A Prospective, Double Blind, Randomized, Controlled Study to Evaluate the Safety and Efficacy of the Deep Transcranial Magnetic Stimulation (DTMS) (with the H-ADD Coil) intended as an aid to Smoking Cessation

Protocol BR-SMOK-01

Date: May 20, 2019

Document No.: BR-SMOK-01

Version No.: Ver 4

APPROVALS:

Name	Position	Date	Signature
Ahava Stein	Regulatory & Clinical Consultant	20 May 2019	Ahava Stein
Prof. George	Principal Investigator	20 May 2019	
Avraham Zangen	Principal Investigator	20 May 2019	

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ABBREVIATIONS

AE adverse event

APB abductor pollicis brevis

BSRT Buschke Selective Reminding Test

CQR Continuous Quit Rates

CRF Case Report Form

FTND Fagerstrom Test of Nicotine Dependence

GCP Good Clinical Practice

ICH International Conference on Harmonization

IEC Independent Ethics Committee

IEC/IRB Independent Ethics Committee/Institutional Review Board

IRB Institutional Review Board

MMSE Mini-Mental State Exam

MNWS Minnesota Nicotine Withdrawal Scale

MT motor threshold

NCI National Cancer Institute

PFC prefrontal cortex

SCID Structured Clinical Interview for DSM Diagnosis

TASS Transcranial Magnetic Stimulation Safety Questionnaire

TCQ-SF Self-administered Tobacco Craving Questionnaire

TMS Transcranial Magnetic Stimulation

1. STUDY SYNOPSIS

Name of Device: Brainsway Deep Transcranial Magnetic Stimulation (DTMS) device (H-ADD Coil).

Device Description: The Brainsway DTMS device is intended as an aid to smoking cessation. The device technology is based on the application of Deep TMS by means of repetitive pulse trains at a determined frequency.

Objectives: The aim of the study is to evaluate the safety and efficacy of DTMS compared to sham treatment as an aid to smoking cessation in chronic (≥10 cigarettes/day) cigarette smokers.

Patient Population: The intention is to enroll a minimum of 224 subjects. The subjects will be of all racial, ethnic and gender categories, ranging from 22 to 70 years of age. Patients will be recruited from both academic and private research centers.

Structure: The study is a randomized, prospective, 4 month, double blind, multicenter study (see study flow chart in Attachment 1).

Blinding: The treatment administrator, study rater, all study personnel and subjects will be masked to the treatment being administrated**.**

Concurrent Control: The study group will receive active DTMS treatment and the control group will receive inactive, sham treatment.

Sample Size: A maximum of 270 subjects (135 in each treatment group) from approximately 20 sites will be enrolled in the study.

Study Objectives:

Primary Objective:

The primary objective is to compare the four-week continuous quit rate (CQR), representing abstinence during a consecutive 4 week period, between the two treatment groups. Weekly abstinence is defined as a subject's self-report (in diary) of no smoking (0 cigarettes/day during the whole week), confirmed by urine cotinine levels ≤200ng/ml. A missing confirmatory test will be considered negative, if the previous and the following weekly or 4 month follow-up confirmatory tests are negative. Quit rates are defined as the ratio of the number of patients meeting the quit criterion for at least 4 consecutive weeks to the number of patients initially treated and having at least one post-baseline assessment.

Secondary Objectives:

- To compare the four-week continuous quit rate (CQR), representing abstinence during a consecutive 4 week period, between the two treatment groups. Weekly abstinence is defined as a subject's self-report (in diary) of no smoking (0 cigarettes/day during the whole week), confirmed by urine cotinine levels <200ng/ml. A missing confirmatory test will be considered negative, if the previous and the following weekly or 4 month follow-up confirmatory tests are negative. Quit rates are defined as the ratio of the number of patients meeting the quit criterion for at least 4 consecutive weeks to the total number of patients having assessments during a consecutive 4 week period.
- The secondary objective is to compare number of cigarettes smoked per day (per diary data) for all subjects.

Exploratory Objectives:

- Weekly point prevalence abstinence rates.
- Number of cigarettes smoked per day (per diary data) for non-quitter subjects only.
- Effect on withdrawal symptoms as measured by weekly scales measuring nicotine craving and dependence/withdrawal, including the Fagerstrom Test for Nicotine Dependence (FTND), Minnesota Nicotine Withdrawal Scale Self-Report (MNWS), Tobacco Craving Questionnaire–Short Form (TCQ-SF) and Nicotine Craving Scale.

Safety Objectives:

- To evaluate the incidence, severity and frequency of all Adverse Events (AE), related and unrelated to the device treatment, including seizures.
- To evaluate possible cognitive changes using the Mini Mental State Exam (MMSE) and the Buschke Selective Reminding Test (BSRT) cognitive tests.
- Vital signs and hearing loss measured by auditory threshold testing will be evaluated.

Study Sponsor: NIDA, Brainsway Ltd.

Principle Investigators: Drs. Mark George, Kathleen Brady and Abraham Zangen

2. INTRODUCTION

2.1. General

Smoking is the leading cause of preventable deaths in the world. Tobacco use causes more than 5 million deaths per year worldwide (http://www.who.int/tobacco/health_priority/en/). Each year, an estimated 443,000 people die prematurely from smoking or exposure to secondhand smoke, and another 8.6 million live with a serious illness caused by smoking. Despite these risks, approximately 46.6 million U.S. adults smoke cigarettes (http://www.cdc.gov/chronicdisease/resources/publications/aag/osh.htm).

Smoking is not merely a destructive habit, but also a serious addiction. Most smokers use tobacco regularly because they are addicted to nicotine (Abuse, 2009). Addiction can be described as a persistent state in which there is diminished capacity to control compulsive drug-seeking, regardless of whether it involves risk of negative consequences (Hyman and Malenka, 2001). It is well documented that most smokers identify tobacco use as harmful and express a desire to reduce or stop using it and nearly 35 million of smokers want to quit each year. Unfortunately, more than 85 percent of those who try to quit on their own relapse, most within a week. New treatments for tobacco addiction are essential to help curtail the public health burden that tobacco use represents (Abuse, 2009).

2.2.Treatment

Smoking cessation can be achieved with or without assistance from healthcare professionals or the use of medications. Methods that have been found to be effective include interventions directed at or via health care providers and health care systems; medications including nicotine replacement therapy (NRT), Bupropion and nicotine receptor partial agonists (e.g., cytisine and varenicline); individual and group counseling; and Web-based or stand-alone and computer programs.

Nicotine replacement therapy (NRT) approved by the FDA, exists in the form of a patch, gum, lozenges, spray and inhalers and delivers nicotine in a form that does not involve the risks of smoking. NTRs are meant to be used for a short period of time and should be tapered down to a low dose before stopping.

Bupropion is FDA-approved and is marketed under the brand name Zyban. Bupropion approximately doubles the chance of quitting smoking successfully after three months. One year after treatment, the odds of sustaining smoking cessation are still 1.5 times higher in the bupropion group than in the placebo group. The evidence that is available suggests that bupropion is comparable to nicotine replacement therapy, but somewhat less effective than varenicline (Chantix) (Wu et al 2006). Epileptic seizures are the most important adverse effect of bupropion. The most common adverse effects are dry mouth, nausea, insomnia, tremor, excessive sweating and tinnitus and less common adverse effects include unusual behavior changes, depression, agitation and hostility.

Cytisine (Tabex) is a plant extract that has been in use since the 1960s in former Soviet-bloc countries. It was the first medication approved as an aid to smoking cessation, and has very few side effects in small doses.

Varenicline tartrate is a prescription drug marketed by Pfizer as Chantix in the U.S. (under FDA approval) and as Champix outside the U.S. Synthesized as an improvement upon cytisine, varenicline decreases the urge to smoke and reduces withdrawal symptoms. Two systematic reviews and meta-analyses supported by unrestricted funding from Pfizer, one in 2006 (Wu et al 2006) and one in 2009 (Mills et al 2009), found varenicline more effective than NRT or bupropion. A 2011 review of double-blind studies found that varenicline has increased risk of serious adverse cardiovascular events compared with placebo (Singh et al 2011). Varenicline may cause neuropsychiatric side effects; for example, in 2008 the U.K. Medicines and Healthcare products Regulatory Agency issued a warning about possible suicidal thoughts and suicidal behavior associated with varenicline (Drug Safety Update 2008).

Alternative approaches to smoking cessation include acupuncture, hypnosis, smokeless tobacco, electronic cigarettes, as well as other therapies. These methods are not legitimate smoking cessation aids as scientific studies showed no difference between these methods and placebo or no rigorous, peer-reviewed studies have been conducted.

2.3.Transcranial Magnetic Stimulation

The subjective and physiological effects of smoking are caused by the central actions of nicotine (Jarvik et al., 2000), the primary constitute of tobacco. Nicotine, like other drugs of abuse, activates the mesolimbic dopamine system, which originates in the ventral tegmental area (VTA) and projects to reward-related brain areas such as the prefrontal

cortex (PFC), nucleus accumbens (NAc), amygdala and hippocampus (Vizi and Lendvai, 1999). Decreased activity of the brain reward system during nicotine withdrawal has been associated closely with craving, relapse and continued nicotine consumption (Epping-Jordan et al., 1998). Repeated drug administration induces neuroadaptations associated with abnormal dopaminergic activity in the mesocorticolimbic circuitry, resulting in altered cortical neurotransmission and excitability (Feil and Zangen, 2010).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive means of stimulating cortical neurons (Wassermann and Lisanby, 2001). Repetitive TMS has been tested as a treatment of various neuropsychiatric disorders associated with abnormal dopamine activity and altered cortical excitability (Feil and Zangen, 2010). Low-frequency rTMS ($\sim$1 Hz) induces in most cases a decrease in cortical excitability, whereas high-frequency rTMS (>5 Hz) generally increases excitability (Feil and Zangen, 2010; Hoogendam et al., 2010).

Several lines of evidence suggest that rTMS over the prefrontal cortex (PFC) can affect processes involved in nicotine addiction. First, animal studies demonstrated that rTMS to the frontal regions of rats enhanced release of dopamine in the hippocampus and NAc (Keck et al., 2002; Zangen and Hyodo, 2002). Moreover, high-frequency rTMS of the human prefrontal cortex (PFC) has been shown to induce dopamine release in the caudate nucleus (Strafella et al., 2001). Hence, it has been suggested that high-frequency rTMS may be useful in disorders associated with subcortical dopamine dysfunction, such as addiction (Strafella et al., 2001).

Secondly, stimulation of the dorsolateral PFC (DLPFC) can affect cue-induced craving. A single session of rTMS of the left DLPFC inhibits craving induced by the presence of appetitive food (Uher et al., 2005) and course of rTMS sessions of the left DLPFC inhibits craving induced by smoking related cue (Amiaz et al., 2009). Direct current stimulation (DCS) of both left and right DLPFC reduces alcohol (Boggio et al., 2008) and nicotine (Boggio et al., 2008) craving induced by drug-associated cues.

