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Dear Dr. Cunningham and Dr. Boren,

New evidence has recently been published in 2020 to support the effectiveness, safety and durability of Deep Transcranial Magnetic Stimulation (Deep TMS or dTMS) for patients with treatment resistant obsessive-compulsive disorder (OCD) as demonstrated in the previously published feasibility and pivotal studies (Carmi 2018 and 2019). Based upon the new peer-reviewed evidence of 8 studies/sub-analyses including real world evidence representing level I – III papers, we request coverage reconsideration for Deep TMS for patients with treatment-resistant OCD in LCD L33398 (Transcranial Magnetic Stimulation) effective 1/13/2020. and the addition of ICD-10 diagnostic codes F42.2 and F42.8 to associated article A57528 (Billing and Coding).

This letter provides a background of OCD, current treatment continuum, an overview of Deep TMS technology, a summary of the published evidence and a recommended coverage policy (endorsed by the Clinical TMS Society (CTMSS)) including appropriate patient selection criteria and the Deep TMS treatment protocol.

Background

Patients with OCD suffer with obsessions, compulsions, or both. Obsessions are repetitive, intrusive, and distressing thoughts, ideas, images, or urges often experienced as meaningless, inappropriate, and irrelevant. These obsessions persist despite efforts to suppress, resist, or ignore them. Compulsions are repetitive, stereotyped behaviors and/or mental acts that are used to diminish the anxiety and distress associated with the obsessions. The obsessions and compulsions cause the patient distress and take up a significant amount of time. Most patients engage in significant avoidance behaviors because of their obsessions and compulsions. The clinical definition and diagnostic criteria of are specified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and includes the degree of insight (good, fair, poor, absent, delusional) as well as the presence of tics.

Several inclusive models have been used to explain the neurobiology of OCD. One is the executive control model, where the deficits are defined as lack of impulse control and behavioral inhibition. Another is

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modulatory control, where the deficit is in regulating socially appropriate behaviors. Additionally, there is the uncertainty disorder, which is defined as an imbalance between input suppression and inhibition. Regardless of the model, an imbalance in regions of the cortical-striatal-thalamic-cortical (CSTC) pathway are present. This pathway consists of multiple parallel interconnected loops between cortical and subcortical areas whose role is to determine which actions are selected as important and which are ignored. These regions include the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), cingulate cortex, caudate nucleus, striatum and thalamus. Abnormalities in the functioning of this pathway results in impulsivity, compulsivity, obsessions, uncertainty, deficits in attentional allocation, sensory-motor gating, and the modulation of motor activity, in addition to many other deficits.

The lifetime prevalence of OCD is 2.3%, and the 12-month prevalence is 1.2%[1]. Approximately 2.24M adults suffer annually from OCD in the U.S. and 36.6% (820k) seek professional treatment[3]. By comparison, major depressive disorder has a lifetime prevalence of 15%[2]. Up to 50% of OCD patients OCD are found to be treatment-resistant[4-6], representing an estimated 410k patients annually.

The course of OCD is usually *chronic*, often with waxing and waning symptoms. Some patients experience an episodic course, whereas a minority of patients experience a deteriorating course. Even with treatment, remission rates are low. The course of OCD is often complicated by the co-occurrence of other neuropsychiatric disorders. *90% of adults with OCD have at least one other diagnosis, most commonly mood and anxiety disorders.* Specifically, 63% have a lifetime history of mood disorder, 41% have major depressive disorder, 23–32% have comorbid obsessive-compulsive personality disorder, 29% have a lifetime history of tic disorder, and 12% have schizophrenia[7]. Two out of five patients with OCD have significant occupational impairment and cannot work. OCD ranks 10th in the World Bank and World Health Organization causes of disability. The burden from OCD comes from neuropsychiatric illness costs, general health care utilization cost, unemployment, and reduced productivity over time.

OCD is diagnosed clinically, by a psychiatrist or a psychologist in a diagnostic interview. There are no imaging or laboratory examinations for OCD. The standardized rating scale for severity is the Yale-Brown Obsessive-Compulsive Scale (YBOCS), which is a clinician rating scale that takes approximately 40 minutes to administer the first time in detailed format and 20 minutes to re-administer at follow-up.

