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CHANGES:

Version No.	**Responsible Person**	**Description of Change**	**Implementation Date**
1.0	Oct 06,2013	Yiftach Roth	Initial Release
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DEEP TMS SYSTEM FOR TREATMENT OF OBSESSIVE COMPULSIVE DISORDER

(HAC Coil)

INSTRUCTIONS FOR USE

The system is used for patient treatment by prescription only under the supervision of a licensed physician

BRAINSWAY LTD.

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The Brainsway Deep TMS System Instructions for Use provide instructions for the users and administrators of the Deep TMS System necessary for the safe and effective operation of the system. Please read and thoroughly understand the Instructions for Use before operating the system. If any part of the Instructions for Use is not clear, contact the Brainsway Customer Support for clarifications. The Instructions for Use should always accompany the unit, and all personnel operating the unit must know its location.

TABLE OF CONTENTS

1. CONVENTIONS USED IN THE INSTRUCTIONS FOR USE

This section contains important regulatory information and safety warnings regarding use of the Brainsway Deep TMS System. To enhance readability, emphasized text and graphic symbols are used to identify important Warnings, Cautions, Procedure Instructions and special Notes. Examples of these elements are shown below.

Points of Emphasis

Italic or **bold** text denotes points of emphasis.

Warnings and Precautions

A Warning is a statement that alerts the user to the possibility of injury, death or other serious adverse reactions associated with the use or misuse of the device. A Caution is a statement that alerts the user to the possibility of a problem with the device associated with its use or misuse. An example is shown below.

Warning and Precautions

Use of the Brainsway DTMS System requires the user to observe the warnings and precautions detailed below.

Notes

General notes are used to provide general information or references to other sections in the manual. An example is shown below.

NOTE **Instructions for Placement of the Personal Cap are provided in section 15.2.2.**

Important notes are used to identify procedures or steps that must be performed to ensure normal or optimal system performance. A typical example is shown below.

NOTE **These treatment parameters serve as the default treatment setting for the Brainsway Deep TMS System and should be used as the treatment setting for all patients. These settings were used to establish safety and efficacy in the Brainsway Deep TMS System clinical trials.**

2. USER REQUIREMENTS

- Patients already on Obsessive-Compulsive Disorder (OCD) treatments (psychotropic medications and/or psychotherapy) should be maintained at their current dosages during the DTMS treatment
- The Brainsway Deep TMS System should be operated by a qualified user trained by a representative of Brainsway Ltd.
- Before operating the Brainsway Deep TMS System, the following document should be carefully reviewed by the user.
- In addition, since the Brainsway Deep TMS coils are operated by a Magstim Rapid, Rapid^2 or SuperRapid^2 stimulator, the stimulator's Operating Manual must be consulted before use. You can find the Magstim Rapid/Rapid^2/SuperRapid^2 Operating Manual CD in the Magstim package supplied by Brainsway.
- The user should provide the patient with the Patient Guide prior to treatment so that the patient has sufficient time to review the information about the device and the procedure and discuss this information with his/her physician and family.
- The treatment administrator must be able to observe patients and identify significant adverse reaction during or immediately after treatment and if necessary make adjustments (consistent with the Operator Manual) or determine if interruption of the treatment or termination of the treatment should be considered (after discussions with the doctor).
- A healthcare provider must be qualified and available on premises to monitor the patient for seizure activity and to provide seizure management care.

  Instructions for seizure management procedures may include:
  - presence of physician or nurse trained in seizure management;
  - presence of or ready access to, life-support equipment (oxygen, suction, blood pressure monitor, intravenous equipment, CPR equipment); and
  - access to anti-seizure medications.

3. INDICATIONS

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 (OCD).

4. PRINCIPLE OF OPERATION

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 (rMT) of the foot, for the treatment of Obsessive Compulsive Disorder (OCD), using a flexible coil conforming to the shape of the head.

5. CONTRA-INDICATIONS

The Brainsway Deep TMS System **must not** be used 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.

6. GENERAL WARNINGS AND PRECAUTIONS

Use of the Brainsway DTMS System requires the user to observe the warnings and precautions detailed below.

Patient Monitoring Warnings and Precautions:

- Long-term effects of exposure to rTMS are unknown. Experimental and observational evidence indicates that exposure to the type of magnetic fields produced by the Deep TMS System does not present any significant risk of acute or long-term adverse effects.
- Treatment provider must observe patients and advise patients and their families to monitor behavioral changes, such as increases in depression, suicide attempts and ideations, increased aggressiveness, euphoria or irritability; and that if such behavioral changes appear, they should inform their physician immediately
- Brainsway Deep TMS treatment should be discontinued in any patient who has a continued significant adverse reaction or discomfort during or immediately after treatment. Temporary mild discomfort at the site of stimulation is normal during and/or shortly after treatment.
- During treatment with the Deep TMS System, 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. Sstop rTMS if a user reports, or if a treater observes that an earplug has loosened or has fallen out.

Seizure Monitoring Warnings and Precautions:

- Generalized seizures have been reported with the use of TMS in the clinical trial literature. 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, as stated below. Stimulation parameters outside of those studied in the clinical study and recommended for use in these Instructions for Use have not been tested for safety during brain stimulatio.
- Be alert for signs of an imminent seizure and terminate the treatment session if those signs appear. If a medication that may alter the seizure threshold has been

taken since the last treatment session (or its' dosage altered), the motor threshold determination should be repeated prior to the next treatment session. Patients at potential increased risk of seizure include those who have:

History (or family history) of seizure or epilepsy, history of stroke, head injury, or unexplained seizures;

Presence of other neurological disease that may be associated with an altered seizure threshold (such as cerebrovascular accident [CVA], cerebral aneurysm, dementia, increased intracranial pressure, head trauma, or movement disorder); Concurrent medication use such as tricyclic antidepressants, neuroleptic medications, or other drugs that are known to lower the seizure threshold; Secondary conditions that may significantly alter electrolyte balance or lower seizure threshold;

No quantifiable motor threshold such that TMS dosage cannot be accurately determined.

- Deep TMS treatments can induce seizures, although the probability of this occurring is very low. Therefore, visual monitoring by the treatment administrator for signs of seizures must be maintained throughout the treatment. For example, hand or leg tremors continuing after the end of a train may be an indication of seizure onset. The treatment session must be terminated immediately if such signs appear. Furthermore, patients should be instructed that alcohol consumption or certain medications may increase probability of a seizure, in order to prevent or minimize the risk of seizure occurrence.
- In general, TMS guidelines (1998 National Institute of Neurological Disorders and Stroke (NINDS) Workshop) for rTMS stimulation parameters should be followed in order to reduce the potential risk of seizure.

Device Interaction with the Environment Warnings and Precautions:

- The system is used for patient treatment by prescription only under the supervision of a licensed physician.
- The strong magnetic pulses generated by the Coil induce eddy currents in any

conductive medium such as the human body, nearby metallic objects or electronic devices.

