SPONSOR EXECUTIVE SUMMARY

neuroAD™ THERAPY SYSTEM FOR THE TREATMENT OF MILD TO MODERATE ALZHEIMER'S DISEASE
NEURONIX LTD.

DEN160053

MARCH 21, 2019

TABLE OF CONTENTS

Page

TABLE OF CONTENTS
(continued)

Page

TABLE OF CONTENTS
(continued)

Page

LIST OF TABLES

Page

LIST OF TABLES
(continued)

Page

LIST OF FIGURES

Page

LIST OF FIGURES
(continued)

Page

1.0 SUMMARY

1.1 Disease Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the gradual onset of dementia. AD is a devastating and irreversible disease resulting in cognitive and functional decline, tremendous stress on family members and caregivers, ultimately resulting in the patient's death. There are 5.7 million people in the United States (US) living with AD, 5.5 million of whom are age 65 years or older. Those who suffer from AD experience a host of symptoms including: memory loss, problems in executive functions, challenges in planning or problem solving, confusion, trouble understanding verbal and spatial relationships, trouble speaking, and decreased or poor judgment. As the disease progresses, cognitive and functional abilities continue to deteriorate until the person requires assistance with even the most basic activities of daily living, such as bathing, dressing, eating, and using the bathroom. Those who progress into more severe stages of AD may become bed-bound and require 24 hour care. AD and its associated conditions (e.g., pneumonia) are now the third leading cause of death in the US.[1]

1.2 Current Therapies and Unmet Need

Out of the top 10 leading causes of death in the US, AD is the only disease which cannot be prevented, cured or even slowed down in its progression. There are only four approved drugs which are currently used for treatment of AD – three cholinesterase inhibitors (ChEI) and an NMDA blocker – as well as an approved combination therapy. These drugs offer symptomatic benefit, for a limited period of time (between 6 to 12 months), after which deterioration resumes. Notably, no new types of drugs have been approved during the past 20 years, and no near-term approvals are anticipated based on ongoing studies. Failed clinical trials have unfortunately been commonplace in this treatment space since the 1990's, including at the latest stages of clinical research – over 400 such compounds have failed in clinical testing.

The unsuccessful history of development of new treatment options for AD is widely recognized by regulators, patients and caregivers, and physicians who treat AD. As noted by U.S. Food and Drug Administration (FDA or the Agency) Commissioner Gottlieb,[2] making new treatment options for AD available to the public is a priority of FDA. The Agency also acknowledged the unmet need in AD treatment options by granting expedited access pathway ("EAP") status for the neuroAD Therapy System (neuroAD) because the device "*may offer significant, clinically meaningful advantages over existing legally marketed alternatives; and the availability of the device may be in the best interest of patients (e.g. addresses an unmet medical need.)*." AD patients and their caregivers are also keenly aware of the need for new treatment options.

1.3 Scientific Basis of neuroAD

Transcranial Magnetic Stimulation (TMS) is a technology that allows for discrete non-invasive probing and modulation of cortical excitability and functions.[3] TMS, if applied repetitively, produces an electromagnetic field in the brain that induces a modulation in brain cortical excitability.[4] The biological mechanism explaining the effects of high-frequency repetitive TMS (rTMS) on the brain has been suggested to involve an increase in synaptic plasticity.[5] TMS has been studied extensively since being introduced in 1985 for various psychiatric and neurological conditions, including posttraumatic stress disorder, schizophrenia, and Parkinson's disease. TMS is currently FDA-cleared in the US for treatment of refractory depression,[6] migraine headache with aura,[7] and

Obsessive Compulsive Disorder (OCD).[8] A delayed, offline effect is possible for TMS treatments and has been reported in TMS studies.[9] It is estimated to have been used in millions of treatments of patients in the US.[10] TMS is recognized as effective and safe, with the primary side effects reported to be transient headache, neck pain, local pain, tooth ache, and paresthesia.[11]

The neuroAD Therapy System combines rTMS with cognitive training and was developed to provide an adjunctive (add-on) treatment for patients with mild to moderate AD. The device has been under clinical investigation for approximately 10 years, with the first-in-man ("FIM") study taking place in 2009. Since the FIM study, the device has been investigated in a number of clinical trials throughout the world, including a US Pivotal Study. It received the European Conformity ("CE") mark in 2012, and is approved and distributed in Europe, Australia, and Israel for treatment of AD.

1.4 Device Description

The neuroAD Therapy System delivers non-invasive, magnetic stimulation to induce electrical currents directed at spatially discrete regions of the cerebral cortex for the stimulation of cortical neurons. TMS intensity is based on the patient's daily Motor Threshold (MT) as determined by standard procedures.[12] Concurrent with TMS administration, the neuroAD Therapy System also administers adaptive computer-based cognitive training exercises targeted to the same region of the cerebral cortex that is being stimulated. TMS is believed to make the targeted regions of the cerebral cortex more receptive to the cognitive training.

The proposed indications for use are:

> *The neuroAD Therapy System is intended for neuro-stimulation concurrently combined with cognitive training. neuroAD Therapy System is indicated for the treatment of mild to moderate dementia of the Alzheimer's type in patients with a baseline ADAS-Cog score up to 30. neuroAD Therapy System may be used in conjunction with other pharmacological and non-pharmacological therapies.*

neuroAD was designed as an adjunctive treatment to provide a safe, clinically significant benefit in patients over and above the Standard of Care (SOC). It does not require patients to discontinue use of other treatments. As described further below, the majority of patients in the US Pivotal Study were taking pharmacological treatments. Therefore, the benefits seen with neuroAD were in addition to the benefits already achieved by drugs, without any observed increase in side effects. Further, neuroAD complies with all internationally-accepted TMS safety guidelines.[13] In sum, neuroAD affords physicians the opportunity to apply a multifaceted approach to treating AD, and affords patients the opportunity for additional benefit over and above the standard of care today, with minimal increased risk.