Addiction represents the pathological usurpation of neural processes that normally serve reward-related learning and, hence, it may be considered as a strong habitual memory (Hyman et al., 2006). There is ample evidence suggesting that upon their retrieval, established memories, like addiction, become labile and enter a transient state, in which they can be changed, weakened or erased (Nader et al., 2000; Dudai, 2006; Lee et al., 2006). The rationale for stimulating the DLPFC immediately after presentation of

drug/food-associated cues is that such stimulation would reactivate the addiction memory traces, causing them to be labile for interference by rTMS.

Thirdly, the DLPFC is involved in decision-making processes (Rorie and Newsome, 2005). These processes are altered by direct current stimulation of both left and right DLPFC (Fecteau et al., 2007) and increased risk taking by low-frequency rTMS over the right DLPFC (Knoch et al., 2006).

Addiction is associated with increased impulsivity and risk-taking leading to altered decision-making processes (Knoch et al., 2006). Therefore, high-frequency rTMS of the right DLPFC might reduce impulsivity and enhance inhibitory control, which can lead to a reduced consumption of cigarettes.

Several human studies have begun to evaluate the effects of rTMS protocols applied to the PFC on drug craving and consumption in nicotine (Eichhammer et al., 2003; Johann et al., 2003; Amiaz et al., 2009, Li et al, 2013 and Wing et al 2012). Johann and colleagues (Johann et al., 2003) reported decreased levels of tobacco craving after single rTMS session over the left DLPFC. In addition, a single session of rTMS over the right DLPFC can reduce cocaine craving (Camprodon et al., 2007). Eichhammer and colleagues (Eichhammer et al., 2003) in a cross-over, double-blind, placebo-controlled study demonstrated a reduction in cigarette consumption (measured 6 hours following treatment) but craving levels remained unchanged after two rTMS sessions over the left DLPFC. Amiaz and collegues (Amiaz et al., 2009) found that 10 days of high-frequency rTMS over the DLPFC reduced cigarette consumption and nicotine dependence. In addition, the rTMS blocked craving induced by smoking cues. However, the effect tended to dissipate after the 10 daily sessions and the reduction in cigarette consumption was not significant 6 months after treatment termination. Moreover, only 10% among those responded to the treatment had quit totally from smoking (Amiaz et al., 2009). Li et al (Li et al 2013) treated subjects with real high-frequency rTMS or sham TMS over the DLPFC in two visits with 1 week between visits. The participants received cue exposure before and after rTMS. Stimulation of the left DLFPC with real rTMS reduced craving significantly from baseline. When compared with neutral cue craving, the effect of real TMS on cue craving was significantly greater than the effect of sham TMS. More decreases in subjective craving induced by TMS correlated positively with higher Fagerström Test for Nicotine Dependence score and more cigarettes smoked per day. These four studies demonstrate that high-frequency rTMS of the DLPFC can attenuate nicotine consumption (Eichhammer et al., 2003; Amiaz et al., 2009) and craving (Johann

et al., 2003; Li et al 2013). However, the significance and duration of these effects are limited and further investigation is required to identify the appropriate stimulation parameters and targets needed to enhance the effectiveness of such treatment.

One possible reason for these partial effects on nicotine consumption might be the superficial magnetic stimulation by the figure-8 coil, which does not reach into the deep layers of the cortex. It is known that nicotine addiction involves various areas of the brain reward system, in which most of them are deeper than the superficial layers of the cortex, like the anterior cingulated, orbitofrontal cortex, nucleus accumbens, and amygdala.

Another area of interest which was not stimulated using the superficial rTMS is the insula. A recent study explored the role of insula damage in addiction. In a retrospective design assessing changes in cigarette smoking after brain damage, results revealed that smokers with brain damage involving the insula were significantly more likely than smokers with brain damage not involving the insula to undergo a disruption of smoking addiction (Naqvi et al., 2007). This finding is consistent with the crucial role of the insula in cravings for food, cocaine and cigarettes, as reported by neuroimaging studies (Bonson et al., 2002; Pelchat et al., 2004; Wang et al., 2007), and with the role of the insula in processes related to decision-making (Naqvi and Bechara, 2010). Therefore stimulating the insula and the deeper layers of the lateral PFC could be substantially more effective in treating nicotine addiction.

2.4.Brainsway's Deep Transcranial Magnetic Stimulation.

Given these theoretical, animal and preliminary human data, we hypothesized that a course of deep high-frequency using a specific coil for deep stimulation, over the right and left lateral PFC and insula may reduce impulsivity, nicotine dependence, and craving for cigarettes in response to smoking-related cues as well as cigarette consumption. Deep Transcranial Magnetic Stimulation (DTMS) is a new form of TMS which allows direct stimulation of deeper neuronal pathways than standard TMS. This new form of TMS makes use of Brainsway's novel H-coils which are designed to allow deeper brain stimulation related to the control of motivation, reward and pleasure, specifically, fibers connecting the DLPFC and the insula, without a significant increase of electric fields induced in superficial cortical regions, as tested on a phantom brain (Roth, 2002).

A preliminary study using the DTMS system was conducted at Beer Yaakov Mental Health Center (Beer Yaakov, Israel) in which 115 subjects were randomized to one of six

study arms (Sham, 1Hz and 10Hz, with and without smoking cue). The main objective of the current study was to evaluate the efficacy and safety of Deep TMS for Smoking Cessation and Nicotine addiction in subjects suffering from COPD. The Deep TMS treatment efficacy was verified both by objective urine Cotinine levels and subjective self-reported number of cigarettes smoked. Results were available for 77 subjects. Evaluation of the change in Cot/Cre, adjusted to the baseline measurement of Cot/Cre revealed a significant reduction in cotinine levels in the 10Hz stimulation groups (with and without smoking cue). Sham and 1Hz treatment groups did not show a significant reduction. Evaluation of the adjusted mean of the change in smoked cigarette numbers according to the self-report revealed a significant reduction in all study groups. Two-way ANCOVA analysis revealed a significant treatment effect. Greater degree of reduction was found in the 10Hz groups (with and without smoking cue) compared with the Sham and 1Hz groups, which is consistent with the results found for the change in urine Cotinine levels. A good correlation (Pearson) between the objective urine test and the self-reported endpoint was observed in the 10Hz groups (with and without smoking cue) and the Sham with smoking cue group. Response was defined as a reduction of at least 50% in self-reported number of cigarettes smoked on the last TMS session relative to screening day. Response rates for the 10 Hz stimulated groups were superior to both the 1Hz and the Sham groups. Abstinence rates were calculated according to both, self-reported number of cigarettes smoked on the last TMS session and by cotinine measurements. All self-reported abstinence rates were confirmed by cotinine measurements. Abstinence rates were much greater for the 10Hz with smoking cue and 10Hz without smoking cue groups than the Sham and 1Hz groups. The abstinence rate in the 10Hz with smoking cue group was higher (although not statistically significant) compared with 10Hz without smoking cue group, indicating an effect of the smoking cue before each treatment of the high frequency stimulation on abstinence. Taking into account the four different outcomes the most effective results were observed in the 10Hz group with smoking cue. Overall the treatment was well tolerated and without significant side effects, except for headaches which are expected, transient and resolved shortly after the treatment. No serious adverse events were reported. This study demonstrated the safety of the Deep TMS treatment, as well as the therapeutic effects in an addiction that is notoriously difficult to treat.

Given the absence of an effective treatment for smoking cessation, and in view of the results of the above preliminary study, an additional randomized, controlled study with

10Hz deep stimulation with smoking cues compared to sham stimulation (with smoking cues) may reveal a beneficial effect of DTMS on smoking cessation. To this end, we propose the randomized, controlled, blinded study described in this protocol be conducted to examine the safety and effectiveness of DTMS as an aid to smoking cessation.

3. DEVICE DESCRIPTION

3.1.General Device Description

The HADD-Coil Deep TMS (DTMS) System is composed of the following main components:

1. Helmet containing an active TMS Coil (HADD-Coil), and a sham coil
2. TMS Neurostimulator
3. Cooling System
4. Positioning Device
5. Cart
6. Controller
7. Personal Cap

The Brainsway DTMS System is illustrated in Figure 1 below.

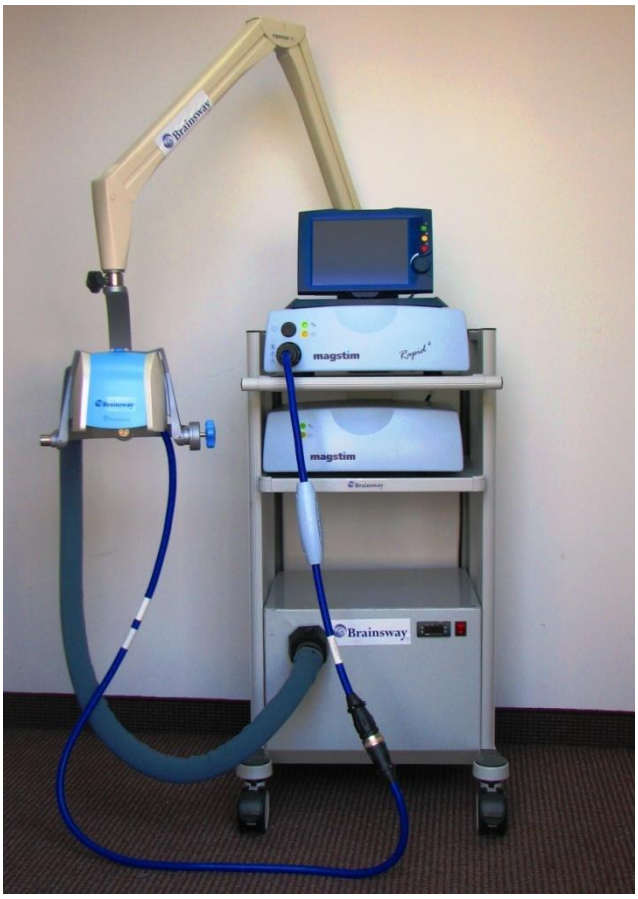

Fig. 1: An illustration of the Brainsway DTMS system

1. The HADD Real Coil

The HADD Coil is designed to stimulate neuronal pathways in the prefrontal and insular cortices.

The HADD-Coil is made of insulated copper wires. The total length is 800 cm, winded into 11 windings and connected in series. The effective part of the coil, in contact with the patient's head has a shape of half a donut. The frame of the inner rim of the half donut is flexible in order to fit the variability in human scalp 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 neurostimulator. In addition, a temperature sensor is included with an appropriate cable.

2. The Sham Coil

The Sham Coil is designed to mimic the auditory artifact and the scalp sensations evoked by the real HADD coil, and to produce activation of facial muscles similar to the effect of a real HADD coil, without stimulating the brain itself. It is encased in the same helmet along with the active coil.