- Particular care must be taken to ensure that leads connected directly to the patient or to other equipment are not in a position where the Coil can couple with them, as this would cause currents to be induced in them.
- Prior to treatment, each patient should be screened for the presence of metallic objects or implants that could affect the safe use of the Deep TMS System.
- Do not discharge the Deep TMS System with the Coil in the vicinity of metallic objects, as this may cause them to be moved and/or damaged.
- Patients must remove any object or device that may be affected by the electric or magnetic field of the Deep TMS System prior to treatment, including earrings, jewelry, hair barrettes, hearing aids, wearable monitors and bone growth stimulators.
- Electronic devices implanted or located near the patient body, may be damaged, moved or heated by the induced magnetic field of the Deep TMS system. Hence, particular care must be given to ensure that there is no implant or electronic or metallic device or object within 30 cm from the coil, and that the coil is not placed near other body locations apart from the head. Operation of the Deep TMS coil within 30 cm from an implanted device could lead to malfunction of the device that may result in patient serious injury or death.
- Do not discharge the Coil in the vicinity of objects sensitive to magnetic fields. Examples are credit cards, floppy disks, cell phones and computer screens.
- The Deep TMS System must not be used in an explosive atmosphere or in the presence of flammable anesthetics.
- The Deep TMS System must not be placed in the restricted access area of a magnetic resonance imaging (MRI) device.
- When the magnetic pulse is delivered, a discharge click is produced by the Deep TMS System and the Coil. This discharge click may startle.
- The Deep TMS System and its accessories must be used in the environmental conditions specified in these Instructions for Use only.
- In case of unstable electricity mains network with voltage fluctuations, the device

may stop operation. Repeated operation of the device with an unstable electricity mains network may damage the device.

Device Electrical and Heating Warnings and Precautions:

- ❖ High voltages are present within this System. Do not remove covers. Refer servicing to qualified personnel. There are no user-serviceable parts in the system. Ensure that the System is not subject to conditions where water/ liquid may be accidentally spilled onto it.
- ❖ No modification of this equipment is allowed.
- ❖ To avoid risk of electric shock, this equipment must only be connected to supply mains with protective earth.
- ❖ To ensure grounding safety, all mains power connections should be made directly to wall power sockets. All of the customer's electrical cabling must conform to local electrical standards. Do not use a terminal block if insufficient sockets are available, as this will form a potential electrical hazard.
- ❖ The device must be used in a mains system with surge protection.
- ❖ The device is not intended for use in a low voltage public network.
- ❖ The Deep TMS System and accessories must not be used if there are any signs of external damage or if any parts are damp or wet.
- ❖ Protection circuits disable the equipment if the temperature of the H-Coil exceeds 38°C.
- ❖ The H-Coil must not be immersed in water, put in an ice bucket, or refrigerated, even if placed within a plastic bag, as condensation may form within the coil. The coils do not have any specialized protection against the ingress of liquids; therefore, conditions where ingress of liquid or the forming of condensation within the coil can occur must be avoided, as the electrical insulation will be compromised.
- ❖ Cooling must only be performed by using Brainsway's cooling system unit.
- ❖ Coil Overheating - due to thermal lag, the surface temperature of the H-Coil may continue to rise after the coil over-temperature protection has been activated and has forced the main unit into a standby condition. Therefore, the coil must be removed from the patient as soon as the stimulator's user interface indicates that the

coil is over-temperature.

Other Warnings and Precautions:

- The Deep TMS System and its accessories must be used in the environmental conditions specified in these Instructions for Use only.
- The head cap supplied by Brainsway is intended for personal use due to hygiene reasons. The cap must not be used on open wounds.

7. USER TRAINING

The user should provide the patient with the Patient Guide prior to treatment so that the patient has sufficient time to review the information about the device and the procedure and discuss this information with his/her physician and family.

The treatment administrator may be a health care provider approved by the psychiatrist. The treatment administrator should have sufficient clinical expertise to monitor the patient during the treatment. That is, the treatment administrator should be able to observe the patient for the potential occurrence of adverse events, including identification of seizure activity. The treatment administrator should be able to determine when treatment interruption or termination should be considered. The treatment administrator should be present in the treatment room with the patient during the treatment session.

8. SPECIAL POPULATIONS

The safety and effectiveness of the Brainsway DTMS System has not been established in the following patient populations or clinical conditions through a double-blind controlled clinical trial:

- 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, occular implants, deep brain stimulators, vagus nerve stimulators, implanted medication pumps, intracardiac lines, or significant cardiac disease; or
- History of substance abuse in the past six months prior to treatment;
- Subject was on high doses of antidepressant or psychotropic medications, which are known to lower the seizure threshold or subjects on Clomipramine;
- Pregnant or nursing.

9. TREATMENT ADMINISTRATION

Treatment parameters for Brainsway Deep TMS System are standardized for each treatment session as follows:

- Magnetic Field Intensity: 100% of patient's measured Leg Motor Threshold (MT).
- Frequency: 20 Hz
- Treatment train duration: 2 seconds
- Inter-train interval: 20 seconds.
- Treatment Session Duration: 18.3 minutes
- No. of Trains: 50
- Number of pulses administered per session: 2000

These treatment parameters serve as the default treatment setting for the Brainsway Deep TMS System and should be used as the treatment setting for all patients. These settings were used to establish safety and efficacy in the Brainsway clinical trials.

The number of treatment sessions consists of 5 daily sessions for 5 weeks, and 4 daily session in the 6^{th} week.

Brainsway Deep TMS treatment may be administered as an adjunct to standard of care. The patient's motor threshold should be re-measured in the case of any medication change and prior to the next treatment session. Ideally, dosages of medication should not be changed during a DTMS treatment course. Similarly, frequency of psychotherapy should not change during a DTMS treatment course.

10. PRODUCT DESCRIPTION

Brainsway's Coil Deep TMS System is composed of the following five main components:

a. A helmet comprising an electromagnetic coil (HAC-Coil) contained in a Helmet. The helmet is the applied part of the device.
b. A TMS neurostimulator (Magstim Rapid or Rapid^2)
c. A cooling system
d. A positioning device
e. A cart

A schematic diagram of the Deep TMS system is presented in Figure 1 below.

Figure 1: A general sketch of the Brainsway H-Coil Deep brain rTMS System,

Accessories needed:

- Personal head cap (supplied by Brainsway):

NOTE The cap is used to aid in coil positioning, and for hygiene reasons.

Instructions for **Placement of the Personal Cap** are provided in section 15.2.2.

- Personal quality earplugs

10.1. The Coil (HAC-Coil)

The HAC-Coil is designed to induce activation of cortical and sub-cortical frontal neuronal structures including medial prefrontal, orbitofrontal and anterior cingulate cortices.

The HAC-Coil is made of insulated copper wires. The total length of the coil is 500 cm, wound into 16 windings, connected in series. The windings are connected to a Magstim cable and a connector. This connector can be connected to the Magstim Rapid, Rapid^2 or SuperRapid^2 stimulator. In addition, a temperature sensor is included, with an appropriate cable.

10.2. Commercial TMS Neurostimulator

A commercial TMS neurostimulator, the Magstim Rapid or the Magstim Rapid^2, is used to deliver electrical stimulation to the brain, enabling controlled output, frequency and pulse duration, and providing indication of coil temperature.

The Magstim Rapid, Rapid^2 and SuperRapid^2 stimulators were cleared by the FDA (K992911 and K051864). These devices were cleared for peripheral nerve stimulation.

The detailed technical specifications of the Magstim Stimulator are available on Magstim Ltd.'s website (www.magstim.com). In addition to detailed information regarding the specific Magstim TMS stimulator, the guide provides an overview of the technique of magnetic stimulation.

10.3. The Cooling System

The Cooling System is designed to maintain ambient temperature in the coils during repetitive operation. The cooling system consists of an external unit and an air hose that

directs the cooled air into the helmet. The air flow cools the coils during pulse trains and maintains them at ambient temperature.