1.5 Supporting Clinical Evidence

In support of the *de novo* request for the neuroAD, Neuronix Ltd. (Neuronix, or the sponsor) has submitted to FDA data for a total of 374 subjects (Active and Sham). The primary evidence of device effectiveness and safety comes from the US Pivotal Study, a prospective, randomized, multi-center, double-blind, sham-controlled investigation in 130 subjects. In addition, two independent studies using the neuroAD device were conducted in Korea (these studies were not sponsored by Neuronix), under very similar protocols to the US Pivotal Study. Ten supplemental investigations,

conducted in both clinical and commercial use settings, are provided as further evidence of device safety and efficacy. These studies consistently show a clinical benefit of neuroAD, with minimal risk.

1.5.1 US Pivotal Study

The US Pivotal Study was a prospective, randomized, multi-center, double-blind, sham-controlled investigation. The design of the study was discussed with FDA in pre-submission interactions prior to initiation. See **Appendix 1** for the full protocol.

The study was conducted at ten clinical centers, which included nine US sites and one site in Israel. 130 subjects were randomized to either:

- Active group – neuroAD Therapy System treatment: TMS stimulation and cognitive training, or
- Sham/control group – sham TMS and pseudo cognitive training

The US Pivotal Study investigated effectiveness using two different assessments: the Alzheimer's Disease Assessment Score – Cognitive (ADAS-Cog) and the Alzheimer's Disease Cooperative Study Clinical Global Impression of Change Scale (ADCS-CGIC), described below:

- Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog)

ADAS intends to measure the severity of the most important symptoms of Alzheimer's disease. Its subscale ADAS-Cog is the most popular cognitive testing instrument used in clinical trials of nootropics. It consists of 11 tasks measuring the disturbances of memory, language, praxis, attention and other cognitive abilities which are often referred to as the core symptoms of AD.

The total score ranges from 0-70 points and measures the number of mistakes counted in the test. A higher result represents greater cognitive dysfunction. AD patients deteriorate on average in the range of 4 to 7 points per annum, depending on the level of their dementia.[14]

ADAS-Cog is globally considered as the gold standard for evaluation of cognitive performance in Alzheimer's dementia, and was used as a primary endpoint in all approved cholinesterase inhibitor drug approval studies (donepezil, rivastigmine, galantamine, and tacrine (which is no longer on the market)). However, there is no established or agreed-upon threshold as to what change in ADAS-Cog constitutes a clinically meaningful change.

A copy of the ADAS-Cog Administration and Scoring Manual is included in **Appendix 2**. In commercial use, the company plans to use a 3rd party vendor to train and certify users in administration of the ADAS-Cog instrument.

- ADCS-Clinical Global Impression of Change (ADCS-CGIC)

The Alzheimer's Disease Cooperative Study – Clinical Global Impression - Change scale (ADCS-CGIC) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past diagnosis with the patient. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating. Assessment is performed using a structured interview with both the patient and the caregiver.

The purpose of the baseline measurement of ADCS-CGIC is to set the reference for future comparison.

The 7-point scale is characterized as follows: 1-very much improved; 2-much improved; 3-minimally improved; 4-no change; 5-minimally worsened; 6-much worsened; or 7-very much worsened.

ADCS-CGIC has been used, in particular, in studies that led to the marketing approval of donepezil, galantamine, and memantine, and in later rivastigmine studies.

By definition, any change measured on the ADCS-CGIC scale is clinically meaningful.[15]

A copy of the ADCS-CGIC questionnaire is included in **Appendix 3**.

The primary objectives of the US Pivotal Study were: (1) to evaluate the efficacy of the neuroAD Therapy System in the improvement of mild to moderate Alzheimer's disease patients' cognitive function compared with Sham after 6 weeks of treatment using ADAS-Cog score; and (2) to demonstrate device safety.

The secondary objectives of the study were: (1) to demonstrate device efficacy using ADCS-CGIC after 6 weeks of treatment; (2) to demonstrate efficacy using ADAS-Cog score after an additional 6 weeks of follow-up; and (3) to demonstrate efficacy using ADCS-CGIC after an additional 6 weeks of follow-up.

The primary endpoint was mean change in ADAS-Cog at week 7 compared to baseline. The secondary efficacy endpoints were mean change in ADAS-Cog at week 12 compared to baseline, and mean ADCS-CGIC score at weeks 7 and 12. The main analysis populations included the Safety Population (all patients), Primary Efficacy (PE) Population,[1] and the Per-Protocol (PP) Population.[2]

1.5.1.1 Safety

In terms of safety, the neuroAD treatment was well tolerated by participating subjects. A relatively similar percentage (p=NS) of Active group subjects (41%) and Sham group subjects (32%) experienced adverse events.

In the Active group, 50 of 63 adverse events reported were determined to be not related or unlikely related to the study procedure (10 events possibly related, 3 events probably related and no events definitely related). Similarly, 48 of the 63 adverse events in the Active group were determined to be unrelated or unlikely related to the study device (8 events possibly related, 5 events probably related, and 2 events definitely related). Both adverse events in the Active group that were definitely device related were headaches that resolved.

All adverse events that were possibly, probably, or definitely related to the study procedure or device were mild in severity and transient, and were event types that were expected when applying TMS.

[1] Primary Efficacy Population – PE Population consists of all randomized subjects with baseline ADAS-Cog score and at least one follow-up visit where ADAS-Cog score is reported.

[2] Per-Protocol Population – PP Population was a subset of the PE Population of subjects who had no major protocol violations likely to affect the outcome and met minimum treatment sessions. Note that 97% of the PE Population belonged to the PP Population, representing the clear majority of the PE Population.

The longest lasting event resolved within approximately 1 week. The most commonly reported related adverse events were headache, skin discomfort, and neck pain. While the most significant risk of TMS reported in literature and guidance,[16],[17],[18] though rare, is inducement of seizures, no seizures were reported in the study.