The Sham Coil is made of insulated cupper wires. The total length is 650 cm, winded as a toroid. The windings are connected to a Magstim cable and a connector. This connector can be connected to the Magstim Rapid stimulator. In addition, a temperature sensor is included with an appropriate cable**.**

3. Commercial TMS Neurostimulator

A commercial TMS neurostimulator, the Magstim Rapid or the Magstim Rapid2, is used to deliver electrical stimulation to the brain, enabling a controlled output, frequency, pulse duration and indication of coil temperature.

The Magstim Rapid and Rapid2 stimulators were cleared by FDA (K992911 and K051864) for peripheral nerve stimulation. The detailed technical specifications of the Magstim Stimulator are available on the Magstim Ltd site (www.magstim.com). In addition to detailed information regarding the specific Magstim TMS stimulator, the website provides an overview of the magnetic stimulation technique, including principles of operation, as well as the clinical applications now feasible, listing about 500 relevant papers.

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

5. The Positioning System

The positioning system includes a helmet that comprises the coils, an adjustable arm (Haseke, Germany) 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.

3.2.Rationale for the Brainsway H1-Coil Deep Brain rTMS

Transcranial magnetic stimulation (TMS) is a non-invasive technique used for treating smoking cessation by stimulating the brain, as described above. However, the standard figure-8 coils have been shown to have a major effect mostly confined to the superficial cortical regions under the windings of the coil. The intensity of the electric field decreases rapidly deeper in the brain (Eaton, 1992; Maccabee et al, 1990; Tofts, 1990; Tofts et al, 1991). Therefore, in order to stimulate deep brain regions, a very high intensity is needed. Such intensity cannot be reached by the magnetic stimulators available today, using standard circular or figure-8 coils. Moreover, the intensity needed to effectively stimulate deeper brain regions would over-stimulate cortical regions leading to undesirable side effects.

The innovative DTMS system was thus developed by Brainsway Ltd. and intended for deep brain stimulation as an aid to smoking cessation. Mathematical models in conjunction with tests performed in a phantom model and clinical studies demonstrated the ability of the system to stimulate, by means of the HADD-Coil, deep brain regions. We hypothesize that the activation of deep brain regions and their interconnecting fibers may serve as a new approach in the treatment of neuropsychiatric illnesses with a prominent advantage over the standard coil which is unable to affect regions as deep as the HADD-Coil.

3.3.Intended Use

The Brainsway DTMS device is intended as an aid to smoking cessation.

3.4.Principles of Use

The HADD-Coil device technology is based on applying deep brain TMS by means of repetitive pulse trains at a determined frequency. A pre-selected treatment protocol is assumed to activate deep brain regions and their interconnecting fibers. This, in turn, may affect the mechanisms involved in the pathophysiology of mental illnesses on one hand, as well as the rewarding circuits, motivation and pleasure on the other hand.

The treatment protocol will start with localization of the optimal spot on the scalp for stimulation of the right abductor pollicis brevis muscle and determination of the individual motor threshold. The coil will then be placed 6 cm anterior to the motor spot.

Each daily treatment session will consist 60 rTMS trains of 10 Hz for 3 seconds with inter-train interval (ITI) of 15 seconds (a total of 1800 stimuli per session) over the prefrontal and insular cortices. Subjects in the control group will receive sham treatment in a similar manner. In the inactive sham treatment, some of the HADD-Coil windings are disconnected and no electric current flows through them. Additionally, the HADD-Coil windings are connected in series to a secondary coil, which is located at the connection between the cooling air pipe and the helmet, far from the patient head. The role of the secondary coil is to increase the auditory output and increase the overall coil inductance. Increasing the inductance leads to a decrease in the output electric field of the coil in the sham mode.

3.5.Study Procedure

The detailed procedures are described in the Instructions for Use in the Investigator's Brochure filed in the study center file. Following is a brief summary. The transition between active and sham modes is performed using a magnetic card reader controller. Prior to treatment, the operator must determine the position for the optimal APB motor cortex stimulation (in which the minimal stimulation intensity is required to induce visible motor activation). The operator inserts his operator card into the card reader to activate the real mode. After finding the position on the subject's head which requires the minimal stimulator output for reaching the motor threshold for

activation of the APB, the operator measures the location on the p subject's cap, using the cap's flexible ruler, as explained in the Instructions for Use in the Investigator's Brochure. The operator then moves the coil to the treatment location and attaches it to the subject's head, as explained in the Instruction for Use. The operator inserts the subject's treatment card programmed to activate either real or sham treatment mode according to the treatment group to which the patient has been randomized. The study personnel do not have any knowledge of whether the treatment mode or sham mode is being activated by the subject's treatment card. Thus, all study personnel, including the operator, the independent rater and study subjects will be blinded to the treatment being administrated. In addition, all the subjects will be TMS-naïve, with no prior experience with TMS. Subjects will be told that face and hand twitching may occur due to either sham or active treatment and they will be instructed to sit with their arms crossed and folded. The independent rater will only see the subject on the morning of the next treatment day. This procedure will guarantee double blinding and reduce any potential bias in the clinical study.

4. OVERALL RATIONALE FOR THE STUDY

In light of the positive results of the safety and efficacy, feasibility trial in Beer Yakov Mental Health Center with the DTMS treatment with the HADD-coil for treatment of smoking cessation (as described in section 2.3), a controlled, randomized, double-blind trial will be carried out, in which the DTMS treatment will be compared to sham treatment. This study is meant to confirm a lack of bias in the results of the pilot study. The Brainsway DTMS device is intended as an aid to smoking cessation. A study design was chosen that would evaluate the safety and effectiveness for this intended use. Treatment will be administered over a 6 week period and follow-up assessments will be conducted at 4 months. The treatment period is sufficient to investigate the effects of the DTMS treatment.

The clinical study design includes multiple measurements of safety and effectiveness parameters. The design is meant to demonstrate that the device shows superiority compared to sham treatment over six treatment weeks, at the 4 months follow up. The study design allows the results to clearly demonstrate that DTMS treatment is superior to sham treatment for the intended treatment paradigm.

5. OBJECTIVES

The aim of the study is to evaluate the safety and efficacy of DTMS compared to sham treatment as an aid to smoking cessation in chronic (≥10 cigarettes/day) cigarette smokers.

5.1. Primary Objective

The primary objective is to compare the four-week continuous quit rate (CQR), representing abstinence during a consecutive 4 week period, between the two treatment groups. Weekly abstinence is defined as a subject's self-report (in diary) of no smoking (0 cigarettes/day during the whole week), confirmed by urine cotinine levels ≤200ng/ml. A missing confirmatory test will be considered negative, if the previous and the following weekly or 4 month follow-up confirmatory tests are negative. Quit rates are defined as the ratio of the number of patients meeting the quit criterion for at least 4 consecutive weeks to the number of patients initially treated and having at least one post-baseline assessment.

5.2. Secondary Objectives

- To compare the four-week continuous quit rate (CQR), representing abstinence during a consecutive 4 week period, between the two treatment groups. Weekly abstinence is defined as a subject's self-report (in diary) of no smoking (0 cigarettes/day during the whole week), confirmed by urine cotinine levels <200ng/ml. A missing confirmatory test will be considered negative, if the previous and the following weekly or 4 month follow-up confirmatory tests are negative. Quit rates are defined as the ratio of the number of patients meeting the quit criterion for at least 4 consecutive weeks to the total number of patients having assessments during a consecutive 4 week period.
- The secondary objective is to compare number of cigarettes smoked per day (per diary data) for all subjects.

5.3.Exploratory Objectives

Additional endpoints include:

- Weekly point prevalence abstinence rates, defined as the ratio of the number of subjects meeting the weekly abstinence criterion to the number of subjects initially treated and having at least one post-baseline assessment.
- Number of cigarettes smoked per day (per diary data) for non-quitter subjects only.
- Effect on withdrawal symptoms as measured by weekly scales measuring nicotine craving and dependence/withdrawal, including Fagerstrom Test for Nicotine Dependence (FTND), Minnesota Nicotine Withdrawal Scale Self-Report (MNWS), Tobacco Craving Questionnaire–Short Form (TCQ-SF) and Nicotine Craving Scale.

5.4.Safety Objectives

- To evaluate the incidence, severity and frequency of all Adverse Events (AE), related and unrelated to the device treatment, including seizures.
- To evaluate possible cognitive changes using the Mini Mental State Exam (MMSE) and the Buschke Selective Reminding Test (BSRT) cognitive tests.
- Vital signs and hearing loss measured by auditory threshold testing will be evaluated.

6. OVERVIEW OF STUDY DESIGN

The proposed study will compare smoking cessation in two groups of subjects. One group will be assigned to the DTMS treatment (HADD-coil), and the other group will be assigned to the sham treatment (sham coil). This is a prospective, 6 month, double blind, randomized, controlled, multi-center trial in outpatients recruited in both academic and private research centers. A maximum of 270 subjects will be enrolled in the study. The study population will consist of chronic ($\geq$10 cigarettes/day) cigarette smokers motivated to stop smoking and who represent the target population for the use of the DTMS treatment. Subjects of all ethnic and gender categories, ages ranging between 22-70 years will be included in the study. The study is comprised of three periods:

1. Pre-study screening and Baseline Phase;
2. Treatment Phase; and
3. Follow up Phase.

Subjects will be screened for study eligibility according to the inclusion and exclusion criteria described in the study protocol. Subjects who meet the eligibility criteria and are willing to sign an informed consent form will be enrolled in the study. The subjects' demographic and baseline characteristics, as well as their overall medical condition will be assessed prior to treatment administration.

Eligible patients will be randomized to one of two treatment groups. Randomization will be employed to avoid bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (e.g. demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across the treatment groups.

In the *treatment trial period* patients will be randomized to one of two treatment groups (treatment or sham). The treatment group will receive 3 weeks of daily DTMS treatments with the HADD-coil, followed by 3 weekly DTMS treatments, for a total of 18 treatment sessions and 1800 magnetic stimulations per treatment session. The control group will receive the same treatments with a sham coil, for a total of 18 treatment sessions, as well. Each DTMS session will consist of 60 trains. The duration of each train will be three seconds and the inter-train interval will be 15 seconds. All subjects will undergo the same treatment regimen, regardless of the assigned treatment group.

Subjects will be asked to select a target quit date (TQD within 7-14 days of the first treatment session. Participants will be asked to refrain from smoking nicotine for at least two hours prior to the baseline visit and prior to each treatment session. Prior to treatment stimulation onset, a smoking related cue will be presented to the subject. Immediately after the offset of the smoking cue presentation (while memory is reactivated) active or sham DTMS stimulation will be administered. It has recently been demonstrated that in nicotine-deprived smokers, reward and attention circuits are reactivated by mere exposure to smoking-related images, in contrast with neutral images (Due et al., 2002). The preliminary study conducted with the Brainsway DTMS device (described in section 2.3) found that induction of craving by a smoking cue immediately prior to DTMS over the prefrontal and insular cortices induces a stronger effect on nicotine addiction relative to DTMS treatment alone. We propose that presentation of the smoking cue causes the nicotine-related memories and associated craving to become activated and therefore, labile for interference, as previously suggested (Amiaz et al., 2009; Dudai, 2006).