10.4. The Positioning System

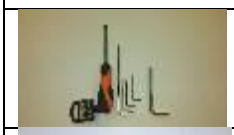
The positioning system includes a helmet that comprises the Coil, an adjustable arm connected to the helmet, and a device that enables rotation and displacement of the helmet in three dimensions. The positioning device enables accurate and comfortable placement and positioning of the coil over the patient's head.

10.5. The Cart

The mobile medical cart contains the cooling system, controller and stimulator, enabling mobility of the system inside the treatment area by a trained operator. Mobility outside of the treatment area must be performed by two people who have been trained by Brainsway.

10.6. Accessories

The system contains the following accessories for operation:

Item	Description	Item	Description
	Coil Adaptor		Screen Cable Connector
	Stimulator Cable Connectors		Stimulator Power Supply Cable Connector
	Cooling System Power Supply Cable Connector		Cooling System Air Hose
	Tool Kit		EMG – Electrodes
	Foot Switch Assembly		

11. ELECTRICAL SAFETY AND EMC

The Brainsway's Deep TMS System was tested by the Standards Institution of Israel (SII) Laboratory (Tel Aviv, Israel) for compliance with the following standards:

- IEC 60601-1-1:2000, Medical Electrical Equipment - Part 1: General Requirements for Safety; Safety Requirements for Medical Electrical Systems.
- IEC 60601-1-2, (Second Edition, 2001), Medical Electrical Equipment - Part 1-2: General Requirements for Safety - Collateral Standard: Electromagnetic Compatibility -- Requirements and Tests.

The Brainsway's H-Coil deep TMS System complies with the IEC 60601-1 standard and with the IEC 60601-1-2 standard.

List of Relevant Standards.

- Brainsway's Deep TMS System complies with the following standards:
- EN 980: 2003 - Graphical symbols for use in the labeling of medical devices
- EN 1041:1998 - Information supplied by the manufacturer with medical devices
- ISO 14971:2007- Medical devices - Application of risk management to medical devices
- EN ISO 10993-1:1997 - Biological evaluation of medical devices - Part 1: Evaluation and testing
- EN ISO 13485:2012 - Medical devices - Quality management systems - Requirements regulatory purposes
- EN ISO 14155-1:2003 - Clinical investigation of medical devices for human Part 1: General requirements
- EN ISO 14155-2:2003 - Clinical investigation of medical devices for human subjects - Part 2: Clinical investigation plans
- IEC 60601-1-1:2000, Medical Electrical Equipment - Part 1: General Requirements for Safety; Safety Requirements for Medical Electrical Systems.
- IEC 60601-1-2:2001; Medical electrical equipment -- Part 1-2: General requirements for safety - Collateral standard: Electromagnetic compatibility - Requirements and tests
- EN IEC 60601-1-4:1996 +A1:1999 - Medical electrical equipment -- Part 1-4: General requirements for safety - Collateral standard

12. TECHNICAL SPECIFICATIONS

PHYSICAL SPECIFICATIONS	
Weight	122.5 kg
Height	2050 mm
Cart Length	680 mm
Cart Width	625 mm
Total Width	1400 mm
ELECTRICAL SPECIFICATIONS	
Voltage	110-120 VAC (USA) 220-240 VAC (Europe)
Frequency	60 Hz (USA) 50 Hz (Europe)
Fuse Rating	2X20A (USA) 2X16A (Europe)
OPERATIONAL SPECIFICATIONS	
%MT Range	60% to 140%MT
Frequency Range	0.02-30 Hz
Train Duration Range	1-20 seconds
Inter-Train Interval Range	10-60 seconds
Induced Electric Field at 1.5 cm at 1.0 SMT	100 V/m (nominal)
Pulse Type	Biphasic sinusoid
Pulse Width	310 μsec (nominal)

COIL MAXIMUM OPERATING PARAMETERS						
	Maximum No. of Trains at % Power with Cooling (Per Hour)					
Operating Protocol	50%	60%	70%	80%	90%	100%
2 Sec Trains, 20 Hz Frequency, 20 sec inter-train interval	130	120	100	90	60	40

13. OPERATION AND STORAGE CONDITIONS

Brainsway's Deep TMS System is susceptible to environmental influences. The following table presents the permissible environment conditions for storage and operation:

OPERATION AND STORAGE CONDITIONS	
Coil's Operating Temperature:	15 ºC to 30 ºC
Storage Temperature:	-10 ºC to 50 ºC
Atmospheric Pressure Range:	500 hPa (50KPa) to 1060 hPa (106KPa)
Relative Humidity Range:	10% to 80% Non-Condensing
Altitude	Up to 3000 Meter

14. SYSTEM MOBILITY

Attention - DTMS systems have wheels, the wheels must be locked during treatment.

Mobility of the system – within the treatment area, one trained operator can move the device.

Moving the system out of the treatment area should be performed by a minimum of two persons who received an orientation from Brainsway on how to move to the device.

15. THE TECHNOLOGY

The Brainsway DTMS System produces a time varying magnetic field and based on Faraday's Law, which asserts that a time-varying magnetic field produces an electrical current in an adjacent conductive substance, the DTMS system achieves its effect. During DTMS, the conductive substance is the brain, in particular the region of the cortex that lies beneath the DTMS System coil. The electric current induced in this region of the cortex travels in a path orthogonal to the direction of the alternating magnetic field with the point of maximum field strength and greatest current located beneath the coil located in the helmet which is placed on the patient's head transmitting magnetic pulses to the patient's brain. The induced current is tangential to the scalp at the cortical surface, and diminishes in magnitude with increasing depth. In the targeted area of the cortex, where field strength achieves the stimulation threshold, it is postulated that neuronal depolarization occurs. This type of magnetic field is not intended to induce a seizure during therapeutic use. The peak magnetic field strength achieved with each pulse in the cortex is maximally 0.4 Tesla, with alternating magnetic fields between 1 and 10 KHz. Although the mechanism of action is unknown, it is hypothesized that the Brainsway DTMS System causes neuronal depolarization and changes in brain functional activity that may be associated with various physiological changes in the brain associated with symptomatic relief in subjects with OCD.

16. USER INSTRUCTIONS

Detailed instructions for operation of Brainsway's Deep TMS System are provided below:

16.1 Preparing the System

16.1.1 Operating Environment

For the proper operation of the cooling system, the treatment room must be equipped with an air conditioning system, which maintains the room temperature 15-30°C.

16.1.2 System Assembly and Positioning

16.1.2.1 Position the system such that the rear side of the cart is at least 20 cm from any wall or surface, to ensure appropriate air exchange for the cooling system.

NOTE **Do NOT block the rear vent or position the rear vents against a wall or other surface in order to prevent overheating.**

16.1.2.2 Make sure that the cart's wheels are locked before operation.

16.1.2.3 Turn on the air conditioner in the treatment room, and set the temperature between 15°C and 30°C.

16.1.2.4 Connect the H1-Coil's power cable to the Magstim Stimulator's Main Unit, which is located in the cart.

16.1.3 Cooling System Instructions

16.1.3.1 For first-time use at a new site, the system should be operated only by a qualified treatment administrator.

16.1.3.2 Turn on the cooling system at least two minutes before treatment by pushing the button on the front panel of the cooling system.