In both groups, most adverse events were mild in severity. The single severe event (death) occurred in the Active group and was determined to be unrelated to the study device or procedure by the site investigator and medical committee. Given the age of the study population, it was not unusual that an unrelated patient death occurred during the study.

Two serious adverse events were reported in the Active group and one in the Sham group, all determined to be unrelated to the study procedure or device. In the Active group, these events included one case of asthenia, which resolved in 6 days, and one death (as discussed above). In the Sham group, one serious event (urinary retention) was reported. One additional unrelated serious adverse event (cervical fracture due to a fall at home) was reported in a patient recruited for the study, prior to randomization and commencement of any study-related procedures. This patient was never randomized.

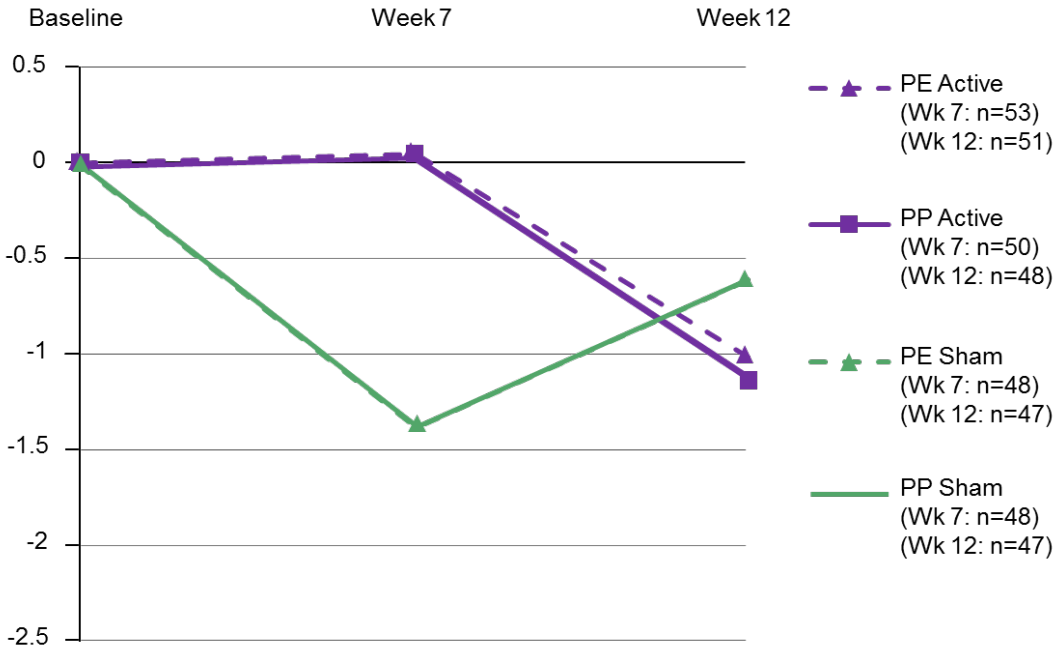
Thus, the study demonstrated the highly favorable safety profile of the neuroAD Therapy System, with no evidence of significant risk to patients. In addition to a low rate of adverse events, the study also found a high rate of treatment compliance (93% of subjects attended ≥ 26 out of 30 sessions). Few subjects withdrew from the study and none discontinued due to an adverse event. Both of these factors support that the treatment is well tolerated.

1.5.1.2 Effectiveness

The primary efficacy analysis was performed on the PE Population, evaluating change in ADAS-Cog score at week 7 compared with Baseline. The analysis of the primary endpoint revealed minimal mean change in ADAS-Cog at 7 weeks in the Active group (mean change of 0.07) compared to the Sham group (-1.38) in the overall Pivotal Study population. This difference was not statistically significant. Therefore, the original primary endpoint assessing mean change in ADAS-Cog at 7 weeks was not achieved. Similar results were obtained for the Per-Protocol (PP) Population (0.04 and -1.38, respectively, also non-significant).

However, by 12 weeks, which was a pre-specified secondary endpoint of the study, the change in the Active group improved in the PE Population (mean difference from baseline of -1.03) and the improvement originally observed in the Sham group had decreased (-0.61). Similar results were obtained for the PP Population (-1.13 and -0.61, respectively). These differences were also not statistically significant.

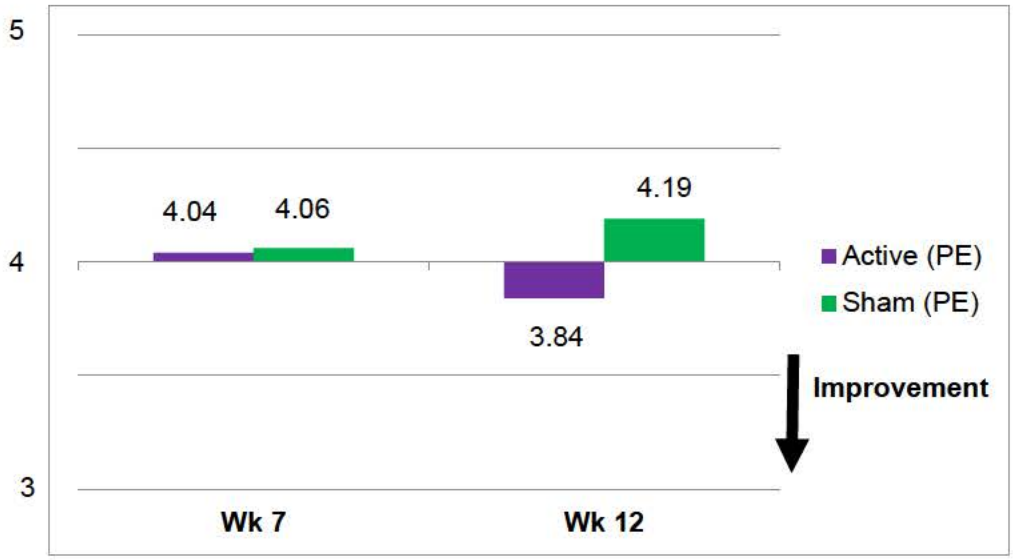
Figure 1: Mean Change in ADAS-Cog from Baseline to Weeks 7 and 12, US Pivotal Study (All Patients)