The study design is directed towards a comparison, between active treatment and sham, at 6 weeks and 4 months follow-up.

Efficacy will be assessed using the primary efficacy measure of abstinence, where abstinence is defined as a subject's self-report (in diary) of no smoking (0 cigarettes/day), confirmed by urine cotinine levels $\leq$200ng/ml. Additionally, several subject assessment scales will be used during the course of the study to assess nicotine craving and nicotine withdrawal symptom.

Safety will be assessed, including monitoring of adverse events, vital signs, physical examination and auditory threshold testing. The Mini-Mental State Exam (MMSE) and the Buschke Selective Reminding Test (BSRT) cognitive tests will also be used to assess changes in cognition and memory during the study period.

Details on the timing of all treatments and assessments are given in the Time and Events Schedule in Attachment 1 of the Protocol. The anticipated enrollment period is approximately six months and therefore, the complete duration of the study is expected to last 1 year, during which time 270 subjects will be enrolled at approximately 20 sites. The masked, randomization status will be maintained for the entire time of subject enrollment, until the last subjects have completed the study.

7. STUDY POPULATION

7.1.General Considerations

The study will recruit male and female chronic cigarette smokers from the general population, aged 22-70 who are motivated to quit smoking. Subjects will be recruited by advertisements in the newspapers and specific websites and treated in academic and private research centers. Informed consent will be obtained from potential subjects according to local and national IRB requirements. Candidates will be screened with a medical interview, physical examination and a safety screening questionnaire for transcranial magnetic stimulation (Keel 2001).

7.2. Subject Inclusion Criteria:

Subjects must fulfill the following criteria:

- Male or female subjects, 22-70 years old.
- Current, chronic (≥10 cigarettes/day) smokers, who smoke for more than 1 year, with no period of abstinence for greater than 3 months during the past year.
- Subjects who are motivated to quit smoking (with responses "very likely," or "somewhat likely" to the motivation questionnaire).
- Satisfactory answers on safety screening questionnaire for transcranial magnetic stimulation (Keel 2001).
- Gave informed consent for participation in the study.

7.3. Subject Exclusion Criteria:

- Currently on Nicotine Replacement Therapy (NRT) or smoking cessation drugs (e.g., Zyban, Chantix, etc.) or undergoing behavioral smoking cessation interventions.
- Cognitive or functional disability, diagnosed according to DSM-5 criteria.
- Active psychiatric disorder according to DSM-5 (Axis I and Axis II) criteria within the last year.
- Current alcohol or other substance abuse or dependence.
- Alcohol or other substance abuse or dependence during the last 12 months before recruitment.
- Subject is smoking any other form of tobacco or other substances.
- Subject is taking psychotropic medications on a regular basis.
- Subjects with a high risk for severe violence or suicidality as assessed during the screening interview.
- Subjects who suffer from an unstable physical disease such as high blood pressure (>150 mmHg systolic / diastolic > 110 mmHg) or acute, unstable cardiac disease.
- History of epilepsy or seizure (EXCEPT those therapeutically induced by ECT).
- Increased risk of seizure for any reason, including prior diagnosis of increased intracranial pressure (such as after large infarctions or trauma), or history of significant head injury or trauma with loss of consciousness for ≥ 5 minutes.
- History of any metal in the head (outside the mouth).
- Metallic particles in the eye, implanted cardiac pacemaker or any intracardiac lines, implanted neurostimulators, intracranial implant (e.g., aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or implanted medical pumps.

- Individuals with a significant neurological disorder or insult including, but not limited to:
  - Any condition likely to be associated with increased intracranial pressure
  - Space occupying brain lesion
  - History of cerebrovascular accident
  - Transient ischemic attack within two years
  - Cerebral aneurysm
  - Dementia
  - Mini Mental State Exam score of less than or equal to 24
  - Parkinson's disease
  - Huntington's chorea
  - Multiple sclerosis
- Subjects suffering from frequent and severe migraine headaches.
- Subjects suffering from significant hearing loss.
- Subjects taking pro-convulsant medications (e.g., antidepressants or antipsychotic medications).
- Previous treatment with TMS.
- Subjects who cannot communicate reliably with the investigator or who are not likely to cope with the requirements of the experiment.
- Participation in a clinical trial within the last 30 days before the beginning of this clinical trial or similar participation in another clinical trial.
- Known or suspected pregnancy or lactation.
- Women of childbearing potential and not using a medically accepted form of contraception when engaging in sexual intercourse.

8. RANDOMIZATION AND BLINDING

The subjects will be randomized into the study and stratified by site. If a subject meets the eligibility criteria, he/she will be equally allocated (with a 1:1 ratio) to one of the two (2) treatment groups, based on a stratified randomization scheme random number generator.

9. ADMINISTRATION OF TREATMENT

The treatment administrator will determine all motor thresholds (MTs) and administer the treatments. An independent rater will evaluate the patient following treatment and complete the subject assessment scales. The principle investigator, treatment administrator, independent rater and study subjects will all be blinded to the treatment being administered. At the beginning of the trial individual MTs will be measured by placing the assigned coil above the hand area of the motor cortex. All studied groups will receive stimulations over the prefrontal cortex, 6 cm anterior to the 'hot spot' (i.e., the left dorsolateral prefrontal cortex) for stimulation of the abductor policies brevis in the hand area. Each DTMS treatment (for active and sham groups) will be conducted as follows: Before starting each treatment, treatment administrators and subjects will be instructed to insert earplugs to lessen any possible adverse effect on hearing. Then, the MT will be measured by delivering single stimulations to the motor cortex. The MT is measured by gradually increasing the intensity. This is done by using the single pulse mode and applying one pulse every 5 sec, i.e. 0.2 Hertz. The electrical activity in abductor pollicis brevis is then recorded using surface electrodes. Threshold is defined as the lowest intensity of stimulation producing motor evoked potentials of at least 50μV in 5 of 10 trials. After defining the motor threshold, the coil will be positioned anterior to the hot spot (i.e., the left dorsolateral prefrontal cortex) using the ruler on the subject's cap, and an rTMS session will be performed at 120% of the motor threshold. At the beginning of each treatment session the operator will apply one short trial train of 0.5 sec, 10 Hz, at a power output of 120% of the MT to test whether the subject responds well to the train. The operator will ask the subject if the treatment is tolerable. In case of excessive motor activation, the coil will be moved up to 1 cm forward, and the operator will re-evaluate whether the problem has been resolved. In case the problem has not been resolved, the operator may tilt the coil along the right-left axis, and again re-evaluate whether the problem has been resolved.

In case the subject has difficulty sustaining the trial train, the operator will apply trial trains gradually, in order to help the subject become accustomed to the treatment [the detailed scheme is specified in the Instructions for Use]. At the baseline (first) treatment the subject should receive a treatment at a power output of 100% of the measured motor threshold. At treatment #2 the subject should receive a treatment at a power output of 110% of the measured motor threshold. At treatment #3 and on the subject should receive

a treatment at a power output of 120% of the measured motor threshold. This is in order to help the subject become accustomed to the treatment.

The MT of each subject will be determined once a week. In case the MT found is higher or lower than the value found at the baseline by more than 5%, the operator should re-determine the MT. In case the MT is still higher than the value found at the baseline by more than 10%, then the treatment intensity should be set based on 110% (and not higher) of the MT found at the baseline. For example, if the MT found at baseline was 60% of the stimulator power output, then the maximal value of MT used for computation of treatment intensity can be no more than 66% of the stimulator power output (i.e. treatment will be applied at no more than 66 X 1.2 of the stimulator power output). In case the MT is lower than the value found at the baseline by more than 5%, then the principal investigator should approve the MT value, and the treatment intensity should be set based on the MT value found.

The treatment group will receive the following dose of DTMS treatment: 10 Hz, 120% MT, 3 sec pulse train, 15 second intertrain interval, 60 trains, total of 1800 pulses per session with duration of about 18 minutes per session each day. The control group will receive inactive/sham treatment with identical parameters. Study subjects will be asked a forced choice question whether they think they received a real or a sham treatment and the reason for their response, at the end of the first treatment session. Subjects will be told that face and hand twitching may occur due to either sham or active treatment and they will be instructed to sit with their arms crossed and folded.

During the treatment procedure, the treatment administrator will observe the subject closely for any sign of imminent seizure activity or muscle twitching. Presence of a physician or nurse trained in seizure management, emergency equipment (oxygen, suction, blood pressure monitor, and CPR equipment) and antiepileptic medications will be readily available in the immediate vicinity. Subjects will be informed of the risk of permanent hearing loss if an earplug should become detached or fall out. Subjects will be asked to immediately report any loosening or detachment of an earplug during DTMS and treatment will be stopped if a subject reports or if an investigator observes that an earplug has loosened or has fallen out. In the case of coil overheating a warning is displayed and the treatment administrator is instructed to remove the coil from the subject. The coil will cool down within several minutes and then treatment is resumed. Any events of coil overheating, removal and treatment resumption will be recorded.

Subject participating in the study will not be allowed to meet with each other before, during and after assessment or treatments in order to maintain study blinding.

10. CONCOMITANT THERAPY

The following medications will not be allowed throughout the study: antidepressants, stimulants, and antipsychotics indicated for psychotic episode.

The following medication will be allowed throughout the study: Insomnia medications prescribed prior to commencement of treatment may be continued during the study (up to 3mg Lorivan, or equivalent).

Only the following insomnia medications (one or more) may be prescribed during the course of the study:

- Zolipidem (p.r.n. up to 10 mg/day orally or Zolipidem CR (6.25 or 12.5 mg/day orally).
- Zaleplon (p.r.n. up to 20 mg/day orally)
- Zopiclone (p.r.n up to 15 mg/day orally or eszopiclone (p.r.. up to 3 mg/day orally)
- Benzodiazepines up to a dose equivalent to 3.0 mg of Lorazepam or equivalent

Acetaminophen or other medications for treatment of local pain, dental pain or headaches will be allowed, as necessary.
Medications for general medical conditions will be allowed. All medications taken by a subject (prescription or nonprescription) must be documented in the concomitant therapy section of the CRF. This includes medications taken within 30 days before treatment initiation and during the course of the study.
For any medication given as a treatment for a new or worsening condition, the condition must be documented on the Adverse Event Form of the CRF.