16.1.3.3 At the end of the treatment, turn off the Cooling System.

16.1.3.4 Do not touch any of the cooling system buttons except for the power button (Fig. 24).

16.1.4 Magstim Stimulator Instructions

16.1.4.1 Make sure all the switches are turned off.

16.1.4.2 The Magstim stimulator has two gray cables connected to the mains. In addition, the cooling system cable is connected to the mains. Ensure that all three cables are connected to three separate power outlets.

NOTE **The power cables may present a tripping hazard. Ensure that all three cables are safely out of the user and the patient's path.**

16.1.4.3 Refer to Magstim Rapid or Rapid^2 Stimulator User's Manual for operation instructions. You can find the Magstim Rapid/Rapid^2/SuperRapid^2 Operating Manual CD in the Magstim package supplied by Brainsway.

16.2 Treatment Instructions

16.2.1 Initial Preparations

16.2.1.1 Ask the patient to complete the TMS safety questionnaire provided in Appendix B of the Instructions for Use.

16.2.1.2 Make sure the Coil's air cooling hose is connected between the Helmet and the cooling system.

16.2.1.3 Seat the patient in a (hospital supplied) chair in a comfortable position. Ensure that the patient is positioned at the proper height such that the helmet may be comfortably positioned on the patient's head.

16.2.1.4 Ensure that the patient puts earplugs in his/her ears. The earplugs must have a rating of at least 30 dB of noise reduction. Verify that the earplugs are properly in place. Instruct the patient to report any loosening or detachment of the earplugs during the treatment.

16.2.1.5 Ensure that the patient removes any hair jewelry, barrettes, other hair accessories and earrings.

16.2.1.6 Ensure that the first joint of the arm, projects from the cart at an angle of about 45°. This should be the state of the arm during the process of finding the Motor Threshold (MT), and during the treatment.

NOTE **Ensure that the positioning arm and the helmet are out of the way to avoid collision with the patient's head.**

16.2.2 Placement of the Personal Head Cap

NOTE

For hygienic purposes use a new Personal Head Cap for each patient. The patient's personal head cap may be re-used during all of his/her treatment sessions.

16.2.2.1 Put the personal head cap (supplied by Brainsway) on the patient's head, with the frontal edge of the cap attached to the forehead close to the eyebrows (Fig. 2). Make sure that the cap's middle red line is along the head midline (Fig. 2).

Figure 2: Hold the cap by the frontal edge of the cap (left), and attach it to the patient's forehead, such that the frontal edge of the cap is above the eyebrows (right).

16.2.2.2 Pull the cap's ear covers down in order to stretch the cap over the head and stretch the left and right peripheral straps across the left and right ear covers (Fig. 3).

Figure 3: Pull the cap's ear covers downward (left) and stretch the peripheral straps across them along the sides of the cap (right).

16.2.2.3 Stretch the left and right peripheral straps and fasten them at the back of the patient's head using the Velcro straps (Fig. 4).

Figure 4: Stretch the left and right peripheral straps and fasten them over the back of the patient's head.

16.2.2.4 Fasten the cap's chin strap using the Velcro straps (Fig. 6). After fastening, lift the left side of the strap, pull down the left ear cover, and re-attach the chin strap (Fig. 5). Follow the same procedure on the right side (Fig. 6).

Figure 5: Fasten the cap's chin strap.

16.2.2.5 Attach the midline flexible ruler along the midline of the cap, with the zero mark on the patient's nasion (Fig. 6). The ruler's scale lines must be contiguous with the cap's midline (Fig. 7).

Figure 6: Attach the flexible ruler along the cap's midline, with the 0 mark on the patient's nasion.

Figure 7: Ruler scale lines are contiguous with the cap midline

16.2.2.6 Measure the distance from nasion to inion, DN-I (Fig. 8), using the midline ruler.

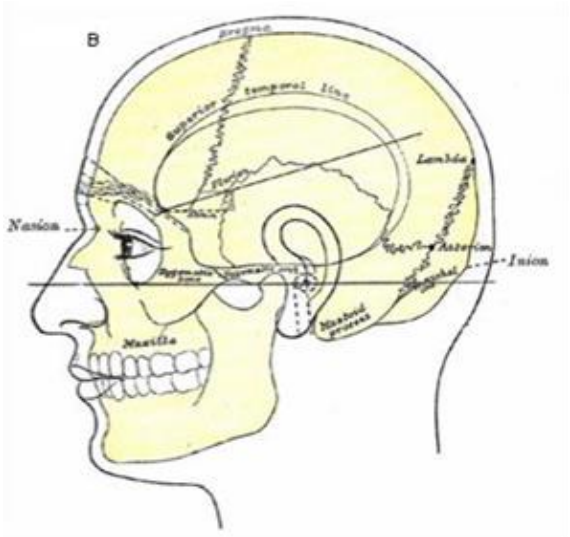


Fig. 8 – Nasion to Inion Distance

16.2.2.7 Place the lateral-medial flexible ruler, such that the 25cm scale mark on this ruler lines up with the point along the midline ruler whose distance from the nasion is 40% of the nasion-inion distance (DN-I). In the example shown in Fig. 9, this point is “15.7” (15.7 cm from nasion).

Figure 9: Place the lateral-medial flexible ruler at the point along the midline ruler with a distance from the nasion equal to 40% of the nasion-inion distance (DN-I).

16.2.2.8 Attach the lateral-medial ruler perpendicular to the midline ruler, with the zero mark on the left side of the patient (Fig. 10).

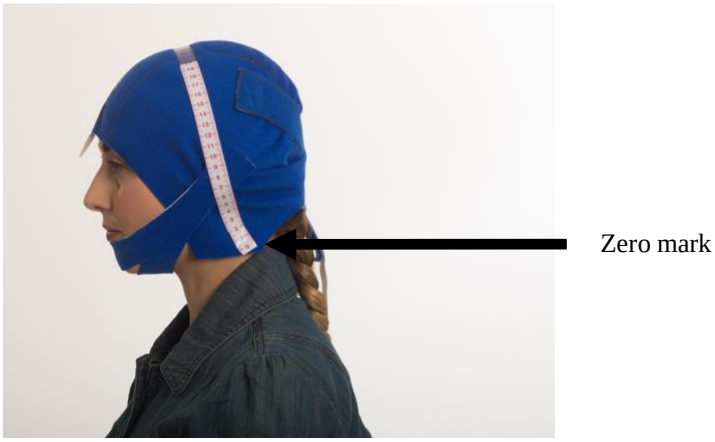


Figure 10: Attach the lateral-medial flexible ruler perpendicular to the midline ruler, with the zero mark on the left side.

16.2.3 Finding the individual motor threshold (MT)

16.2.3.1 The motor threshold must be determined for each patient at his baseline treatment, and then once a week during the course of the treatment. Motor threshold may be determined by visual inspection. Yet, in any case that a twitch was observed at certain stimulator intensity in 3 out of 6 trials, the minimal threshold must be at or below this value.

16.2.3.2 Position the H-Coil over the patient's head at the appropriate location for the leg tibialis motor stimulation. The front end of the coil cover should intersect the cap's midline ruler at the midline ruler's 8 cm mark. The coordinate on the coil cover at which the cover intersects the cap's midline ruler must be "0" (Fig.11). The front end of the coil cover must be perpendicular to the cap's midline ruler.