*Note that negative numbers indicate improvement

Looking at the secondary endpoint of ADCS-CGIC, at 7 weeks, results for the Active and Sham groups were similar (4.04 and 4.06, respectively; difference non-significant), while at 12 weeks, the Active group improved (mean score 3.84), and the Sham group deteriorated (mean score 4.19). At 12 weeks, the mean between-group difference was -0.35 (favoring the Active group), and the results were statistically significant using a Chi-square analysis for the distribution (Wilcoxon test p-value = 0.11; post-hoc Chi-square test p-value = 0.037). Furthermore, when examining the percentage of patients who showed deterioration on the ADCS-CGIC scale (represented by a score of >4), there was a significant difference between the Active group (8/50 (16%) deteriorated) and Sham group (18/43 (42%) deteriorated). This difference was statistically significant (post-hoc two-sided Fisher's exact test, p-value = 0.01).

Figure 2: Mean ADCS-CGIC, US Pivotal Study (PE Population)



As it is commonly known from the literature that baseline ADAS-Cog interacts with treatment outcome, the Statistical Analysis Plan (SAP) prospectively included baseline ADAS-Cog as a covariate to assess interaction with efficacy outcome. This analysis revealed a statistically significant interaction between treatment group outcome at 7 weeks and baseline ADAS-Cog score (p-value = 0.029). This interaction was even more pronounced at 12 weeks (p-value = 0.0072).

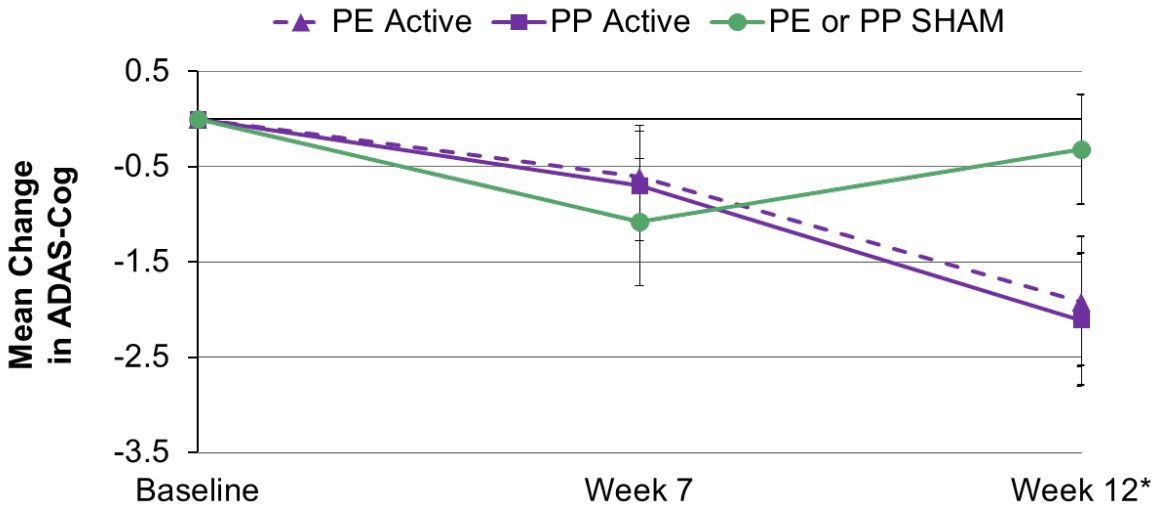
This strong interaction indicates a non-homogeneous effect across different baseline values. Although a specific cut-off for baseline ADAS-Cog was not pre-specified, a cut-off of 30 was selected based on published literature. For example, Rutherford et al.[19] conducted a TMS intervention study on AD patients and concluded that patients with baseline ADAS-Cog ≤ 30 responded better to the intervention than patients with baseline ADAS-Cog > 30. Ito et al.[20] performed a meta-analysis on 52 AD studies (including approximately 20,000 AD patients) and found that baseline ADAS-Cog is a significant covariate affecting the rate of disease progression, and that more demented patients (e.g., patients with baseline ADAS-Cog > 30) deteriorate faster than less affected patients (e.g., patients with baseline ADAS-Cog ≤ 30). Importantly, the subgroup of subjects with baseline ADAS-Cog ≤ 30 represents the vast majority of the study population (85% of the study cohort).

In addition, a cut-off of 30 is supported by review of the data related to cognitive training performance and baseline Motor Threshold, which guides the TMS power setting. The maximum level of performance of patients on the neuroAD Cognitive Paradigms was significantly different (p-value < 0.01) between the two groups (subjects with baseline ADAS-Cog ≤ 30 and subjects with baseline ADAS-Cog > 30), indicating that more severe patients could not engage with and progress through the cognitive training paradigm as well as less severe patients. In addition, analyses showed that patients with lower ADAS-Cog values at baseline had higher baseline Motor Thresholds, and therefore, higher TMS power settings. When comparing Motor Threshold values between groups, subjects with baseline ADAS-Cog ≤ 30 have significantly higher Motor Threshold values than subjects with baseline ADAS-Cog > 30 (p-value = 0.0028). Thus, more seriously affected patients are potentially less likely to benefit from both the cognitive training component and the TMS component of neuroAD treatment.

Based on the pre-planned covariate analysis and literature, a refined treatment population with baseline ADAS-Cog ≤30 was evaluated (referred to as the "Baseline ADAS-Cog ≤ 30 Subgroup"). Analyzing the data among subjects with baseline ADAS-Cog scores ≤30 at 7 weeks showed that both Active and Sham groups improved, with a small and non-significant difference (Active = -0.61 and -0.70 for PE and PP, respectively; Sham = -1.08 for PE and PP).