Continuum of Care and Current Treatments

Over the past few decades, there have been little to no advancements and no new treatment modalities for OCD. The American Psychiatric Association (APA) treatment guidelines from 2013, are identical to the 2007 treatment guidelines and there is consensus with worldwide treatment guidelines. Existing treatments for OCD include medications, psychotherapy, and psychosurgery. Generally, a response to treatment is defined as ≥ 25% - 35% YBOCS reduction from baseline. The YBOCS score is an asymmetrical score, where a reduction of 1 point can be quite significant (e.g., a reduction of obsession time from 9 hours to 3 hours a day). The existing APA 2013 guidelines advise physicians to initiate OCD treatment with

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a serotonin reuptake inhibitor for a patient who is very depressed or very anxious or if the patient had a good response in the past. Cognitive behavioral therapy (exposure and response prevention) is recommended if the patient is not too depressed or anxious; this treatment is based on availability or patient preference. If patients do not respond to either medication or therapy, both treatments can be combined.

Five medications are approved by the FDA for OCD: Fluoxetine, Paroxetine, Sertraline, Fluvoxamine and Clomipramine, all of which are serotonin reuptake inhibitors. These medications generally require higher doses and longer duration (≥ 12 weeks) in order to see an effect when compared to medications for depression. All of the previously listed medications have been available for close to 30 years, and 40-60% of patients with OCD do not show any response. Furthermore, many patients who show a response still remain with moderate OCD. These patients also experience unpleasant side effects, or the medications lose efficacy over time, resulting in discontinuation.

OCD is a chronic illness, and biological treatments are not expected to cure the disorder. Pharmacological interventions require continuous dosing at the same level that was effective to achieve response. Exposure and response prevention treatments and cognitive therapy are administered with a bolus, skills acquisition phase and subsequently patients continue with less frequent maintenance treatment. Patients who are unsuccessfully treated in the outpatient setting can transition to partial hospitalization or residential treatment if available in their region. The most refractory patients are eligible for psychosurgery or Deep Brain Stimulation (DBS), but patients relapse when their stimulators are turned off. Practically, only patients who reach mild severity or remission can be expected not to introduce new treatments into their regimen and wait for their disease to worsen. OCD patients who remain with moderate severity will then attempt treatments they have avoided in the past. Because of this there are very few published durability studies, and there is no consensus definition of durability. In a meta-analysis of 24 randomized controlled studies with over 1600 patients analyzed at 4 weeks and 3-6 months post cognitive behavioral therapy, almost 80% of patients remained symptomatic after treatment and there was no durability at 3-6 months, only at 4 weeks post treatment.

The primary effective type of therapy for OCD is a specialized form of cognitive behavioral therapy called exposure and response prevention (ERP). During ERP the patient's OCD symptoms (obsessions or compulsions) are provoked in a controlled setting where the patients are taught to control their anxiety. This procedure is repeated at home as daily homework. ERP is done for longer durations with escalating provocations. Patients who benefit from this treatment typically work with an exposure and response prevention therapist for their whole life, because new obsessions and compulsions develop over time. Exposure and response prevention is considered the first line for insightful patients with non-comorbid and non-extreme OCD. Patients with comorbid disorders generally do not participate with prolonged exposures or do daily homework because of its anxiety-evoking qualities.

Surgical interventions for OCD are reserved for treatment refractory OCD patients. These are patients who failed to respond to three full medication trials, and six months of exposure and response therapy

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including three times a week face-to face appointments. The results are promising because neurosurgery results in response for 60% of the few patients who utilize this route of treatment. However, most patients are afraid of the risks of an invasive neurosurgical procedure.

TMS Technology

Transcranial magnetic stimulation (TMS) uses electromagnetic coils over the skull to induce an electrical current in the underlying neurons, thereby depolarizing a particular area of the brain. Repetitive trains of pulses, repetitive transcranial magnetic stimulation (rTMS) can induce longer lasting changes (neuroplasticity), particularly when this procedure is repeated over multiple days. Traditional rTMS technology uses an electromagnetic figure-8 coil to stimulate neurons focally. Deep TMS or Deep rTMS uses H-coils to stimulate much deeper and broader regions. While traditional Figure-8 coils penetrate .7 cm subdural and impacting a volume of 3 cm^3, the Deep TMS H7-coil for OCD penetrates 3 cm subdural impacting a volume of 75 cm3 and stimulating millions of more neurons than with the Figure-8 coil.