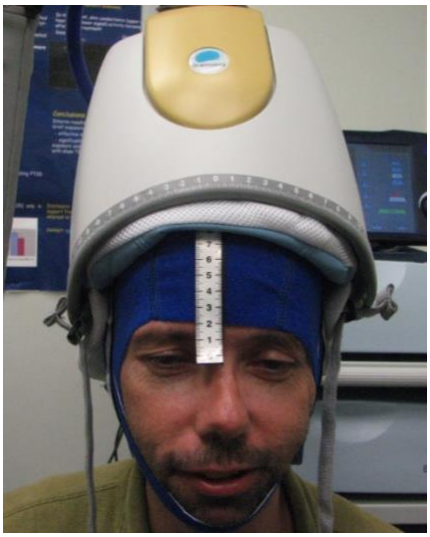


Figure 11: A demonstration of positioning the coil cover preparatory to MT determination.

16.2.3.3 Set the stimulator output to an initial value of 50%, and apply single pulses. Wait at least 5 sec between consecutive pulses. In case of no motor response, increase the power output in increments of 5%. Find the minimal threshold for motor activation at the initial position.

16.2.3.4 Find the exact location of the leg tibialis-associated motor cortex by fine displacement of the coil. The coil can be moved upward-downward by the arm, and backward-forward by the connection box axis (See Fig. 12). In addition the helmet can be rotated freely in three dimensions, and when desired the helmet

position and orientation can be fixed with the fixation screw (Fig. 12). Move the helmet in increments of 1 cm along lateral-medial and posterior-anterior axes, using the coordinates on the cap's rulers. After finding the threshold at a certain point, and moving the coil to a new point, gradually reduce the power output, until the threshold at the new location is found. The leg tibialis motor cortex is identified as the site of lowest stimulus intensity) or an observable twitch in the leg. The motor threshold is determined by the intensity of the stimulator at this site. Twitches in any digit muscles in three out of six stimulations may indicate that, the minimal threshold is at or below this value.

16.2.3.5 After finding an optimal position, move the coil 1 cm in each direction (right, left, front, back), and find where the threshold to elicit motor response is minimal.

16.2.3.6 For patients who have a difficulty to find resting leg motor threshold (rMT), the active leg motor threshold (aMT) (with the leg and toe extended) is generally lower than the resting motor threshold. Hence, for such patients, find the active MT (aMT). The resting MT (rMT) is on average higher by 15%. Hence, if for example a patient has aMT of 40% of the stimulator power output, the stimulation intensity, which is equivalent to 100% of the rMT, should be 115% of 40%, which is 46%.

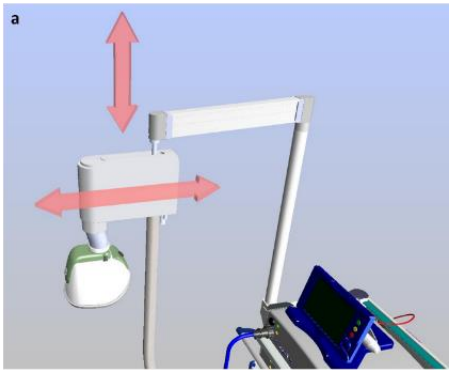


Figure 12: A Positioning Device with the HAC-Coil helmet, showing the means of displacement along the upward-downward and the antero-posterior axes.

16.2.4 Recording the MT location

16.2.4.1 Write down the value along the cap's midline ruler at which the ruler intersects the coil cover's front end. This value is denoted DN-MC (distance from nasion to motor cortex location). Also write down the value on the front end of the coil cover at this location. This value must always be 0.

16.2.4.2 Write down the value along the cap's lateral-medial ruler at which the ruler intersects the coil cover. Also write down the value on the coil cover at this location.

16.2.4.3 Write down the value along the cap's midline ruler at the patient's inion. This value is denoted DN-I (distance from nasion to inion).

16.2.4.4 The coordinates found in the previous sections can be used to position the coil for the next treatment. In future treatment sessions, the procedure of finding the intensity and location of the MT may be considerably shortened compared to the first treatment by initially positioning the coil at the recorded location of the leg motor cortex.

NOTE **Be careful in recording the MT coordinates. A mistake in recording these coordinates will result in an incorrect treatment location. To ensure that the coordinates are within the acceptable range, the distance from nasion to motor cortex location (DN-MC) should be larger than 3 cm and smaller than 15 cm.**

16.2.4.5 If the distance from nasion to motor cortex location (DN-MC) is smaller than 3 cm or larger than 15 cm, repeat stage 15.2.3.1 (to find the exact location of tibialis motor cortex).

16.2.5 Positioning the coil at the treatment location

16.2.5.1 Position the coil on the mid line of the head so that the coordinate on the coil cover at which the cover intersects the cap's midline ruler is "0". Move the coil 4 cm forward along the cap's midline ruler from the location found for the minimal MT for activation of the leg motor cortex.

16.2.5.2 Fix the coil to the patient's head at the treatment location, and fasten it loosely to the patient's head using the chin strap (Fig. 13).

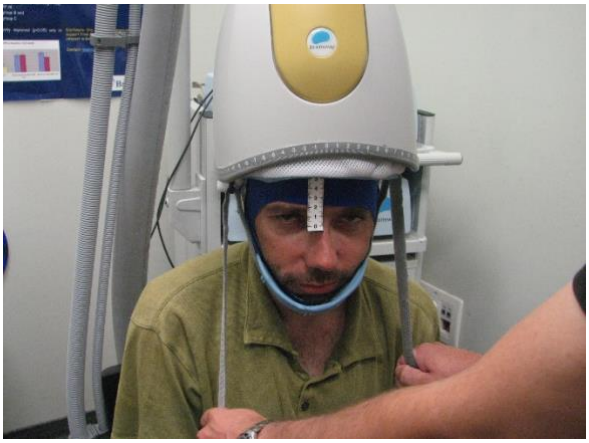


Figure 13: Fasten the coil to the subject's head using the chin strap.

16.2.5.3 Pull down the rear side of the coil cover so that the cover edge will be below the subject's inion (Fig. 14).

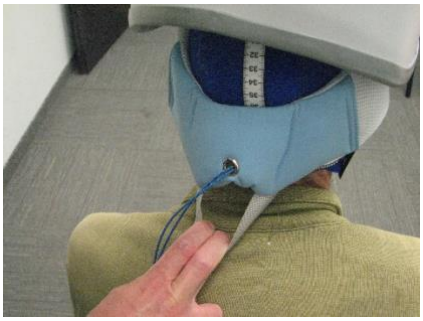


Figure 14: Pull down the rear side of the coil cover.

16.2.5.4 Attach the coil in the horizontal plane by pulling the two rear wires coming out of the rear black bead (Fig. 15).

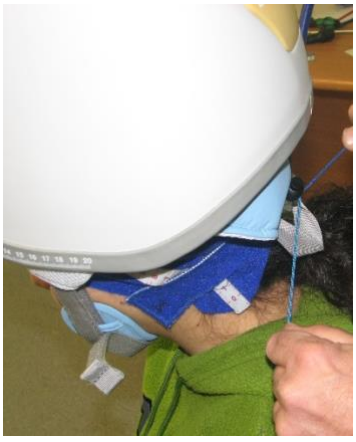


Figure 15: Pull the two rear wires coming out of the rear black bead.