11. STUDY EVALUATIONS

11.1. Study Procedures

11.1.1. Overview

The Time and Events Schedule provided in Attachment 1 summarizes the frequency and timing of treatment and assessments. The trial will consist of 3 phases:

1. Pre-study Screening phase;
2. Baseline Phase;
3. Treatment phase (6 weeks); and
4. Follow-up phase (4 months).

Efficacy measures to be used in the study include:

- Self-reporting (nicotine inventory) of cigarette consumption
- Biochemical Verification using urine cotinine levels (nicotine metabolite)
- Nicotine Craving Scale (7 point VAS scale)
- Self-administered Fagerstrom Test of Nicotine Dependence (FTND)
- Minnesota Nicotine Withdrawal scale (MNWS)
- Self-administered Tobacco Craving Questionnaire (TCQ-SF)

Safety evaluations will include adverse event monitoring, vital signs, physical examination, auditory threshold testing, MMSE and BSRT cognitive tests.

11.1.2. Pre-Study Screening Phase

Potential subjects will be given complete information describing the study treatment and their role in the trial, and they will be encouraged to ask any questions regarding the trial. The risks and requirements of this clinical research trial will be explained to each potential subject. Those volunteering to take part will read and sign the Informed Consent Form for participation in the clinical research trial before any trial-related procedures are performed. Upon obtaining the signed informed consent, inclusion and exclusion criteria will be reviewed to verify the subject's eligibility.

During the screening visit, participants will undergo a clinical interview including a demographic questionnaire, documentation of medical history, physical examination, concomitant medications, Structured Clinical Interview for DSM Diagnosis (SCID), smoking history and habits and motivation to quit smoking.

11.1.3. Baseline Phase

Eligible subjects will be assessed at Baseline for their self-report of cigarette consumption, confirmed by a quantitative assessment of urine cotinine levels (nicotine metabolite). Urine cotinine levels will be measured from a urine sample and sent to a core laboratory for analysis.

The following nicotine craving and nicotine dependence/withdrawal questionnaires will also be administered at baseline, in order to measure the subjects' baseline levels. Subjects will be requested to refrain from smoking for two hours before the baseline visit and before all treatment/assessment visits.

1) Nicotine Craving Scale (7 point VAS scale)
2) Self-administered Fagerstrom Test of Nicotine Dependence (FTND) (Heatherton et al., 1991)
3) Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes and Hatsukam 1986).
4) Self-administered Tobacco Craving Questionnaire (TCQ-SF) (Troop et al., 2003).

Cognitive test questionnaires, including MMSE and BSRT, will be reported at baseline.

Baseline data are defined as the data generated during the baseline visit prior to the first DTMS/sham treatment. Subjects who have completed all assessments at the baseline visit will be randomized to either the DTMS treatment group or the sham control group.
The baseline visit should be performed within 7 days of the screening visit.

11.1.4. Treatment Phase

During the treatment phase subjects will receive daily prefrontal DTMS, 5 days per week for 3 consecutive weeks, followed by one weekly session for three weeks (for a total of 18 treatments over 6 weeks). Subjects will be asked to select a target quit date (TQD). The TQD will be scheduled within 7-14 days of the first treatment session, to allow for a minimum of 7 days of treatment before the quit attempt. Subjects will be instructed not to try to quit smoking prior to their TQD.

Subjects will be asked to refrain from smoking for two hours prior to the baseline visit and prior to all the treatment sessions. Prior to treatment stimulation onset, a smoking related cue/provocation will be presented to the subject. The smoking cue/provocation will consist of holding and handling a cigarette from the brand of cigarettes the subject is

accustomed to smoke and viewing smoking related pictures for a period of 5 minutes. Immediately after the offset of the smoking cue/provocation presentation (while memory is reactivated) active or sham DTMS stimulation will be administered.

During the treatment phase, assessment visits will be performed weekly at weeks 2, 3, 4, 5 and 6 weeks from start of treatment. Assessment visits will be performed prior to the treatment session. Participants will be asked to keep a record of their smoking behavior on a diary card. At each of the weekly visits, smoking behavior will be evaluated, diary cards reviewed, information collected on changes in concomitant medications and adverse events, and urine cotinine levels monitored. Nicotine craving and nicotine dependence/withdrawal questionnaires will also be administered at each of the weekly visits. Subjects will be provided with a self-help educational booklet on smoking cessation ("Clearing the Air: How to Quit Smoking…and Quit for Keeps" National Cancer Institute 95-1647) and up to 10 minutes of brief counseling regarding smoking cessation will be provided at the end of each weekly visit in accordance with AHRQ Guidelines.

All procedures to be performed during the different visits are listed in the Time and Events Schedule in Attachment 1.

11.1.5. Follow up Phase

At the end of the 6-week period, participants who had quit smoking will be scheduled for a follow-up visit at 4 months (from the screening visit). Those who continue to smoke will complete an "end of study" form and will not be required to return for further follow-up. The 4 month follow-up visit will include the same assessments and questionnaires as the weekly visits. All attempts will be made to minimize drop-out and ensure that the study subjects present for the 4 month follow-up visit, including periodic study reminders.

All follow-up procedures are shown in the Time and Events Schedule (Attachment 1).

11.2. Efficacy and Safety Evaluations

All subjects will undergo the following efficacy and safety evaluations at each of the follow-up visits. All efficacy and safety measures and the time table for performing them are shown in the Time and Events Schedule provided in Attachment 1 to the study protocol.

11.2.1. Nicotine Use Inventory - Self-report of Number of Cigarettes Smoked

Participants will be asked to keep a record of their smoking behavior on a daily diary card, including the number of cigarettes smoked each day. The information recorded on the diary cards will be reviewed at each visit. The number of cigarettes smoked per day and the length of time since last cigarette will be reported on the daily diary cards. The number of cigarettes smoked recorded on the subjects' diary will be used to assess abstinence.

11.2.2. Biochemical Verification – Urine cotinine samples

Quantitative assessment of urine cotinine levels (nicotine metabolite) will be performed. Urine cotinine levels will be measured from a urine sample and sent to a core laboratory for analysis. The cotinine assessment will be performed at Baseline, at the weekly visits during the treatment phase and at the 4 month follow-up visit. The biochemical verification of cigarette smoking will be used to assess abstinence.

11.2.3. Nicotine Craving Scale (7 point VAS scale)

A Nicotine Craving Scale, based on a 7 point Visual Analogue Scale (VAS), where 1 is defined as "Very definitely not" and 7 is defined as "Very definitely", and on which the subject will mark his/her subjective craving in response to the question - "How much do you crave a cigarette right now?" will be used. This "desire to smoke" rating has been shown to be sensitive to assess self-reported levels of craving in nicotine smoking (Schuh and Stitzer, 1995; King and Meyer, 2000). The results of the Nicotine Craving Scale will be recorded at Baseline**,** at each treatment during the 6 weeks of treatment and at the 4 month follow-up visit. The Nicotine Craving Scale will be administered before the smoking cue prior to each treatment, after the smoking cue before each treatment and after each treatment.

11.2.4. Fagerstrom Test of Nicotine Dependence (FTND) (Heatherton et al., 1991)

The Fagerstrom Test for Nicotine Dependence (FTND) assesses physical nicotine dependence. The earlier Fagerstrom Tolerance Questionnaire was improved by modification, and a revised scoring for the FTQ, called the Fagerstrom Test for Nicotine Dependence (FTND) was developed. The FTND consists of six of the original items (nicotine rating and inhalation have been eliminated) with revised scoring for two of the items (TTF - Time to the first cigarette of the day, and CPD - Cigarettes per day). The FTND has acceptable levels of internal consistency, and is closely related to biochemical indices of heaviness of smoking. The FTND scores will be assessed at Baseline, at the weekly visits during the treatment phase and at the 4 month follow-up visit.

11.2.5. Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes and Hatsukami 1986)

The Minnesota Nicotine Withdrawal Scale (MNWS) is the one most frequently used scales for assessing nicotine withdrawal symptoms. This eight-item scale measures withdrawal symptoms (i.e., craving, irritability, anxiety, difficulty concentrating, restlessness, increased appetite or weight gain, depression, and insomnia) listed in the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM–IV; American Psychiatric Association 1994) and these symptoms are generally scored on an ordinal scale ranging from 0 (not present) to 4 (severe). The MNWS has been validated in multiple studies (Hughes, 1992; Hughes, et al 1991; Hughes et al 1986). In both the Hughes (1992) and Hughes et al. (1991) studies, although observer ratings of MNWS withdrawal symptoms were not highly concordant with self-ratings, both sets of ratings were sensitive to abstinence effects, showing evidence of good reliability and validity for the scale. The MNWS scores will be assessed at Baseline, at the weekly visits during the treatment phase and at the 4 month follow-up visit.

11.2.6. Tobacco Craving Questionnaire (TCQ- SF)

The Tobacco Craving Questionnaire (TCQ) is a valid and reliable 47-item self-report instrument that assesses tobacco craving in four dimensions: emotionality, expectancy, compulsivity, and purposefulness. A short, 12-item version of the TCQ was constructed by selecting three items from each of the four factors that exhibited optimal within-factor reliability (Cronbach's alpha coefficient) and inter-item correlation. These items are rated

on a Likert-type scale from 1 (*strongly disagree*) to 7 (*strongly agree*). The TCQ–SF reliably measures the same multidimensional aspects of tobacco craving as the TCQ when tested under different experimental conditions and over repeated assessments (Heishman et al., 2003; Singleton et al., 2003). The use of the TCQ–SF is recommended in clinic and research settings where time may be limited, yet a multidimensional assessment of tobacco craving is desired. The TCQ–SF scores will be assessed at Baseline, at the weekly visits during the treatment phase and at the 4 month follow-up visit.

11.2.7. Mini-Mental State Exam (MMSE)

The mini-mental state examination (MMSE) or Folstein test is a brief 30-point questionnaire test that is used to assess cognition. It is commonly used in medicine to screen for dementia. In the time span of about 10 minutes, it samples various functions, including arithmetic, memory and orientation. The MMSE test includes simple questions and problems in a number of areas: the time and place of the test, repeating lists of words, arithmetic, language use and comprehension, and copying a drawing. Any score over 24 (out of 30) is effectively normal. The normal value is also corrected for degree of schooling and age. It was introduced by Folstein et al in 1975, and is widely used with small modifications. Subjects will be assessed for cognitive changes using the MMSE, at Screening, Baseline, at the 6 week visit and at the 4 month follow-up visit.

11.2.8. Buschke Selective Reminding Test (BSRT)

The Buschke Selective Reminding Test (BSRT) (Buschke, 1973 (40)) is used to provide a traditional measure of verbal learning and memory using 12-word lists, 10 trials, and 2-hr delayed free recall, followed by reacquisition of the list (10 trials) (4 alternate forms). Since subjects are only reminded of words not recalled on the previous trial, this task provides more information on encoding and retention than other list learning tasks. This task is especially sensitive to anterograde amnestic effects of ECT and other interventions (41). The primary dependent measure will be total words correctly reported at the second administration (reacquisition). Subjects will be assessed for cognitive changes using the BSRT, at Baseline, at the 6 week visit and at the 4 month follow-up visit.