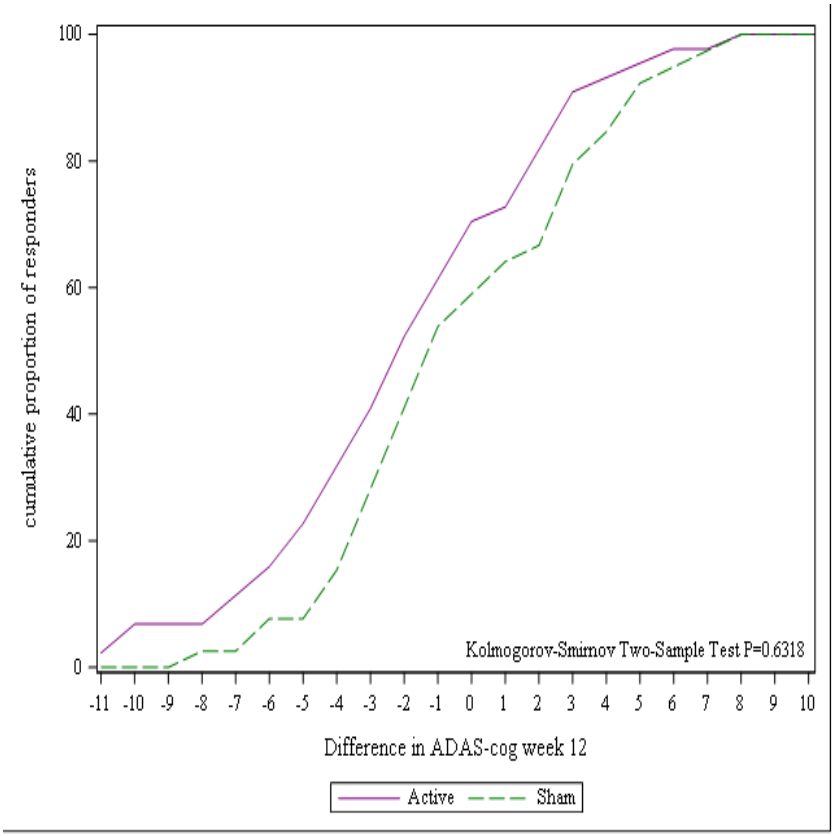
At 12 weeks in the Baseline ADAS-Cog ≤ 30 Subgroup, the Active group continued to improve while the Sham group deteriorated towards baseline (Active = -1.92 and -2.11 for PE and PP, respectively; Sham = -0.32 for PE and PP). In terms of between-group difference for mean change in ADAS-Cog at 12 weeks, the Active group significantly outperformed the Sham group in the PP Population (difference -1.79, p-value = 0.049) and neared statistical significance in the PE Population (difference -1.61, p-value =0.07).

Figure 3: Mean Change in ADAS-Cog, US Pivotal Study (Baseline ADAS-Cog ≤ 30 Subgroup)



Furthermore, when examining the response rate of subjects ("S-curves"), it is clear that for every threshold selected, the Active group in the Baseline ADAS-Cog ≤ 30 Subgroup outperforms the Sham group at 12 weeks. Moreover, benefit was observed in the vast majority of Active subjects at this time point, which was demonstrated by improvement or absence of deterioration compared to baseline (i.e., change ≤ 0). Per the S-curve analysis, more than 70% of the Active subjects show either improvement or no deterioration with ADAS-Cog-change ≤ 0, at 12 weeks in the PE Population. Interestingly, about one-third of Active subjects show remarkable improvement of at least -3 to -4 points. In addition, more than double the number of Active subjects (31.8% PE, 31.7% PP) in the Baseline ADAS-Cog ≤ 30 Subgroup showed an improvement of ≤ -4 points on ADAS-Cog than in the Sham group (15.4%).

Figure 4: S-Curve for Change in ADAS-Cog at 12 Weeks, US Pivotal Study (Baseline ADAS-Cog ≤ 30 Subgroup)



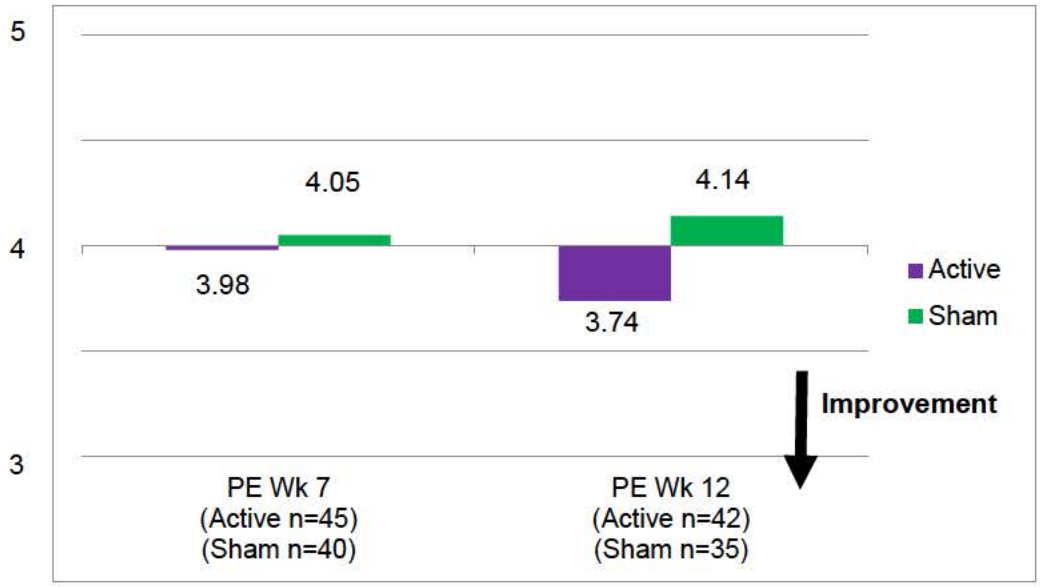
In terms of ADCS-CGIC, for the PE and the PP Populations, the Active arm of the Baseline ADAS-Cog ≤ 30 Subgroup reported a lower (i.e., improved) mean ADCS-CGIC score than the Sham arm at each time point.