16.2.5.5 A typical position of the helmet at the treatment location is shown in Fig. 16.

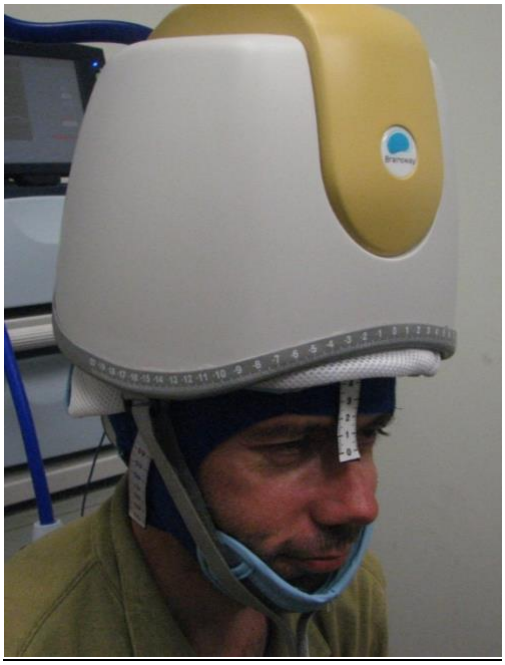
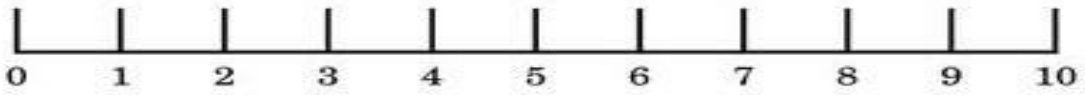


Figure 16: The coil helmet attached to the head at the treatment location.

16.2.6 Provocation induction

Prior to initiation of each treatment, OCD symptoms must be provoked for each subject in an individual manner for up to 5 minutes. The provocations are tailored towards the subjects' specific obsessions and compulsions created by the caregiver in a hierarchy format consisting of internal & external provocations. The operator then provokes the patient using this hierarchy as a guide to provoke. The symptom provocation must induce a stress level between 4-7 on a visual analog scale (VAS) in order to proceed with the DTMS treatment (as shown below).



(No Distress) (Extreme Distress)

16.2.7 Administration of Treatment

16.2.7.1 Turn on the cooling system, by pushing the power button at the front of the cooling system (Fig. 17). Wait two minutes before beginning a session. After

two minutes of operation the temperature displayed on the front panel of the cooling system should be below 14°C.

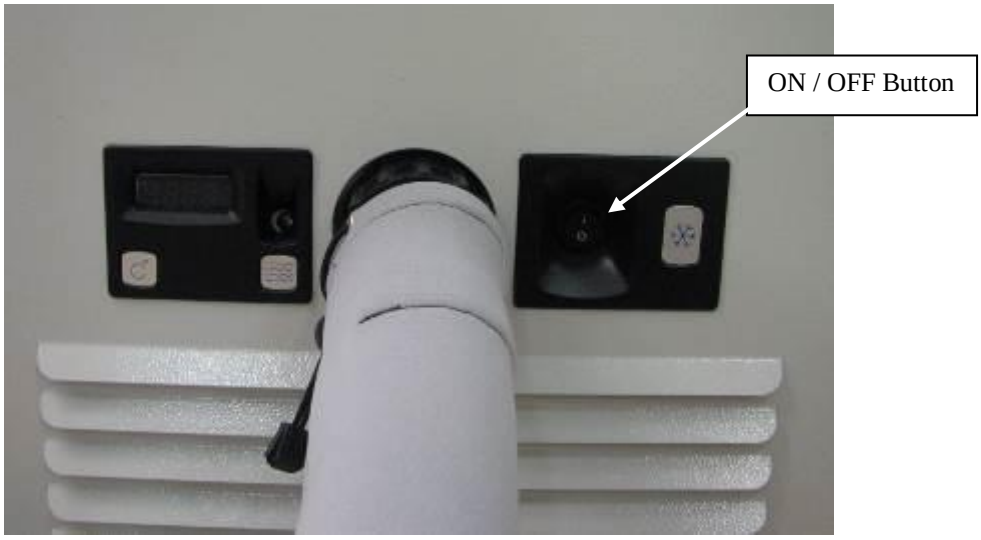


Figure 17: Operate the cooling system, by pushing the black power button.

NOTE

When the cooling system red light is lit (on the left panel) it indicates a high water level. Open the bottom lead in the front of the cart, pull out the water container, empty the water, slide it back to its place in the cart and close the panel, verify that the red light is off (Fig. 18).

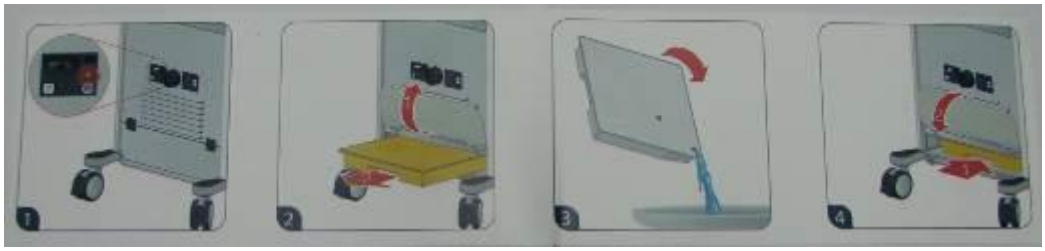


Fig. 18: water empty guide from cooling system

NOTE

Accurate placement of the coil is critical for the reproducible application of TMS. The treatment administration section assumes that MT location has already been determined for the specific patient. If not, return to Section 15.2.3, "Finding the Individual Motor Threshold". Consider re-evaluating the patient's motor threshold level in case of any change, e.g., change in

patient antidepressant medications, change in patient's hairstyle which may alter the distance from the coil to the patient's scalp.

NOTE **Make sure that both the system user (the operator) and the patient are wearing ear plugs during the treatment (the repetitive pulses).**

16.2.7.2 Apply one short trial train of 0.5 sec, 20 Hz, at a power output of 100% of the Leg MT. Test whether the patient responds well to the train. Ask the patient if the treatment is tolerable. In case of excessive motor activation or patient discomfort, move the coil up to 1 cm forward, and test whether the problem has resolved. After the maximum allowable forward displacement, the coil will be positioned such that its front end intersects the cap's midline ruler at the point marked 0 cm.

16.2.7.3 In case the patient has difficulty to sustain the trial train, treatment may be ramped up as follows, to increase patient comfort and help accommodate the treatment:

a. Apply a trial train of 0.5 sec, 20 Hz, at a power output of 100% of the MT.
b. Apply a trial train of 1 sec, 20 Hz, at a power output of 100% of the MT.
c. Apply a trial train of 2 sec, 20 Hz, at a power output of 100% of the MT.

NOTE **Remind the patient that scalp discomfort is attenuated with successive treatments.**

16.2.7.4 Apply the treatment according to the following preset treatment parameters:

Stimulator power output:

a. 100% of the measured leg motor threshold (MT).
b. Frequency: 20 Hz.
c. Train duration: 2 sec.

d. Inter-train interval: 20 sec.

e. Number of trains: 50.

NOTE

These treatment parameters serve as the default treatment setting for the Brainsway Deep TMS System and should be used as the treatment setting for all patients. These settings were used to establish safety and efficacy in the Brainsway Deep TMS System clinical trials.