Deep TMS technology for OCD

The BrainsWay H7-coil TMS system is composed of four main components: an electromagnetic H7-coil, TMS stimulator, cooling system and positioning arm. Additionally, each patient receives a personal head cap and positioning grid for the duration of their treatment. The H1 coil was FDA cleared in January 2013 for the treatment of major depressive disorder (MDD). The H7-coil was FDA cleared in August of 2018 for the treatment of obsessive-compulsive disorder (OCD)[8] and the H4 coil was FDA cleared in 2020 for smoking addiction. The experimental system has two coils in the same helmet, a sham and active coil, the sham coil has a similar acoustic artifact as the active coil, and it administers a superficial stimulation to maintain blinding. The system assigns the active or sham coil based on the patient ID during the high frequency treatment.

TMS technicians and clinicians undergo hands on training and certification by BrainsWay for the use of the system. The patient undergoes a YBOCS checklist, and using the YBOCS checklist results, a hierarchy of obsessions and compulsions is created. The hierarchy aides in creating a list of patient specific internal and external provocations to evoke moderate to severe distress. Subsequently, the provocations are reviewed between the clinician and the TMS system technicians, in preparation for the patient's TMS treatment course.

The system operator (TMS technician) determines the motor threshold (MT) of the lower extremity with the active coil using single pulses, and then advances the coil 4cm anteriorly to the treatment position. The patient's OCD symptoms are provoked for up to 5 minutes using individualized internal and external provocations previously designed by the clinician. The targeted distress level from the provocation is between 4-7/10 on a visual analog scale (VAS). When the appropriate distress level is reached, the TMS protocol is initiated following the instructions in the IFU (100%MT, 20Hz, 2sec, 20sec ITI, 2000 pulses over 18.3 mins) using either the active or sham coil in a blinded fashion. This procedure is repeated five days a

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week for twenty-nine treatments. The MT must be re-determined at least once a week, if there are any medication changes (for several days after steady state is reached), or if there any clinical causes that effect the seizure threshold such as significant changes in sleep or caffeine intake. The first treatment usually takes one hour, the daily treatment usually takes thirty to forty-five minutes, and the weekly re-measurement takes forty-five to sixty minutes.

The seizure risk with TMS is low (Tendler et al. 2018 & 2020; Zibman et al. 2019), but it is higher in patients with epilepsy and other preexisting neuronal lesions (Bae et al. 2007; Pereira et al. 2016). TMS emits an audible click with each pulse. Even though the sound may not sound very loud, it is a repetitive noise heard many times over the course of multiple days and may cause hearing loss. All patients and operators must use hearing protection rated at least 30 dB of noise reduction. TMS is contraindicated in any patients with ferromagnetic or conductive material in the head.

In the pivotal multicenter clinical trial (**Carmi et al. 2019 Attachment 1)**, there were no differences between the active and sham coil in the incidence of adverse events. The most common adverse event was headache. There was only one drop out due to pain. In clinical practice, the following adverse events are anticipated: headaches, facial pain, brief dizziness, and seizures.

Evidence:

A summary Table of Deep TMS evidence papers is provided in **Attachment 2.** Study descriptions and outcomes of these papers are described below:

The H7 system was evaluated for OCD in a pilot single-center study followed by a multicenter clinical trial. The pilot study randomized 41 treatment resistant OCD subjects who were stabilized on their medications for eight weeks to one of three study arms **(Carmi et al. 2018 Attachment 3).** Fourteen subjects received sham treatment, sixteen subjects received high frequency (20Hz) Deep TMS treatment and eight subjects received low frequency (1Hz) Deep TMS treatment. All treatments were administered following symptoms provocation, and EEG measurements during a Stroop task were acquired to examine changes in error-related activity. The results of the interim analysis demonstrated that only 2 out of 8 patients in the low frequency group had decreased YBOCS. These results supported abandoning the low frequency arm of the study. Two subjects withdrew consent at the beginning of the study for personal reasons; and the remaining subjects completed the study in its entirety and without significant adverse events. The only reported adverse events were transient headaches, which resolved shortly after the treatment began. The high frequency group (20Hz) change in YBOCS was significantly larger than sham and the response rate significantly higher than sham for at least one-month following treatment. Notably, the clinical response in the HF group correlated with increased Error Related Negativity (ERN) in the Stroop task, an electrophysiological component that is attributed to ACC activity.

These promising results were the basis for the multicenter study.