At 7 weeks, the Active arm in the Baseline ADAS-Cog ≤ 30 Subgroup improved, and the Sham arm deteriorated (mean scores of 3.98 for PE/PP and 4.05 for PE/PP, respectively; difference non-significant).

At 12 weeks, the Active arm in the Baseline ADAS-Cog ≤ 30 Subgroup continued to improve (mean score 3.74/3.69 for PE/PP, respectively), and the Sham arm continued to deteriorate (mean score 4.14 for both PE/PP). Thus, the Active group outperformed the Sham group on average by -0.40 in the PE Population or -0.45 in the PP Population, and results were statistically significant (Wilcoxon test p-value = 0.10/0.07 for PE/PP respectively; Chi-square test p-value = 0.041/0.035 for PE/PP respectively).

In the Baseline ADAS-Cog ≤ 30 Subgroup, only 5 out of 42 (11.9%) subjects worsened on the ADCS-CGIC scale in the Active arm versus 14 out of 35 (40.0%) subjects in the Sham arm. This difference was statistically significant ($p<0.01$, two-sided Fisher's exact test).

Figure 5: ADCS-CGIC Score by Visit and Study Group, US Pivotal Study (Baseline ADAS-Cog ≤30 Subgroup)



Finally, when considering a post-hoc dual-end point analysis in the Baseline ADAS-Cog ≤ 30 Subgroup (combining subjects' performance on both ADAS-Cog and ADCS-CGIC), the Active group outperforms the Sham group, and the difference is statistically significant (Chi-square test p-value = 0.0463). Importantly, 64.3% of the Active group either improved or did not change on both ADAS-Cog and ADCS-CGIC (defined as ADAS-Cog ≤ 0 and ADCS-CGIC ≤ 4, respectively) compared to 42.9% of the Sham group. In addition, only 7.1% of the Active group reported worsening on both measures compared to 22.9% of the Sham group.

Based on the study results, the company elected to limit the indicated population to those who showed greater and more consistent benefit from neuroAD Therapy System treatment, both in terms of mean improvement and less variability in outcomes: patients with baseline ADAS-Cog ≤30. In this population (the Baseline ADAS-Cog ≤ 30 Subgroup), the positive outcomes observed at 12 weeks, in both ADAS-Cog (difference of -1.79 over Sham, PP Population) and ADCS-CGIC (difference of -0.45 over Sham, PP Population), provide strong evidence of the device benefit.

Thus, in summary, the effectiveness analyses show the following:

- Although the pre-specified primary endpoint of the study (ADAS-Cog improvement at 7 weeks compared to baseline) was not met, there was evidence of increasing improvement over time, with 12-week results showing improvement in the Active group compared to 7-week results, while the Sham group deteriorated toward baseline over this time period.
- There was clear evidence of a relationship between baseline ADAS-Cog and outcome, with patients with a baseline ADAS-Cog ≤30 performing better than those with a baseline ADAS-Cog > 30. This baseline variable (although not the specific threshold) was pre-specified as a covariate in the protocol. The specific threshold of 30 was selected based on literature and is consistent with the understanding of the effects of the neuroAD treatment combining TMS and cognitive training on subjects.
- Benefit in both ADAS-Cog (difference of -1.61 and -1.79 points favoring the Active group for PE and PP Populations, respectively, p = 0.07 and p = 0.049) and ADCS-CGIC (difference of

-0.40 and -0.45 points favoring the Active group for PE and PP, respectively, Chi-square p = 0.041 and p = 0.035) was shown at 12 weeks for patients with a baseline ADAS-Cog ≤ 30.

- For the selected subgroup of subjects with baseline ADAS-Cog ≤ 30, regardless of the ADAS-Cog cut-off selected, the Active group outperforms the Sham at 12 weeks, with over 40% of Active patients showing at least a 3-point improvement and more than 70% showing either improvement or no change (change ≤ 0) at 12 weeks compared to baseline. Only 11% of Active group subjects showed deterioration, compared to 40% of Sham group subjects.
- In a post-hoc dual-endpoint analysis, 64.3% of patients either improved or did not deteriorate on both ADAS-Cog and ADCS-CGIC endpoints (defined as a score of ≤ 0 on ADAS-Cog and ≤ 4 on ADCS-CGIC). The magnitude of benefit on each scale is consistent, and the evidence of benefit in two scales further supports the positive treatment effect (Fisher's Exact Test, p = 0.0463).

1.5.2 Korean Studies

Two studies using the neuroAD device were conducted in Korea by independent investigators (these studies were not sponsored by Neuronix). See **Section 6.3** for additional details on the design and results of these two studies. The Korean Pilot Study was conducted under a similar protocol as the US Pivotal Study. Based on the findings of the Korean Pilot Study, the investigators, independent of Neuronix (and before the results of the US Pivotal Study were known), concluded that milder patients were the most likely to respond to neuroAD System treatment, as outlined in the published paper on this study.[21] To confirm this hypothesis, the Korean Pivotal Study was designed in a similar manner to the Korean Pilot Study and the US Pivotal Study, except that study enrollment was limited to mild AD patients with baseline ADAS-Cog 17-30. This cut-off for the baseline ADAS-Cog (i.e., ≤30) is identical to the cut-off for the proposed indicated subgroup from the US Pivotal study, and therefore can serve as an independent confirmatory study to validate this subgroup. Both the Korean Pilot Study and the Korean Pivotal Study used the same treatment procedure as the US Pivotal Study, as well as ADAS-Cog follow-up assessments at 7 and 12 weeks following treatment initiation.