16.2.7.5 During the treatment session the operator must keep a constant eye contact with the patient. Operator should monitor the patient and pay attention to any excessive motor activation or facial muscle activation, which may indicate a risk of seizure. In any case of excessive hand motor activation, the treatment must be stopped. In any case of excessive neck motor activation, the treatment must be stopped. In any case of excessive leg motor activation, the treatment must be stopped.

16.2.7.6 In any case of any motor activation which lasts after the end of the train, the treatment must be stopped and the treatment should be terminated.

NOTE

In case of emergency treatment may be immediately halted by pushing the RED stop button, on the stimulator UI screen. If a seizure occurs, follow your institution's standard operating procedures for first response emergency.

16.2.7.7 Remind the patient that the Brainsway Deep TMS treatment will cause clicking sound and may produce a tapping sensation on the head. This discharge click may startle.

16.2.7.8 During the treatment, monitor the temperature displayed on the stimulator UI screen. In the event of overheating, the stimulator software should disable the system's operation. If this occurs, release the H-Coil's chin strap and remove the coil from the patient's head. The cooling system will cool the coil to normal temperature within three minutes and then the coil may be replaced on the patient's head and treatment may be resumed.

16.2.7.9 In case the stimulator stopped in the middle of a session without any indication of overheating, resume the session by pushing the icon “Resume” on the stimulator UI screen.

16.2.7.10 Acetaminophen or other medications may be administered for the treatment of local pain, dental pain or headaches as necessary.

16.2.7.11 At the end of each treatment, turn off the cooling system.

16.2.7.12 At the end of the day of treatment, turn off the stimulator.

17. MAINTENANCE & CALIBRATION

Each coil should be returned to Brainsway every three years for a thorough examination. Brainsway will send a reminder regarding the required replacement two months prior to the expiry of the three-year period.

For stimulator maintenance and calibration please refer to the stimulator user’s manual.

18. CLEANING

The coil helmet, positioning device, cart and stimulator components may be cleaned using an isopropyl alcohol-moistened cloth. Ensure that the equipment has dried thoroughly before use.

19. LIFE EXPECTANCY

The life expectancy of the deep TMS system is ten years. This period includes replacement of accessories such as coils and cooling system.

Brainsway will keep track of replacement dates and will take care of replacement of any required component as part of the routine service procedure.

20. TROUBLESHOOTING

If the unit fails to operate normally, check the following points to determine whether the fault can be corrected by the simple measures suggested below. If it cannot be corrected, or if the fault is not listed in the malfunction column, disconnect the power cord and contact your service center at Brainsway Ltd for assistance.

Malfunction	Troubleshooting
Session stopped without over-heating	In case the stimulator stopped in the middle of a session without any indication of overheating, resume the session by doing the following: Push the red STOP button, push the green ARM button, and push the icon "Resume" on the stimulator UI screen. The session will proceed from where it stopped.
Session stopped due to coil over-heating	If the session stopped and there is an indication of over-heating on the stimulator screen, release the H-Coil's chin strap and remove the coil from the patient's head. The cooling system will cool the coil to normal temperature within three minutes and then the coil may be replaced on the patient's head and treatment may be resumed. Interruption of up to 5 min is not considered a protocol deviation.
H-Coil Falls	Contact Brainsway immediately and send the coil to Brainsway for a thorough examination. Continued use of the coil after a fall might result in a malfunction.

21. User Assistance Information

In the occurrence of any malfunction, please contact Brainsway:

Brainsway LTD:
19 Hartom St., Bynet Building, Har Hotzvim,
Jerusalem, 9777518, POB 45169,
Israel
Tel: +972-2-582-4030
Fax: +972-2-581-2517

Brainsway USA Offices:
2-98 Decker Blvd, Bala Cynwyd,
PA 19004
USA
Tel: 1-844-3867-001 or 1-844-DTMS-001
Fax: 1-844-3867-002 or 1-844-DTMS-002

European Authorized Representative:
Obelis s.a.
Bd. General Wahis 53, 1030 Brussels,
Belgium
Tel: +32-2-732-59-54
Fax: +32-2-732-60-03
Email: mail@obelis.net

APPENDIX A: CLINICAL STUDY RESULTS

Following is a summary of the effectiveness of the Brainsway Deep Transcranial Magnetic Stimulation (DTMS) device based on the clinical study results.

The Brainsway DTMS device has demonstrated a positive, statistically significant and clinically meaningful benefit for the treatment of OCD, based on the primary efficacy endpoints of the multicenter, clinical study and supported by the secondary efficacy endpoints.

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 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, etc.) 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.

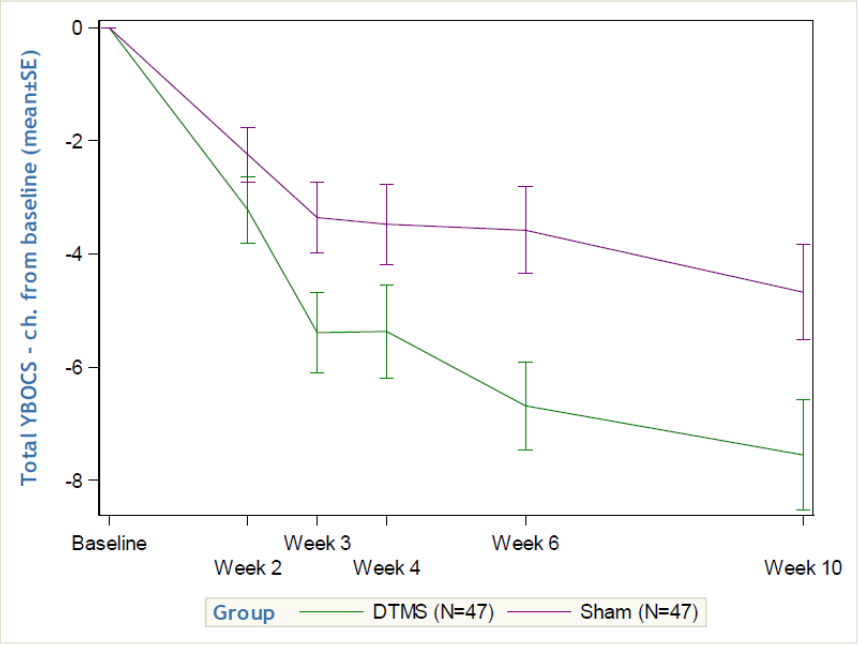


Figure 2: YBOCS Change From Baseline Over Time (mITT)

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 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 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.

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).