11.3. Efficacy Measures

All subjects will undergo the following efficacy measures.

11.3.1. Abstinence and Continuous Quit Rates (CQR)

Abstinence is defined as a subject's self-report (section 11.3.1) of no smoking (0

cigarettes/day), confirmed by urine cotinine levels ≤200ng/ml (section 11.3.2). The "cut-off" value of urine cotinine) is recognized as 200 ppm or 200ng/ml) for the determination of abstinence. Subjects with cotinine levels above this value will be considered to have not stopped smoking. Continuous Quit Rates (CQR) is defined as the ratio of the number of patients meeting the quit criterion (i.e., abstinence during a consecutive 4 week period) to the number of patients initially treated, will be assessed at Baseline, at the weekly visits during the treatment phase and at the 4 month follow-up visit.

11.3.2. Nicotine Dependence (Craving and Withdrawal) Symptoms

Nicotine Dependence (Craving and Withdrawal) Symptoms will be measured by changes in the following scales:

- The Nicotine Craving Scale weekly means will be calculated and compared between treatment and sham groups.
- The Fagerstrom Test for Nicotine Dependence (FTND) composite score (sum of component scores) will be calculated and compared between treatment and sham groups.
- The Minnesota Nicotine Withdrawal Scale (MNWS) scores for the eight individual symptoms will be calculated and statistical comparisons will be performed for each individual symptom, comparing the treatment group to the sham group. Composite withdrawal symptom scores (sum of component scores) will also be calculated and compared.
- Tobacco Craving Questionnaire (TCQ- SF) composite tobacco craving scores (sum of component scores) will also be calculated and compared between treatment and sham groups.

11.4. Safety Measures

All subjects will undergo the following efficacy measures.

11.4.1. Body Examinations

- A physical examination will be completed at Baseline, at the 6 week visit and at the 4 month follow-up visit.
- Body height, weight and vital signs will be completed at Baseline, at the 6 week, visit and at the 4 month follow-up visit.
- A urine pregnancy test will be performed in all females of childbearing age at screening.

11.4.2. Hearing

Subjects will be informed of the risk of permanent hearing loss if an earplug should become detached or fall out and subjects will be instructed to immediately report any loosening or detachment of an earplug during DTMS, and treatment will immediately be stopped if a subject reports or if an investigator observes that a subject's earplug has loosened or has fallen out. Treatment administrators will also be instructed to wear earplugs during the treatment. Auditory threshold testing will be performed at the Screening visit and at the end of the 6 week treatment period.

11.4.3. Transcranial Magnetic Stimulation Safety (TASS) Questionnaire

A screening questionnaire for transcranial magnetic stimulation will be completed at the screening visit.

11.4.4. Cognitive Evaluation

Evaluation using the Mini-Mental State Exam (MMSE) and the Buschke Selective Reminding Test (BSRT) for detection of cognitive changes will be completed at Screening (MMSE only), at Baseline, and at the 6 week and 4 month follow-up visits.

11.4.5. Adverse Events Reporting

Subjects will be instructed to report AEs as they occur. AEs will be assessed at each study visit after informed consent has been obtained.

11.5. Additional Measures

All subjects will undergo the following additional measure.

11.5.1. Assessment of Motivation to Quit Smoking

Subjects will be asked a motivational question, “How likely is it that you will stay off cigarettes after treatment?” in order to assess their motivation to quit smoking at the Screening visit. The responses include “very likely,” “somewhat likely,” and “not likely”. A response of “very likely” or “somewhat likely” will qualify the subject for inclusion into the study.

12. SUBJECT COMPLETION / WITHDRAWAL

12.1. Completion

A subject will be considered to have completed the study if he or she completed all required assessments until the 6 week follow-up visit. Subjects who prematurely discontinue study treatment for any reason before completion of the continuation phase will not be considered to have completed the study.

12.2. Withdrawal from the study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow up
- Withdrawal of consent
- Subject is not compliant with requirements of the study, including inclusion criteria and exclusion criteria
- The study is prematurely stopped or halted (e.g. clinical halt)
- The investigator believes that for safety reasons (e.g. an adverse event) it is in the best interest of the subject to stop treatment
- Subject's motor threshold cannot be located.
- Subject becomes pregnant.
- Subject has significant tremor in any limb.
- Subject experiences a seizure.
- Subject misses > 4 treatments during the daily treatment phase or > 3 consecutive treatments.

When a subject withdraws before completing the study, the reason for withdrawal will be documented on the CRF.

13. STATISTICAL CONSIDERATIONS

13.1. Study Design and Objectives

This is a prospective, randomized, 4 month, double blind, controlled trial in outpatients recruited from hospitals and clinics, using a sequential two-stage adaptive design with one interim analysis at approximately 65% of the expected information.

The aim of this study is to evaluate the safety and efficacy of DTMS compared to sham treatment as an aid to smoking cessation in chronic (>10 cigarettes/day) cigarette smokers.

13.2. Study Endpoints

13.2.1. Primary Efficacy Endpoint

The primary endpoint is the four-week continuous quit rate (CQR), representing abstinence during a consecutive 4 week period. Weekly abstinence is defined as a subject's self-report (in diary) of no smoking (0 cigarettes/day during the whole week), confirmed by urine cotinine levels $\leq$200ng/ml. A missing confirmatory test will be considered negative, if the previous and the following weekly or 4 month follow-up confirmatory tests are negative. Quit rates are defined as the ratio of the number of patients meeting the quit criterion for at least 4 consecutive weeks to the number of patients initially treated and having at least one post-baseline assessment.

13.2.2. Secondary Efficacy Endpoints

The secondary endpoints are:

- The four-week continuous quit rate (CQR), representing abstinence during a consecutive 4 week period for subjects having assessments during a consecutive 4 weeks period, therefore the quit rates are defined as the ratio of the number of patients meeting the quit criterion for at least 4 consecutive weeks to the total number of patients having assessments during a consecutive 4 week period.
- The number of cigarettes smoked per day (per diary data) for all subjects (quitters and non-quitters).

13.2.3. Exploratory Efficacy Endpoints

Additional endpoints include:

- Weekly point prevalence abstinence rates, defined as the ratio of the number of subjects meeting the weekly abstinence criterion to the number of subjects initially treated and having at least one post-baseline assessment.
- Number of cigarettes smoked per day (per diary data) for non-quitter subjects only.
- Withdrawal symptoms as measured by weekly scales measuring nicotine craving and dependence/withdrawal, including the Fagerstrom Test for Nicotine Dependence (FTND), Minnesota Nicotine Withdrawal Scale Self-Report (MNWS), Tobacco Craving Questionnaire–Short Form (TCQ-SF) and Nicotine Craving Scale.

13.2.4. Safety Endpoints

- The incidence, severity and frequency of all Adverse Events (AE), related and unrelated to the device treatment including seizures.
- Cognitive changes using the Mini Mental State Exam (MMSE) and the Buschke Selective Reminding Test (BSRT) cognitive tests.
- Vital signs and hearing loss measured by auditory threshold testing will be evaluated.

13.3. Study Hypothesis

In this study we will test the following hypotheses:

- H_0: $CQR_{DTMS} = CQR_{SHAM}$
- H_1: $CQR_{DTMS} \neq CQR_{SHAM}$

Where: CQR_{DTMS} is the continuous quit rate in the DTMS arm and CQR_{SHAM} is the continuous quit rate in the Sham group.

13.4. Sample size

The preliminary clinical study evaluated the safety and efficacy of the DTMS as an aid in smoking cessation, at three weeks and at six months follow-up. The three week point prevalence quit rate was 44% in the treatment group and 13% in the sham group. The six month point prevalence quit rate was 33% in the treatment group and 9% in the sham group. Although, the three week point prevalence quit rate showed a significant improvement in the treatment group compared to the sham group, the point prevalence

quit rate did not meet the standard requirement for evaluating smoking cessation, i.e., at least a 4 week continuous quit rate. Furthermore, the six month data had its limitations, including a long term time point and high drop-out rate. Therefore, we looked at the clinical results provided in support of FDA approval of other smoking cessation aids, including Zyban (Bupropion hydrochloride) and Chantix (Varenicline). The mechanism of action of Zyban which aids smoking cessation is the increase in dopamine release, which is also one of the mechanisms of action of the DTMS treatment.

The quit rates (i.e., based on abstinence from week 4 of the study through week 7) were 49% in the treatment group receiving Zyban compared to 36% in patients receiving Nicotine Replacement Therapy (NRT) and 23% in the placebo group. In two other studies, subjects treated with Chantix had an abstinence rate during weeks 9 through 12 of 44% compared to 30% in patients treated with Zyban and 17% and 18% in patients receiving placebo.

For the purpose of sample size calculation the weighted average of the quit rates for smoking cessation treatments (including Zyban, Chantix, NRT and DTMS) (38.6%) and the weighted average of the quit rates for placebo/sham (18.4%) will be used. Using the above weighted averages we can assume a placebo/sham success rate of 18%, and a minimally important difference of 20%.

The study is designed to have 80% power with a two-sided level of significance of 5% to detect to detect a difference of 20% in the CQR in the DTMS group compared to the control group, and one planned interim analyses using the Lan De-Mets alpha spending approach with a Pocock type spending function (the calculations were performed using the SAS SEQDESIGN procedure).

Given this design we will require a total number of 164 (82 per arm) subjects at most. Allowing for a potential 37% drop-out 270 subjects will be randomized. The dropout rate was continuously monitored in a blinded way, and the total number of subjects to be enrolled was adapted accordingly.

13.5. Interim Analysis (was not performed – will be detailed in the SAP)

One (1) interim analysis is planned after 106 subjects (approximately 65% information) will complete at least the 6 week visit. The main goal of this interim analysis is to stop the study in case of success, i.e. the CQR in the DTMS group is statistically significantly higher than that in the sham arm.

13.4.1. Procedure

After all the relevant data will be entered into the database and a soft lock to the database will be performed. An independent un-blinded statistician (not the study statistician) will perform the assessment of the primary and safety endpoints. In order to maintain scientific integrity of the study, no major protocol changes will be made after the interim analysis.

13.4.2. Blinding

ONLY the un-blinded statistician and members of the interim decision committee will be exposed to the interim report. All parties having access to the interim analysis will be identified and documented. The members of the DSMB may also have access to the unmasked information of the interim analysis if requested by the DSMB chairman. Investigators and company directors will only be informed of a decision to continue or to discontinue the trial, or to implement modifications in trial procedure. The un-blinded statistician who is responsible for conducting the interim analyses should ensure that the unmasked data is not available to any unauthorized person within or outside the company.

13.4.3. Decision Rules

The following decisions upon the interim analysis report are planned:

- Stop the study in case of severe safety concerns.
- Stop the study in case of success i.e. if the CQR in the DTMS group is statistically significantly higher ($p<0.03154$) than in the sham arm.
- Otherwise, continue the study without changes in the protocol.