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A post-hoc analysis was conducted on the behavioral data to test the hypothesis that stimulation would induce long-term modifications to cognitive functions associated with error monitoring (**Alyagon et al. 2020 Attachment 4):** Pre- and Post-treatment Stroop data was available for 12 patients of the active group and 10 patients of the sham group. Analysis demonstrated that response time was improved with Deep TMS but not in the sham treatment group. Deep TMS restored speed/accuracy tradeoff similar to that seen in healthy population.

The pivotal study was a multicenter trial that included 99 outpatients from 11 sites, using the most effective parameters from the preliminary study (20Hz) in a prospective double blinded fashion (**Carmi et al. 2019 Attachment 1).** Subjects had current *moderate to severe OCD* and were stabilized on their OCD medications for at least eight weeks. The study consisted of three phases: screening phase (approximately 2-3 weeks, with no treatment); 6-week treatment period (daily treatment with Deep TMS or sham); and a follow-up visit 4 weeks after the study ended (the 10-week visit).

Of significance in the pivotal study protocol design, was that the Intent to Treat (ITT) analysis and the Modified Intent to Treat (mITT) analysis sets to assess outcomes. The Intent to Treat (ITT) analysis set (all patients who received at least one active/sham treatment) was *predefined in the protocol as the main analysis set for safety*. The Modified Intent to Treat (mITT) analysis set (all patients who met eligibility criteria and received at least one active/sham treatment) was predefined in the protocol as the *main analysis set for efficacy (primary and secondary outcomes)*. Five patients in the study were found to not meet study inclusion criteria (changed medication during treatment) and therefore removed from the study analysis before unblinding. The primary and secondary effectiveness outcomes (mITT) are further identified below at 4- and 6-week time points (treatment) and at 10 weeks (4-week follow-up).

The **primary endpoint** was the change in the YBOCS score from baseline to week 6. The YBOCS score decreased by 6.7 points in the Deep TMS group and 3.6 points in the sham group at the 6-week visit (p=0.0157). The estimated slope in the Deep TMS group was -6.0 points across 6 weeks versus only -3.3 in the sham group. The difference between the slopes of 2.8 points over 6 weeks was found statistically significant (p=0.0127). The reduction in the YBOCS of 6.0 points is clinically meaningful and statistically significant when compared to sham. The effect size of 0.69 demonstrates a difference between the two groups, which is large enough and consistent enough to be clinically important.

The secondary endpoints of the study include the change from baseline compared to six weeks and ten weeks of the Clinical Global Impression Severity scale (CGI-S), Sheehan disability score, YBOCS score, response rate, partial response rate and remission rate. The change from baseline at the 10-week visit, demonstrates the YBOCS score decreased by 7.6 points in the Deep TMS group and by 4.7 points in the sham group. At the 10-week visit, the adjusted YBOCS score decreased by 6.5 points (95% CI: [4.3;8.7]) in the Deep TMS group versus 4.1 points (95% CI: [1.9;6.2]) in the sham group; these decreases were both statistically significant. The difference between the treatment groups is also statistically significant (p=0.038) and clinically meaningful. Based on the 10-week YBOCS score results, the effect size of the study is 0.62 (Cohen's D). The BrainsWay Deep TMS multicenter study may be considered to have a greater than

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medium to large effect size. Thus, as aforementioned, *the treatment effect is maintained for at least 4 weeks after completion of all treatment sessions, at 10 weeks.*

At the 6-week visit, the response rate (defined as a reduction from baseline of ≥ 30% in YBOCS) in the Deep TMS group was 38.1% versus 11.1% in the sham group. The response rate was significantly higher in the Deep TMS group compared to the sham group (p=0.0033). The partial response rate (defined as a reduction from baseline of at least 20% in YBOCS score) at the 6-week visit in the Deep TMS group was 54.8% versus 26.7% in the sham group. This difference is also statistically significant p=0.0076. The responder results are not only statistically significant but also clinically meaningful, as demonstrated by the effect size expressed in terms of Number Needed to Treat (NNT). Based on the response rates, the effect size as obtained by the NNT = (1/difference in response rates) is 3.7, which means that for every 4 patients treated with the BrainsWay Deep TMS System, 1 subject will have a response due to the device.