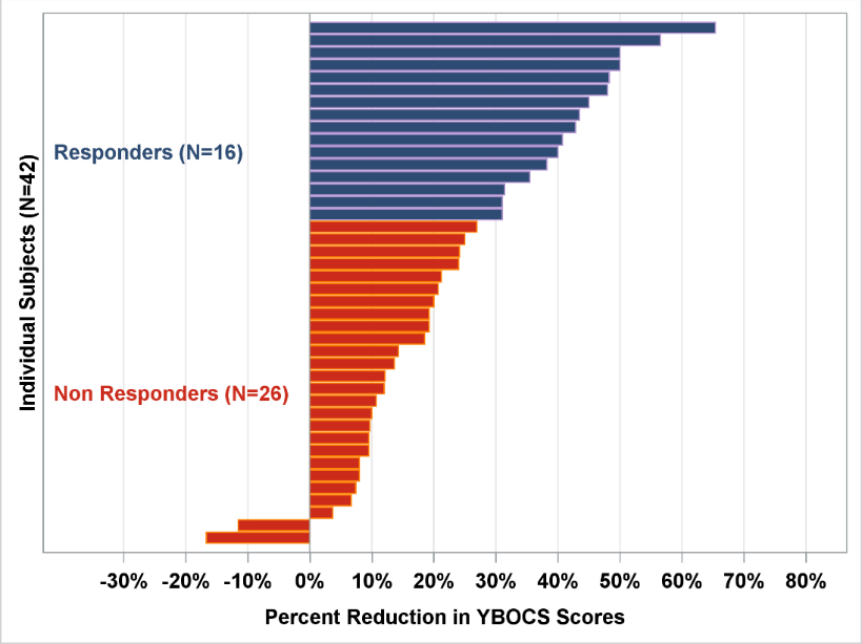


Figure 3: Percent Reduction in YBOCS Scores for DTMS subjects (mITT)

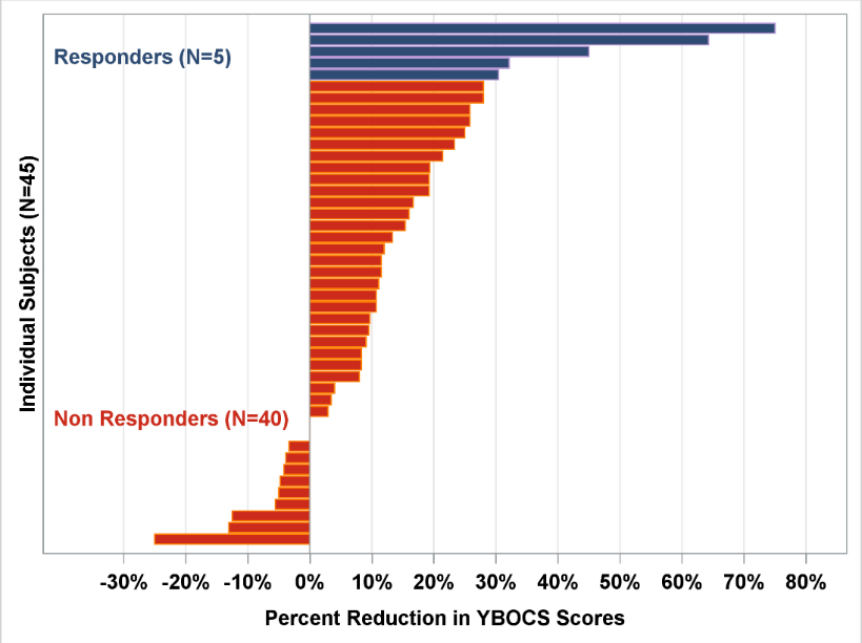


Figure 4: Percent Reduction in YBOCS Scores for Sham subjects (mITT)

Conclusions/Summary

The positive effect of the Brainsway treatment based on the primary efficacy endpoint of change from baseline in YBOCS score was further corroborated by the success of additional secondary efficacy endpoints, including responder analysis, additional supporting OCD assessment scales (CGI Improvement and CGI Severity) and change from baseline in YBOCS scores at 10 weeks (4 weeks following completion of treatment – as described above), thus supporting the consistency of the clinical effect.

The responder results are clinically meaningful, as demonstrated by the effect size expressed in terms of Number Needed to Treat (NNT). Based on the study response rates, the effect size as obtained by the Number Needed to Treat (NNT = (1/difference in response rates) is 3.7, with a 95% confidence interval of 3 to 11. This means that the number of patients that need to be treated with the Brainsway Deep TMS System for one of them to benefit (i.e., have at least a 30% reduction in their YBOCS scores) as compared to treatment with sham DTMS is 4, and that there is a 95% probability that the NNT will be between 3 and 11 in a future identical study.

The Response rate at the 10 week visit was 45.2% in the DTMS group compared to 17.8% in the Sham group. There was also a further increase in the response rate at the 10 week visit (45%) in the DTMS group compared to the 6 week visit (38%), demonstrating a further positive treatment effect maintained over time. The effect size as obtained by the Number Needed to Treat (NNT) was 3.64, which still means that for every 4 patients treated with the Brainsway Deep TMS System, 1 subject will have a response due to the device.

The clinical study has further demonstrated a clear benefit derived from the safety profile of the device. Safety and tolerability of the DTMS treatment were demonstrated during the course of the study, with no differences found in vital signs, physical and neurological examinations, SSI assessments, cognitive examinations (MMSE, BSRT and AMI-SF) and adverse event reporting, between the DTMS treatment and the Sham treatment.

The Brainsway DTMS treatment is well tolerated by OCD patients. The most frequent AE was headache reported by 37.5% of the subjects who received the DTMS treatment, and by 35.3% of the patients 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, etc.) were reported as either mild or moderate and mostly resolved after treatment with or without analgesic medications (e.g. Paracetamol, Ibuprofen). In most of the subjects the discomfort or pain disappeared once the subject became accustomed to the treatment. The clinical study demonstrated that the vast majority of the study subjects either did not experience adverse events or tolerated the side effects of the treatment.

More than 80% of the study subjects received at least 27 out of the 29 treatments and more than 70% of the study subjects received at least 28 out of the 29 treatments. Note that the protocol allowed subjects to miss up to 3 treatments out of the 29 daily treatment sessions. The high percentage of study subjects adhering to the treatment regimen and receiving the required 26 treatments, indicates a treatment that is easily tolerated and supports high compliance.

Medications for the treatment of OCD have considerable side effects, such as stomach upset, sleep disturbance, sweating and reduced interest in sexual activity, with a notable percentage of patients (40-60%) have a partial or no response to medications. The onset of improvement in OCD symptoms may take weeks to months after starting a medication.

In conclusion, The Brainsway DTMS device has demonstrated a positive, statistically significant and clinically meaningful benefit for the treatment of OCD, based on the primary efficacy endpoints of the multicenter, clinical study and supported by the secondary efficacy endpoints.

APPENDIX B: TRANSCRANIAL MAGNETIC STIMULATION SAFETY QUESTIONNAIRE (TASS)

1. Have you ever had an adverse reaction to TMS?	☐ NO	☐ YES
2. Have you ever had a seizure?	☐ NO	☐ YES
3. Have you ever had an EEG?	☐ NO	☐ YES
4. Have you ever had a stroke?	☐ NO	☐ YES
5. Have you ever had a head injury (include neurosurgery)?	☐ NO	☐ YES
6. Do you have any metal in your head (outside of the mouth,) such as shrapnel, surgical clips, or fragments from welding or metalwork?	☐ NO	☐ YES
7. Do you have any implanted devices such as cardiac pacemakers, medical pumps, or intracardiac lines?	☐ NO	☐ YES
8. Do you suffer from frequent or severe headaches?	☐ NO	☐ YES
9. Have you ever had any other brain-related condition?	☐ NO	☐ YES
10. Have you ever had any illness that caused brain injury?	☐ NO	☐ YES
11. Are you taking any medications?	☐ NO	☐ YES
12. If you are a woman of childbearing age, are you sexually active, and if so, are you not using a reliable method of birth control?	☐ NO	☐ YES
13. Does anyone in your family have epilepsy?	☐ NO	☐ YES
14. Do you need further explanation of TMS and its associated risks?	☐ NO	☐ YES

NOTE: A positive screen is any `YES' answer and indicates further investigation by the clinician (but not indicating exclusion from TMS).