13.4.4. Alpha level

The study is designed as a group sequential study with one planned interim analysis with a Pocock type spending function using the Lan De-Mets alpha spending approach.

The study hypothesis will be tested at the time of the interim analysis. If the 2-sided p-value of the comparison of the primary endpoint (CQR) between the two study arms is statistically significant, i.e. <0.03154, the study will be stopped and considered successful. Otherwise, the primary endpoint will be tested at the end of the planned study for a level of significance of 3.154%.

13.6. Randomization

A subject meeting the eligibility criteria will be equally allocated (with a 1:1 ratio) to one of the following 2 treatment groups based on a randomization scheme with blocks stratified by center:

1. DTMS
2. Sham

The randomization scheme will be prepared by the study statistician using the SAS® (version 9.3.) random number procedure. The block size will be variable and study personnel will be blinded to the randomization block size.

13.7. Blinding

The subjects, investigators, raters, and device operators will all be blinded regarding the treatment received. The treatment allocation will be coded into a subject personal card that will be inserted into the device. The device will produce DTMS or Sham treatment according to the pre-programmed card.

13.8. Data Analysis Sets

13.8.1. Intent-to-Treat (ITT) Analysis Set

For safety analysis, the ITT analysis set (ITT-S) will consist of all subjects randomized. In accordance with the ITT principle, all subjects randomized who received at least one treatment (DTMS or Sham) will be kept in their originally assigned treatment group. For efficacy analyses, the ITT analysis set (ITT-E) will consist of all subjects who met all the inclusion/exclusion criteria and were randomized who received at least one treatment (DTMS or Sham) (defined as an average stimulation intensity of at least 110% of the motor threshold during treatment session no. 3 to the last treatment session) and have at least one post-baseline assessment available for analysis.

13.8.1. Completer (CO) Analysis Set

The CO analysis set will consist of all subjects from the ITT-E analysis set who completed at least the six weeks of treatment and assessments related to the primary endpoint.

13.8.2. Per Protocol (PP) Analysis Set

The PP analysis set will consist of all subjects from the ITT-E analysis set without major protocol violations.

13.8.3. Statistical Analysis of Analysis Sets

The ITT-E and ITT-S analysis sets will serve as the main set for efficacy and safety assessments, respectively.

The primary efficacy assessment will also be performed on the CO and the PP analysis sets, as a sensitivity analysis.

13.9. Statistical analysis

13.9.1. General Considerations

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary NC, USA). Baseline demographic and other baseline characteristics, together with safety analyses will be performed on all enrolled subjects. Baseline values are defined as the last valid value prior to study treatment. The standard summary statistics for continuous variables are: N, mean, standard deviation, median, minimum and maximum. The standard summary statistics for categorical variables are: count and percentage. All statistical tests will be two-sided. Where confidence limits are appropriate, the confidence level will be 95%. For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test will be used as appropriate. For comparison of proportions (discrete data), the Chi-squared test or Fisher's exact test will be used as appropriate.

13.9.2. Significance levels and handling of type I error

The overall significance level for this study is 5% using two-tailed tests, except for the treatment by site interaction that will be tested at a significance level of 10%.

The hierarchy approach will be adopted for the primary and secondary endpoints to control the type I error due to multiple endpoint testing. Thus, the primary endpoint will first be analyzed and only if found statistically significant as detailed in section 13.4, will the first secondary endpoint be analyzed; and only if found statistically significant, will the second secondary endpoint be analyzed. This approach will maintain the overall study type I error by continuing to analyze the next end-point in the hierarchy only if the previous endpoint analysis was found significant.

The exploratory end-points will not be part of the hierarchy as descriptive statistics are mainly planned.

13.9.3. Demographic and Other Baseline Characteristics

Demographic and baseline condition related characteristics will be tabulated. Continuous variables such as age and BMI will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count and percentage.

13.9.4. Disposition of Patients

The numbers of subjects who were randomized and who entered and completed each visit of the study will be provided, as well as the reasons for all post-randomization discontinuations, grouped by treatment and by major reason (e.g., lost to follow-up, adverse event, poor compliance). A list of discontinued subjects, protocol deviations, and subjects excluded from the efficacy analysis will be provided as well. Time to withdrawal will also be assessed and presented by Kaplan-Meier curves and will be compared using the Log-Rank test.

13.9.5. Efficacy analyses

- The continuous quit rate (CQR) at the 6 weeks visit will be compared between the study arms with a chi-squared test. In addition the CQR will be modeled with logistic regression; baseline daily number of cigarettes smoked, sex and center will be used as covariates.

Prognostic factors and sensitivity analysis for the CQR at the 6 week and/or 4 month follow-up visits will be performed in the following manner: adjustment for other covariates such as demographics or other baseline characteristics (e.g., sex, age, race and history of smoking) may be performed by adding these variables to the above described logistic model.

- Weekly point prevalence abstinence rates will be analyzed in the same manner.
- Daily number of cigarettes smoked will be presented over time and analyzed with a repeated measures analysis of covariance model. Baseline daily number of cigarettes smoked, sex and center will be used as covariates.

The analysis will be presented for all subjects in the analysis set and for the non-quitters only.

- Effect on withdrawal symptoms as measured by weekly scales measuring nicotine craving and dependence/withdrawal, including Fagerstrom Test for Nicotine Dependence (FTND), Minnesota Nicotine Withdrawal Scale Self-

Report (MNWS), Tobacco Craving Questionnaire–Short Form (TCQ-SF) and Nicotine Craving Scale.

Fagerstrom Test for Nicotine Dependence scores will be presented in tabular form and compared between the treatment arms with chi-squared tests.

Minnesota Nicotine Withdrawal Scale Self-Report scores, Factor structure of Tobacco Craving Questionnaire–Short Form scores, and Nicotine craving scale scores will be presented over time and analyzed with a repeated measures analysis of covariance model. Baseline daily number of cigarettes smoked, sex and center will be used as covariates.

13.9.6. Safety analyses

Adverse events (AE) will be presented by seriousness, severity and relation to treatment by treatment group. Serious adverse events will be listed and discussed individually.

The incidence of potentially clinically significant vital sign measurements (BP, pulse and weight) will be presented at the 6 week and 4 month follow-up visits by treatment group. Descriptive statistics as well as changes from baseline will also be presented by study group at each scheduled visit.

Hearing loss will be presented in a tabular form at the 6 week visit by treatment arm.

MMSE and BSRT will be tabulated at the 6 week and 4 month follow-up visits by treatment group.

13.9.7. Pooling

Subgroup analysis of the primary efficacy endpoint by center will be used to evaluate the poolability of the results. The subject continuous quit status at week 6 by center interaction will be tested with a logistic regression model, using a significance level of 10%. If the interaction is found significant, the reasons for these interactions will be further explored and rationalized. This evaluation may include demographic features, symptoms at presentation, clinical and treatment history, and center comparability in the features found to be associated with the primary efficacy variable. Sites with a small amount of subjects (<10) will be pooled together for this analysis by geographical location.

13.9.8. Handling of missing data

If a subject missed a clinic visit but had been abstinent (i.e., a negative confirmatory test) at the clinical visits prior to and following the missing visit, and claimed abstinence throughout, that subject will be classified as abstinent. Dropouts and subjects lost to follow will be classified as non-abstinent.

Additionally, the following methods of imputation may be used for the primary endpoint as further sensitivity analyses:

- Tolerability/Imputation: Assume all subjects terminated from the study due to tolerability issues are failures. For other subjects, the outcome will be obtained from the last valid assessment.
- Last Observation Carried Forward: Most recent visit with a valid assessment will be carried forward and used for the endpoint determination for these subjects.
- Multiple Imputation: Impute endpoint data using a multiple imputation model based on sex, age, race and history of smoking at baseline, as well as endpoint data computed at each intermediate time-point for all subjects with observed data.
- Best Case Scenario: Assume all subjects with missing data in the active group are successes; Assume all subjects in the sham group with missing data are failures.
- Worst Case Scenario: Assume all subjects with missing data in the active group are failures; Assume all subjects in the sham group with missing data are successes.

14. RISK / BENEFIT ANALYSIS

14.1. Risks

The risks to patients resulting from potential device hazards have been analyzed using the Risk Management Standard - ISO 14971. The different types of hazards were identified and evaluated using risk assessment numerical parameters. Applicable controls for the risks were analyzed. After the implementation of appropriate risk control measures, the level of risk was re-evaluated and found to be acceptable. Most of the identified hazards and risks may be successfully mitigated with appropriate design, manufacturing and appropriate validation methods, such as testing and compliance with international standards and clinical validation in a randomized, double blind, controlled, clinical investigation. Furthermore, instructions manuals and physician training will further mitigate some of the risks.

14.2. Benefits

Studies have demonstrated that high-frequency rTMS of the DLPFC can attenuate nicotine consumption (Eichhammer et al., 2003; Amiaz et al., 2009) and craving (Johann et al., 2003). However, the significance and duration of these effects are limited. One possible reason for these partial effects on nicotine consumption might be the superficial magnetic stimulation by the figure-8 coil, which does not reach into the deep layers of the cortex. It is known that nicotine addiction involves various areas of the brain reward system, in which most of them are deeper than the superficial layers of the cortex, like the anterior cingulated, orbitofrontal cortex, nucleus accumbens, and amygdala. Another area of interest which was not stimulated using the superficial rTMS is the insula. The crucial role of the insula in cravings for food, cocaine and cigarettes, was reported by neuroimaging studies (Bonson et al., 2002; Pelchat et al., 2004; Wang et al., 2007). Therefore stimulating the insula and the dipper layers of the lateral PFC could be substantially more effective in treating nicotine addiction. The Brainsway DTMS is designed to stimulate neuronal pathways related to the control of motivation, reward and pleasure, specifically, over the right and left lateral PFC and insula. Previous feasibility studies on a small number of subjects indicated preliminary safety and effectiveness of the treatment as an aid in smoking cessation.

The purpose of this study is to evaluate the efficacy and safety of the DTMS treatments in chronic smokers as an aid in smoking cessation.

15. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators and the sponsor, and are mandated by regulatory agencies worldwide.

15.1. Definitions

15.1.1. Adverse Event Definitions and Classifications

- **Adverse Event**

An adverse event is any untoward medical occurrence in a clinical study subject. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. (Definition per International Conference on Harmonization [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

- **Serious Adverse Event**

A serious adverse event as defined by ICH is any untoward medical occurrence that meets any of the following conditions:

– Results in death
– Is life-threatening
– Requires inpatient hospitalization
– Results in persistent or significant disability/incapacity, or
– Is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by investigator to have a significant clinical impact.

- **Unlisted (Unexpected) Adverse Event**

An unlisted adverse event, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or the package insert/summary of product characteristics for an approval product) (ICH)

- **Associated With the Use of the Device**

An adverse event is considered associated with the use of the TMS if the attribution is possible, probable, or very likely by the definitions listed above.