At the 10-week visit, the response rate was 45.2% in the Deep TMS group compared to 17.8% in the sham group, with the difference between the Deep TMS group and sham group remaining statistically significant (p=0.0057). There was also a further increase in the response rate at the 10-week visit (45%) in the Deep TMS group compared to the 6-week visit (38%), demonstrating a *further positive treatment effect maintained over time*. The effect size as obtained by the NNT was 3.64, which still means that for every 4 patients treated with the BrainsWay Deep TMS System, 1 subject will have a response due to the device. In the categorical analysis, 70% of the Deep TMS subjects were evaluated by clinicians as having some global improvement (ranging from minimal to very much improved) and 49% reported an "Improved" (moderate to very much improved) clinical state at 6 weeks as a result of the Deep TMS treatment. This is compared to only 58% of subjects in the sham group who reported some improvement with only 21% experiencing a moderate to very much "Improved" clinical state. There is a statistically significant difference (p=0.0112) between the percentage of BrainsWay Deep TMS subjects experiencing an "Improved" clinical state compared to the sham group at 6 weeks. The CGI Improvement results are maintained 4 weeks after treatment at the 10-week visit. At week 6, more subjects had an "Improved" CGI Severity (CGI-S) score in the Deep TMS group (61%) than in the sham group (32.6%), and this difference was reported as statistically significant (p=0.0221). The CGI Improvement and CGI Severity results support and strengthen the significant clinical effect of the BrainsWay Deep TMS treatment.

The differences in the change from baseline in the Sheehan Disability Scale (SDS) scores in the Deep TMS group compared to the Sham group were not statistically significant at 6 or 10 weeks. The improvement in these parameters may be more latent and not yet apparent at 6 or 10 weeks. It should be noted that the SDS assessment scale (and remission rates) are not commonly used as a study endpoint in evaluating SSRI medications in FDA approved NDAs and therefore, the clinical significance of these findings is limited.

Of note on Disability is to the challenge to identify a significant impact on disability rating per the Sheehan scale unless one sees a significant improvement in the YBOCS OCD scale. As a patient improves in their OCD symptoms, the impact on disability will also improve. Based upon improvement in YBOCS from 6 to 10 weeks, it may have been too soon to assess the impact on disability in such a short time frame. It should

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be noted that SSRI studies showed an improvement (change in Y-BOCS) from baseline after 10-13 weeks (from 2.45 to 3.87 points) in medically naïve patients (Soomro et al., 2008), where Deep TMS studies showed an improvement of 3.1 points at 6 weeks in patients who had failed to achieve response to 1 or more medication trials or psychotherapy.

Data from the multicenter pivotal trial was further evaluated to investigate the effect of treatment resistance, as expressed by number of failed medication trials and prior CBT, on the efficacy of Deep TMS in OCD **(Roth et al. 2020 Attachment 5**). The sample was divided into groups containing subjects with insufficient response to one or two medications (1–2 Meds cohort) versus subjects with insufficient response to three or more medications (3+ Meds cohort). In addition, subjects were divided into cohorts who either received prior CBT (of at least 2 months with a therapist) or did not receive prior CBT (Past CBT/No CBT). Response rates and YBOCS change from baseline over time were assessed in each subset. The majority of patients were in the 3+ Meds (63%, 53/84 completers) or Past CBT (68%, 57/84) cohorts. There were no significant differences in age or gender between the cohorts. Response at post-treatment was significantly higher in the Deep TMS group compare to sham in the larger cohorts of 3+ meds (Deep TMS: 41.4%; sham: 8.3%; p=0.0109) and of Past CBT (Deep TMS: 33.3%; sham:3.3%; p=0.0041). This analysis demonstrates that Deep TMS is an effective treatment option for OCD patients, regardless of prior non-response to SRIs ± antipsychotics or CBT sessions. This supports the hypothesis that the mechanism of action of Deep TMS for OCD is different from that of pharmacotherapy or CBT and may be based on direct modulation of the cortical-striatal-thalamic-cortical circuitry.

Storch E. et al. (2020 Attachment 6) performed a post hoc analysis on the multicenter trial to examine predictors and moderators of treatment outcomes. Among the different factors examined, older age, lower baseline severity, and lower baseline functional disability significantly predicted a faster rate of symptom reduction at post-treatment, regardless of treatment condition. Baseline OCD severity moderated treatment outcomes both at post-treatment and follow-up, with Deep TMS showing stronger efficacy relative to sham for those with more severe symptoms (YBOCS>28). Additionally, older age predicted faster symptom reduction from baseline to post-treatment and follow-up, independent of treatment condition.