No serious adverse events, or related AEs, were reported in the Korean Pilot or Korean Pivotal Studies.

Both studies report positive ADAS-Cog outcomes at the 7-week and 12-week time points. When considering only the patients with baseline ADAS-Cog ≤ 30, the between-group difference for mean change in ADAS-Cog at 7 weeks was -2.43 (Korean Pilot Study) and -2.54 (Korean Pivotal Study) in favor of the Active group. The between-group difference for mean change in ADAS-Cog at 12 weeks was –1.70 (Korean Pilot Study) and -1.73 (Korean Pivotal Study) in favor of the Active group. In addition, in both studies, the Active group reported increased improvement between the first and second follow-up visit.

Due to protocol similarities, a meta-analysis combining the US Pivotal and the two Korean studies was performed. Using a weighted mean difference ("WMD") analysis of the mean change in ADAS-Cog, the Baseline ADAS-Cog ≤ 30 Subgroup Active arm demonstrated greater improvement than the Sham arm at 7 weeks (-1.21 favoring the Active arm, 95% CI: -3.53 to 1.12, p-value = 0.31) and at 12 weeks (-1.66 favoring the Active group, 95% CI: -3.03 to -0.29, p-value = 0.017).

Figure 6: Meta-Analysis (US Pivotal + Korean Pilot + Korean Pivotal) at 7 Weeks (Baseline ADAS-Cog ≤ 30 Subgroup)

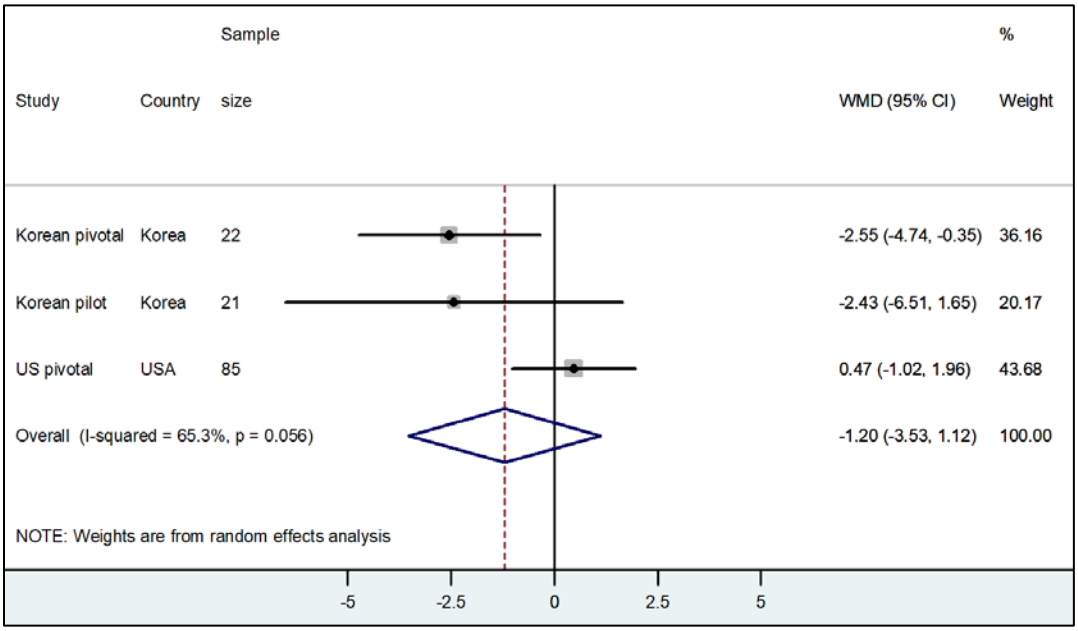
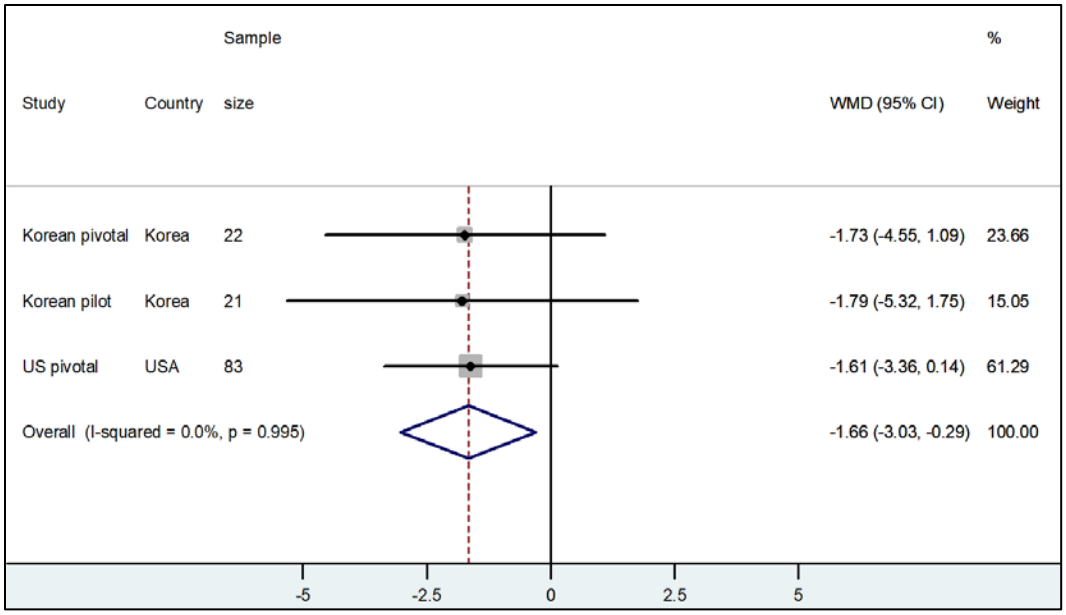


Figure 7: Meta-Analysis (US Pivotal + Korean Pilot + Korean Pivotal) at 12 Weeks (Baseline ADAS-Cog ≤ 30 Subgroup)



In sum, the independent investigators in Korea determined based on the results of the Korean Pilot Study that the subgroup identified in the US Pivotal Study (patients with baseline ADAS-Cog ≤ 30) are most likely to benefit from treatment with the device. They therefore designed and executed the Korean Pivotal Study while limiting the recruited population only to subjects with mild Alzheimer's disease and baseline ADAS-Cog ≤ 30. The positive outcomes of these 2 studies provide additional confirmatory evidence of safety and effectiveness in this subgroup.

