sham group in Figure 4 (mITT). Different colors are used to indicate Responders (≥30% reduction in YBOCS) vs. Non-Responders in each group.

In some published reviews of studies of OCD treatments, a 25 – 35% reduction in the YBOCS score is generally considered to be a "partial response" to an OCD treatment, while a greater than 35% reduction is considered to be a "full response" (e.g.; Koran LM, Hanna GL, Hollander E, Nestadt G, Simpson HB: Practice guideline for the treatment of patients with obsessive-compulsive disorder. Arlington, VA: American Psychiatric Association, 2007; Pallanti S, Hollander E, Bienstock C, Koran L, Leckman J, Marazziti D, Pato M, Stein D, Zohar J: Treatment non-response in OCD: methodological issues and operational definitions. Int J Neuropsychopharmacol 2002; 5:181–191).

Based on this study of the Brainsway DTMS device, a larger proportion of subjects had a "partial response" or "full response" (as defined by Pallanti, et al., (2002)) after being treated with the device for 6 weeks (Figure 3) than did the sham-treated subjects (Figure 4). The numbers of subjects experiencing at least a 50% decrease in their YBOCS scores were small in both treatment groups (Figures 3 and 4).
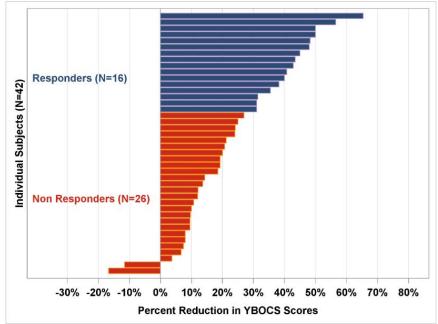
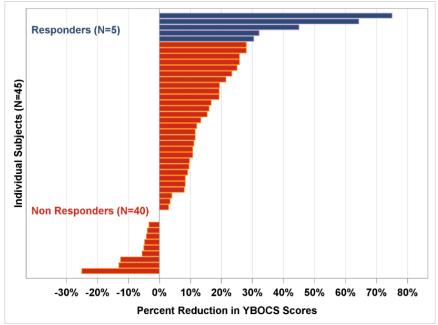**Figure 3: Percent Reduction in YBOCS Scores for DTMS subjects (mITT)**

Figure 4: Percent Reduction in YBOCS Scores for Sham subjects (mITT)

Blinding Assessment

After the first treatment, subjects were asked which treatment (DTSM or Sham) did they think they received. Only 31.4% (16/51) of the subjects who received Sham treatment had a moderate to strong belief that they received Sham. In the DTMS group, 43.8% (21/48) of subjects had a moderate to strong belief that they received the DTMS treatment. 12.5% (6/48) of the subjects in the DTMS incorrectly guessed the treatment they received (i.e., they responded that they

received Sham treatment) and 21.6% (11/51) of the subjects in the Sham group incorrectly guessed the treatment they received (i.e., they responded that they received DTMS treatment). The most frequent answer of subjects in both groups was that they did not know which treatment they received. That is, 43.8% (21/48) of the subjects in the DTMS responded that they don't know, versus 47.1% (24/51) of the subjects in the Sham group. Thus, the majority of the study subjects, 56.3% (27/48) of the DTMS subjects and 68.6% (35/51) of the Sham subjects, were not aware of the treatment they received during the study.

Pediatric Extrapolation
In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

The *Brainsway DTMS System Instructions for Use* are consistent with the clinical data and cover all the hazards and other clinically relevant information that may impact use of the device. The instructions include the risks and benefits associated with use of the device; detailed instructions to prevent seizures, to monitor the patient for seizure activity during treatment, and to provide seizure management care if one were to occur during treatment; and a description of the ear protection to be worn by the patient during use of the device, including the type of protection and its noise reduction rating. The labeling satisfies the requirements of 21 CFR § 801.109 Prescription devices.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the transcranial magnetic stimulation system for neurological and psychiatric disorders and conditions and the measures necessary to mitigate these risks.

Table 8: Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measures
Seizure	Non-clinical performance testing Labeling
Thermal injury	Non-clinical performance testing Thermal safety testing Electrical safety testing Software verification, validation, and hazard analysis Labeling
Hearing loss	Non-clinical performance testing Labeling
Scalp discomfort, dizziness, nausea, pain in neck or jaw, headache, or other adverse effects due to treatment	Labeling
Adverse tissue reaction	Biocompatibility evaluation Labeling
Electrical shock	Electrical safety testing

	Labeling
Device failure due to interference with other devices	Electromagnetic compatibility testing
	Electrical safety testing
	Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the transcranial magnetic stimulation system for neurological and psychiatric disorders and conditions is subject to the following special controls:

1. Performance testing must demonstrate electromagnetic compatibility, electrical safety, and thermal safety.

2. Software verification, validation, and hazard analysis must be performed.

3. The patient-contacting components of the device must be demonstrated to be biocompatible.

4. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
   a. Magnetic pulse output testing;
   b. Magnetic and electrical field testing;
   c. Testing of the safety features built into the device; and
   d. Testing of the sound levels patients are exposed to during device use.

5. The physician and patient labeling must include the following:
   a. The risks and benefits associated with use of the device.
   b. Detailed instructions to prevent seizures, to monitor the patient for seizure activity during treatment, and to provide seizure management care if one were to occur during treatment.
   c. A description of the ear protection to be worn by the patient during use of the device, including the type of protection and its noise reduction rating.

BENEFIT/RISK DETERMINATION

The risks of the device are based on data collected in the randomized controlled clinical study described above. There was one serious adverse event reported in the study but it did not appear to be related to the device. All reported adverse events were minor, reversible, and typical of side effects reported previously with other marketed TMS devices. Audiometry was not performed before, during, or after treatment. However, hearing protection is recommended, the sound intensity produced by the device is lower than that of currently marketed products, and there were no reports of hypoacusis (hearing loss) in the study. Based on this information, the risks associated with the use of the Brainsway DTMS System for the treatment of OCD are considered low.

The probable benefits of the device are based on data collected in the randomized controlled clinical study, which demonstrated a statistically significant difference in the primary effectiveness endpoint (reduction in YBOCS score) when comparisons were made between groups, and that a statistically significant number of subjects responded to treatment with this and other measurements of OCD severity as compared to the number that responded to sham treatment. Some analysis populations (ITT and US subjects) failed to achieve statistical significance for the primary effectiveness endpoint when comparisons were made between groups; however, a clinically relevant reduction in OCD severity was observed for all analysis populations treated with the device, and trends observed for all endpoints suggested a probable benefit irrespective of the analysis population.

Additional factors to be considered in determining probable risks and benefits for the Brainsway DTMS System include:

(1)   A randomized, double blinded, multi-site, sham-controlled clinical trial was provided to evaluate risks and benefits

(2)   Medications that are approved for treatment of OCD produce similar benefits to those obtained when using the Brainsway DTMS System (e.g., reduction of YBOCS score by approximately 6 points); however, these medications can produce problematic side effects such as cognitive changes, and,

(3)   OCD is a debilitating condition, and up to 40 - 60% of patients diagnosed with OCD do not have a satisfactory response to medications.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that for a TMS system for neurological and psychiatric conditions that is intended for the treatment of subjects suffering from OCD, the probable benefits outweigh the probable risks for the Brainsway DTMS System. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

<u>CONCLUSION</u>

The De Novo request for the Brainsway DTMS System is granted and the device is classified under the following:

Product Code: QCI
Device Type: Transcranial magnetic stimulation system for neurological and psychiatric disorders and conditions
Class: II
Regulation: 21 CFR 882.5802