Real-world evidence from post-marketing data on treatment details and outcome measures was obtained on 219 patients from 22 clinical sites with the H7 coil. The primary outcome measure was response (30% reduction in YBOCS score from baseline to endpoint) and the secondary outcome measures were first response (the first time the YBOCS score has met response criteria) and sustained response (when two consecutive YBOCS scores met response criteria). Response rate after 29 Deep TMS treatments was 58% - higher than the 38.1% reported in the multicenter pivotal trial. The onset of effect is relatively quick compared to psychotherapy and pharmacotherapy. Additionally, a continuous gradual reduction in YBOCS was evident up to 40 Deep TMS sessions with a 50% response at 31 days and 78% response at 60 days. **(Roth et al. 2020 Attachment 7)**

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An analysis of OCD Deep TMS responders from a single site including multicenter and open-label participants defined durability as days to loss of efficacy by patient and clinician survey. Three months post treatment was the minimum follow up time for inclusion, unless durability was lost earlier. Durability data was available for 38 responders. By survival analysis, after 3 months the Deep TMS effect was durable in 26/36 (72%) patients and after 6 months in 18/36 (50%) patients. Durability significantly negatively correlated with number of failed medications (p=0.04). Patients with only one prior medication had significantly longer durability (p=0.007; 711 vs. 264 days, respectively). A non-significant tendency of younger patients to have longer durability was observed and in patients with durability longer than 3 months there was a significant negative correlation with age (p=0.012). Prior CBT failure, gender, YBOCS did not correlate with durability. In conclusion, Deep TMS for OCD demonstrated an overall average durability of 426 days and median durability of 201 days. **(Tendler et al. 2020 Attachment 8)**

Other studies:

As many OCD patients have co-morbid mood (major depressive disorder) and anxiety disorders, a post hoc analysis of the OCD pivotal trial data and comparison of the YBOCS and Hamilton Depression Rating Scale (HDRS) data from a subset of OCD patients with MDD comorbidity (YBOCS $\geq$ 20; HDRS21 $\geq$ 16) was conducted between the active Deep TMS (N=9) and sham (N=10) groups **(Harmelech et al. 2020 Attachment 9).** At week 6 treatment endpoint and at 1-month follow-up in subjects with comorbid OCD-MDD, subjects had a 55.6% and 66.7% response rate respectively ($\geq$30% reduction in YBOCS from baseline). Additionally, a statistically significant difference between Deep TMS and sham treated subjects was also seen in the change in Y-BOCS scores at both 6 week and one month follow-up points. The analysis further demonstrated that treating comorbid OCD-MDD patients with the H7 in the protocol cleared for OCD is sufficient to improve their MDD symptoms as well. A statistically significant decrease in HDRS scores from baseline was observed at all time points ($p<0.05$ for weeks 2-4, $p<0.01$ for week 6, $p<0.005$ for 1-month follow- up) in the active Deep TMS group, but not in the sham group ($p>0.05$). 44.4% in the active Deep TMS group showed response at 6 weeks and 55.6% at one-month follow-up vs. 10% and 30% in the sham group.

A sub-group analysis from the real-world evidence registry was conducted to evaluate the clinical impact of Deep TMS treatment on moderate to severe OCD patients with comorbidities. (**Vidrine et al. 2020 Attachment 10**). 38 patients with OCD were treated in accordance with the BrainsWay pivotal trial. 3 subjects were treated for OCD alone, without comorbid depression. The remainder of subjects had comorbid depression as well as additional comorbidities. Most subjects completed the standard 30 sessions and 6 taper sessions, with an average completion of 34 sessions. At the end of 6 weeks, 45% of patients were responders ($\geq$30% reduction in YBOCS from baseline) and 60% were partial responders ($\geq$20% reduction in YBOCS from baseline).

A retrospective chart review from 3 clinics (2009 -2018) was conducted to evaluate the safety of Deep TMS in the treatment of adolescents. 28 patients ages 13-21 were treated (6 with the Neurostar, 21 with the H1, H7 and H4 Deep TMS coils, and 1 patient received both Neurostar and Deep TMS) for Major

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depressive disorder (MDD), bipolar depression, OCD, autism, post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), attention deficit hyperactivity disorder (ADHD), and chronic pain syndrome & GAD. (**Tendler et al. 2019 Attachment 11)**