15.1.2. Relationship to Investigational Device

For all adverse events, the relationship to study device and / or procedure will be determined by the investigator, using the following terms:

- **Probably related:**

Follows a reasonable temporal sequence from study device delivery / retrieval, and cannot be reasonably explained by known characteristics of the patient's clinical data or the surgical procedure applied.

- **Possibly related:**

Follows a reasonable temporal sequence from study device delivery / retrieval but could have been produced by the patient's clinical state or by the surgical procedures regardless of the study device.

- **Probably not related:**

Temporal association is such that the study device is not likely to have had any reasonable association with the observed event.

- **Not related:**

No relationship to study device activation is perceived.

15.2. Procedures

15.2.1. All Adverse Events

All adverse events will be reported from the time a signed and dated informed consent form is obtained until completion of the last study-related procedure. Events meeting the definition of serious adverse events must be reported using the Serious Adverse Event Form, including serious adverse events spontaneously reported to the investigator within 30 days after the subject has completed the study (including post study follow up).

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. All adverse events, regardless of seriousness, severity, or presumed relationship to study treatment must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "Upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study treatment. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions. In the case of a seizure, the investigators will provide to those patients experiencing a seizure a letter documenting that the seizure was experimentally produced. Other potential adverse events which could occur include psychiatric complications (e.g., mania, changes in behavior, hostility, agitation, depression and suicidality), headache, neck pain, intensification of existing headaches, tinnitus, and temporary or permanent hearing loss. The study personnel staff will be responsible for observing the study subjects during the weekly assessments and follow-up visits for such adverse events. In the case of an adverse event, the study investigator will prescribe the appropriate treatment and if appropriate, the subject will be terminated from the study to ensure subject safety.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator all serious adverse events that are unlisted and associated with the use of the treatment. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

15.2.2. Serious Adverse Events

All serious adverse events occurring during clinical studies must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Form, which must be signed by a member of the investigational staff. The initial report of a serious adverse event may be made by facsimile (fax), e-mail or telephone. It is preferable that serious adverse events are reported via fax or e-mail.

Subsequent to a telephone report of a serious adverse event, a Serious Adverse Event Form must be completed by the investigational staff and transmitted to the sponsor within 1 working day.

All serious adverse events that have not resolved by the end of the study, or that have not been resolved upon discontinuation of the subject's participation in the study must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The event can be attributed to agents other that the study treatment or to factors unrelated to study conduct
- When it becomes unlikely any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The cause of death of subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalization for:

- Pre-planned hospitalizations, i.e. before enrollment into the study and which are not related to the disease itself
- Social reasons in absence of an adverse event
- Surgery or procedure planned before entry into the study (must be documented in the CRF)

15.2.3. Pregnancies

Pregnancies occurring during the study must be reported by the investigational staff within 1 working day of their knowledge of the event. Any subject who becomes pregnant during participation in a clinical study for which pregnancy is a standard exclusion criterion must be promptly withdrawn from the study. Follow-up information regarding the outcome of the pregnancy and any postnatal sequaele in the infant will be required.

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Only subjects who have the capacity to provide informed consent will be allowed to enroll in the study. As part of the screening of subjects for entry into the study, the investigator will assess each subject's ability to provide informed consent for participation in the study. The investigator must document the subject's ability to provide informed consent before consent is obtained from the subject.

The protocol includes strict requirements to ensure adequate protection of all subjects participating in the study, including:

- Subjects will be carefully screened using medical, psychiatric and physical examinations before enrollment. Those who are judged to be at high risk for adverse events, self-harm or violence will be excluded.
- Only subjects who have the capacity to provide informed consent will be allowed to enroll in the study, and they may withdraw their consent at any time without having to give a reason and can continue to receive regular, quality conventional therapy.
- Subjects will be fully informed as to the risks of study participation, they are free to withdraw from the study at any time and they will be provided with any new information about the study treatment that becomes available during their participation in the study.
- Informed consent will be obtained from subjects without undue enticement. Subjects will not be coerced in any way to participate in this study. Excessive financial compensation will not be offered to subjects or to investigators.
- Subjects will be screened for medical and psychiatric illnesses that may introduce added health risks.
- Investigators will monitor subjects with regular study visits and may withdraw them at any time on the basis of clinical judgment.
- Safety evaluation will be done at regular intervals, including monitoring for possible adverse events, including tolerability of TMS treatment and concomitant medication.

16.2. Regulatory Ethics Compliance

16.2.1. Investigators Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and if applicable, amendments
- Informed consent from (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments
- Subject recruiting materials
- Information on compensation for study-related injuries or payments to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after IEC/IRB has given full approval of the final protocol, amendments (if any), and the informed consent form, applicable recruiting materials, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the documents being approved.

During the study the investigator will send the following documents to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to subjects
- If applicable, new or revised subjects recruiting materials approved by the sponsor

- Revisions to compensation for study-related injuries or payment to subjects for participations in the study, if applicable
- Investigator's Brochure amendments or new addition(s)
- Summaries of the status of the study (at least annually or at intervals stipulated in guidelines of the IEC/IRB)
- Reports of any serious adverse events
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of death of subjects under investigator's care
- Notification if new investigator is responsible for the study at the site
- Any other requirements of the IEC/IRB

For protocol amendments that increase subject risk, the amendments and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s). At least once a year the IEC/IRB will be asked to review and re-approve this clinical study. This request and approval should be documented in writing. At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form used must be approved by both the sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles set forth in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before entry into the study, the investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort it may entail. Subjects will be informed that the participation is voluntary and that they may withdraw consent to participate at any time, they will be informed that choosing not participate will

not affect the care the subject will receive for the treatment for his/her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the subject is authorizing such access, and agrees to be re-contacted after study completion, by health authorities and authorized sponsor staff, for the purpose of obtaining consent for additional safety evaluation if needed.

The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by name of the subject, subject's signature and date of signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written explanations) and should personally date and sign the inform consent form after the oral consent of the subject or legally acceptable representative is obtained.

16.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study. This data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

17. ADMINISTRATIVE REQUIRMENTS

17.1. Protocol Modifications

The investigator will not modify this protocol without a formal amendment. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

The investigator or other physician in attendance will contact the sponsor representative by fax or telephone regarding any situations requiring a departure from the protocol. If possible, contact will be made before implementing any departure from the protocol. In all cases contact with the sponsor must be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source document will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Pre-study Documentation

The following documents must be available and maintained during the study:

- Approved Study Protocol and amendment(s)
- A copy of the dated and signed written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Regulatory authority approval or notification, if applicable

- Documentation of investigator qualifications (e.g., curriculum vitae)
- Completed financial disclosure form
- Signed and dated clinical trial agreement, which includes the financial agreements
- Other documentation required by local regulations

17.2.3. Subject Identification Register and Subject Screening Log

The investigator agrees to complete a subject identification register to permit easy identification of each subject during and after the study. The subject identification register will be treated as confidential. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by initials and assigned number only. The investigator will also complete a subject-screening log, which reports all subjects who were seen to determine eligibility for inclusion in the study.

17.2.4. Case Report Form Completion

All data relating to the study will be recorded in CRFs. Data will be entered into CRFs in English or Hebrew. The CRFs are to be completed at the time of the subject's visit, so that they always reflect the latest observations on the subjects participating in the study. Every effort should be made to ensure that all subjective measurements (e.g., pain scale information or other questionnaires) to be recorded on the CRF are completed by the same individual who made initial baseline determinations. The investigator must verify that all data entries in the CRFs are accurate and correct.

17.3. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential, Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed sense the formal discontinuation of clinical developments of the investigational products These

documents will be retained for a longer period if required by regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

CRFs will be documented in an EDC system. If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such report.

17.4. Study Completion/Termination

17.4.1. Study Completion

The study is considered completed with the last visit of the last subject undergoing the study.

17.4.2. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time. The investigational site will be closed upon study completion. Reasons for the early closure of an investigational site or termination of the study may include but are not limited to:

- Safety concerns, including a high rate (3%) of suicide or suicide attempts or a high rate of seizures (5%)
- Sufficient data suggesting lack of efficacy
- Inadequate recruitment of subjects by the investigator

17.5. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will oversee the clinical study and advise the Sponsor and investigators involved in the study. The DSMB will consist of at least three independent experts; one expert in the clinical aspects of smoking addiction and treatments (a psychiatrist); an investigator in the field of neurophysiology of smoking cessation (a neurologist); and a biostatician (statistical expert). The responsibilities of the

DSMB is to periodically review and evaluate the accumulated study data for participant safety, study conduct and progress and to make recommendations concerning the continuation, modification, or termination of the clinical study. At the conclusion of the review, the DSMB will recommend continuation of the study without change, modification of the study, or the termination of the study. The DSMB will convene every 6 months. Face-to-face meetings are preferable, but teleconferences or videoconferences are also acceptable.

18. REFERENCES

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Appendix A: Time and Events Schedule

Table 1: Screening and treatment period

			Week 1					Week 2					Week 3					Wk 4	Wk 5	Wk 6	4 MO
Visit	SC	BL	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19
TMS/Placebo			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Informed Consent[a]	√																				
Inclusion/ Exclusion	√																				
Medical history	√																				
Smoking history	√																				
Con Meds	√	√										√					√	√	√	√	√
Physical Examination		√																		√	√
Vital signs[b], height & weight		√																		√	√
Randomization		√																			
Cotinine Sample		√										√					√	√	√	√	√
FTND		√																		√	√
MNWS		√										√					√	√	√	√	√
TCQ-SF		√										√					√	√	√	√	√
Nicotine Craving Scale before smoking cue before treatment			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Nicotine Craving Scale after smoking cue before treatment			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	

Nicotine Craving Scale after treatment			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Daily Smoking Diary		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Auditory Test	√																			√	
Pregnancy Test[c]	√																				
MMSE	√																			√	√
BSRT		√																		√	√
Adverse Events[d]		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

[a] Informed consent has to be obtained prior to any study-related procedure.
[b] Includes pulse and systolic and diastolic blood pressure. Both measurements will be done while the subject is sitting and after 5 minutes of rest.
[c] For females of child-bearing potential.
[d] Monitoring of adverse events begins after the Informed Consent Form is signed and the first study-related procedure is performed, and continues until the last study-related procedure is performed.
[e] all measures will take before rTMS treatment administration.

Appendix B: INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.
I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment and the conduct of the study.

_____

Investigator's Signature Date (Day Month Year)

_____

Name of Investigator (Typed or Printed)

_____

_____

_____

Institution and Address*

_____

Telephone number*

_____

Sponsor's Representative Signature Date (Day Month Year)

_____

Name of Sponsor's Representative (Typed or Printed)

_____

_____

_____

Sponsor Address*

_____

Telephone number*

* If the address or telephone number of he investigator changes during the course of study, written notification will be provided by the investigator to the sponsor and will not require protocol amendment(s).