Health Technology Assessments: Recent analyses such as the Blue Cross Blue Shield Association (BCBSA) tend to assess the pivotal trial and challenge the effectiveness on Intent to Treat (ITT) analysis and not modified ITT (mITT) analysis at 6 weeks. The ITT analysis set (N=100) (received at least one active/sham treatment) was *predefined in the pivotal trial protocol* as the analysis set for safety. The mITT analysis set (*met eligibility criteria and received at least one active/sham treatment*) was *predefined in the protocol* as the analysis set for efficacy (primary and secondary outcomes). Comments were also made at the 6-week patient improvement on disability (Sheehan disability scale (SDS)). The improvement in disability parameters may be more latent and not yet apparent at 6 or 10 weeks. It should be noted that the SDS assessment scale (and remission rates) are not commonly used as a study endpoint in evaluating SSRI medications in FDA approved new drug applications and therefore, the clinical significance of these findings is limited.

The recent published papers reinforce the consistency of the effectiveness data both in level I-III studies as well as in the real-world evidence registry. In reviews of rTMS in the treatment of OCD, metanalyses of many studies which go back 20 years, group all studies with the current Deep TMS literature to state mixed results. Unfortunately, the majority of the traditional rTMS studies with figure 8 coils tended to stimulate varying brain structures, at different frequencies and showed mixed effectiveness. The current evidence of the Deep TMS H7 coil focused on broader and deeper stimulation of the anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC) has shown consistent significant effectiveness in this chronic treatment-resistant OCD population.

> Example from BCBS FEP 2.01.50 effective 1/1/2020 and BCBS MA #297
>
> For individuals who have obsessive-compulsive disorder (OCD) who receive rTMS, the evidence includes a number of small-to moderate sized sham-controlled RCTs and a meta-analysis of these studies. The meta-analysis of 15 RCTs (total n=483 patients, range 18-65 patients) found a benefit of rTMS on patient-reported OCD symptom severity at time points ranging from 2 to 6 weeks, but **there was substantial variability in the stimulation parameters, including the cortical region that was stimulated and the frequency of stimulation**. A more recent RCT compared Deep rTMS to sham in 99 patients for 6 weeks, with an additional 4 weeks of follow-up as a secondary outcome. Using a modified intent to treat (ITT) analysis (n=94), there was a larger mean change from baseline on the primary efficacy outcome; Yale-Brown Obsessive-Compulsive Scale (YBOCS) score in the active treatment group (-6.0 points) than the sham group (-2.8 points), translating to a moderate effect size of 0.69. At 6 weeks, the response rate was 38.1% in the active treatment group compared to 11.1% in the sham group (P=0.003), as measured by a 30% or greater decrease in the YBOCS. **The difference in the primary outcome measure between active and sham groups was not statistically significant in the ITT analysis. There was a benefit for rTMS on clinician-**

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reported measures of improvement, but no significant difference between groups on patient-reported disability and impairment. Additional trials with sufficient sample size and follow-up duration are needed to confirm these results. The evidence is insufficient to determine the effect of the technology on health outcomes.

Current OCD Guidelines have no recent updates. The American Psychiatric Association (APA) OCD Guidelines have not been updated since 2013, and The National Institute for Health and Care Excellence (NICE) since 2005. The Clinical Transcranial Magnetic Stimulation Society (CTMSS) published their Coverage Guidance for TMS treatment of OCD in January 2021 (**Attachment 12**) and specific guidance on patient selection criteria and treatment parameters is included.

Hayes (Mar 2020) technology assessment was referenced in a recent payer policy and stated that concern still remains regarding if rTMS is efficacious in managing OCD symptoms. The review looked at a large number of RCTs (14) and presented mixed findings regarding whether rTMS is superior to sham control treatments for the OCD indication. Recent meta-analyses pooled these small trial results and suggest a potentially beneficial picture of rTMS treatment, but there was a lack of endorsement from national organizations at that time. Most analyses again tend to review all TMS trials and combine the mixed outcomes with that of Deep TMS.

Medical Community Demand:

There are nearly 629 Deep TMS systems in the US (treating MDD) and 216 systems now have the OCD helmets to treat these patients as well. Over two and a half million patient treatments have been performed to date. The H7 coil (OCD) has been used to treat approximately 1,700 patients and 49,000 treatment sessions have been performed to date. Several insurance companies have covered the treatment of OCD on a case-by-case basis, but the majority of patients have been by self-pay.

Based upon the strength of the new clinical and real-world evidence to reinforce the effectiveness and safety of Deep TMS treatment, we appreciate your coverage consideration for this underserved treatment resistance OCD population where a significant unmet medical need exists.

Should you have any questions or require additional information, we are happy to meet with you as well as connect you with an experienced Deep TMS provider.

Sincerely,

Scott Blackman
Director, Market Access
Brainsway

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Attachments:

1. Carmi et al. American Journal of Psychiatry (2019) (Pivotal trial)
2. Deep TMS Evidence Summary Table
3. Carmi et al., Brain Stimulation 11(1):158-165 (2018) (Feasibility Trial)
4. Alyagon U. et al., Brain Stimulation (2020) (Impact on Cognitive function)
5. Roth et al. Psychiatry Research 290. 2020 113179 (Treatment resistance)
6. Storch E. et al. (2020) J. Psychiatric Research (predictors and moderators of response)
7. Roth Y. et al. J. Psychiatric Research (2020) (RWE)
8. Tendler A. et al. CTMSS (2020) (Durability)
9. Harmelech T et al. Brain Stimulation 13 (2020) (co-morbid OCD & MDD)
10. Vidrine R. et al CTMSS (2020) (Moderate-Severe OCD patients with comorbidities
11. Tendler A. et al. Brain Stimulation (2019) (Adolescent Safety)
12. Clinical TMS Society (CTMSS) Coverage Guidance for TMS for OCD (Jan 2020)

Appendixes:

A. Bibliography
B. References

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APPENDIX A: Deep TMS OCD Bibliography (10 papers)

(2) Feasibility Trial (Carmi 2018)

1. Carmi, L. et al. Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients. Brain Stimulation, Jan-Feb 2018;11(1):158-165.

Post hoc analysis deep TMS impact on modification of cognitive function (Alyagon 2020)

2. Alyagon, U. et al. Modifications of cognitive performance in the Stroop task following deep rTMS treatment course in OCD patients. Brain Stimulation. Nov 9, 2020 DOI: https://doi.org/10.1016/j.brs.2020.11.008. 14 (2021) 48-50.

(4) Pivotal Trial (Carmi 2019)

3. Carmi L., et al. Efficacy and Safety of Deep Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Prospective Multicenter Randomized Double-Blind Placebo-Controlled Trial. Am J Psychiatry, 2019 Nov 1;176(11):931-938.

Post-hoc subgroup analysis paper including pats who failed 3-4 meds (Roth 2020)

4. Roth Y. et al, Deep TMS for OCD is efficacious even in patients who failed multiple medications and CBT. Psychiatry Research 2020;290

Post-hoc subgroup analysis of predictors & moderators of treatment (Storch 2020)

5. Storch E. et al. Moderators and Predictors of Response to Deep Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder. Journal of Psychiatric Research, Nov 2020

Post-hoc subgroup analysis: OCD patients w/co-morbid MDD. OCD & MDD outcomes (Harmelech 2020)

6. Harmelech T. et al. Do Comorbid OCD-MDD Patients Need Two Separate dTMS Protocols. Brain Stimulation 13 (2020) 1000-1001

(3) RWE - Registry (Roth 2020)

7. Roth Y. et al. Real-world efficacy of deep TMS for obsessive-compulsive disorder: Post-marketing data collected from twenty-two clinical sites. J. Psychiatric Research. 4 Nov 2020

RWE prospective single site clin outcomes OCD and comorbid MDD abstract (Vidrine 2020)

8. Vidrine, R, et al. Clinical Outcomes using dTMS targeting the DMPFC-ACC in Treatment0Resistant OCD. Poster sessions, CTMSS Annual Meeting 2020

RWE prospective single site and long-term durability abstract (Tendler 2020)

9. Tendler A. et al. Initial report on long-term durability of deep TMS for obsessive compulsive disorder. Poster sessions, Brain Stimulation 13 (2020) 1842-1862 / Abstracts

(1) RWE - Adolescent Safety MDD and OCD RWE, (Tendler 2019)

10. Tendler A, et al. Safety of Deep TMS Coils in Adolescents. Abstracts, Brain Stimulation 12 (2019) e129-e142

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Appendix B: References

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3. Mayerovitch JI, du Fort GG, Kakuma R, et al. Treatment seeking for obsessive-compulsive disorder: role of obsessive-compulsive disorder symptoms and comorbid psychiatric diagnoses. Compr Psychiatry. 2003 Mar-Apr;44(2):162-8.
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