1.5.3 Supplemental Studies

In addition to the US Pivotal Study and Korean studies discussed above, seven other studies assessing ADAS-Cog were identified that also support the risk/benefit profile of the neuroAD (some independent and others sponsored or partially supported by Neuronix). Across all seven investigations, the treatment group in the Baseline ADAS-Cog ≤ 30 Subgroup reported a reduction in mean ADAS-Cog score at early follow-up (ranging from 6-10 weeks) compared to baseline (range: -0.9 to -4.3). Where a second follow-up visit was reported (10-14 weeks), the improvement on ADAS-Cog was maintained. In addition, four of the supplemental studies included a Sham group and, in all of those studies, the Active group outperformed the Sham group at all time points measured. The results of these studies in the Baseline ADAS-Cog ≤ 30 Subgroup are shown in the Forest plots below.

Figure 8: Mean ADAS Cog Change FU-1 (6-10 Weeks), Supplemental Studies (Baseline ADAS-Cog ≤ 30)

Active Patients Only (Left) and Active-Sham Difference (Right)

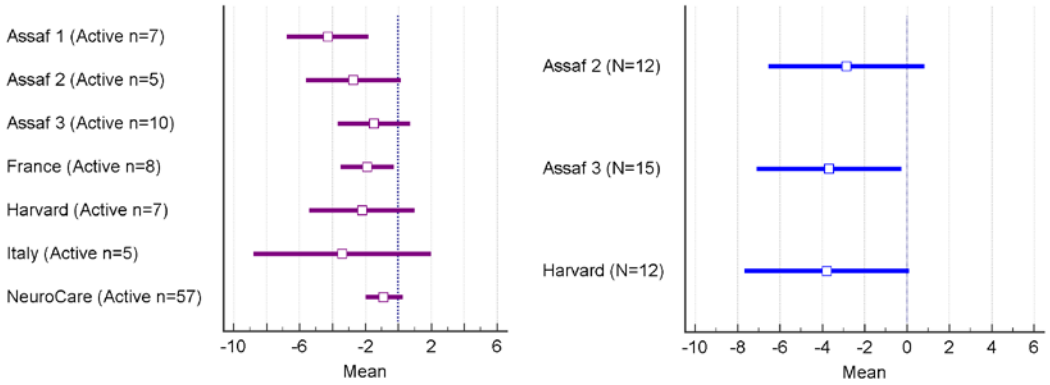
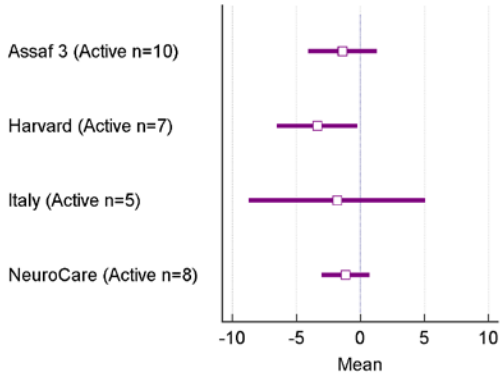


Figure 9: Mean ADAS Cog Change FU-2 (10-14 Weeks), Supplemental Studies (Baseline ADAS-Cog ≤ 30)

Active Patients Only



An additional three independent studies were conducted with the neuroAD (in Thailand, UK and France) which measured different scales than the ADAS-Cog, and all reported improvement following the treatment and over Sham where applicable.

No related serious adverse events were reported to Neuronix for any of these studies.

1.6 Conclusions and Risk-Benefit Analysis

FDA has acknowledged the importance of having a medical device available for the treatment of Alzheimer's disease by granting the neuroAD EAP designation, in recognition that there is an unmet need for new, non-pharmacologic AD treatments. Risk/benefit analysis of the study results supports that the probable benefits to patients outweigh the probable risks, supporting *de novo* clearance of the device.

1.6.1 neuroAD is Safe

The neuroAD Therapy System is a non-invasive medical device, and relies on TMS technology, which has been FDA 510(k)-cleared for multiple other applications and has an established history of safety in millions of treated patients. neuroAD complies with all internationally-accepted TMS safety guidelines.[22] Further, it is intended for adjunctive use along with other therapies, including pharmacotherapies. FDA determined the device was low to moderate risk and therefore eligible for the *de novo* review pathway (instead of the premarket approval ("PMA") pathway for higher risk devices).

Data from extensive clinical experience with the device in studies and commercial use outside of the US for over a decade demonstrates a very favorable safety profile for neuroAD. Safety data from the US Pivotal Study showed that the rate of occurrence of adverse events was similar between the Active group subjects and Sham group subjects, and in both groups most adverse events were mild in severity and transient. The most commonly reported related adverse events were headache, skin discomfort, and neck pain. There were no related serious adverse events as a result of treatment in the US Pivotal Study. There was never a related serious adverse event reported to the sponsor or reported in the literature anywhere in the world, nor has a seizure event been reported. In addition, in contrast to approved pharmacotherapies, no subjects the US Pivotal Study discontinued use of neuroAD due to an adverse event.

Moreover, there was a very high rate of compliance (93% of subjects attended ≥ 26 out of 30 sessions) in the US Pivotal Study, further demonstrating that the treatment is well tolerated.

1.6.2 neuroAD Demonstrates Consistent Improvement in the Baseline ADAS-Cog ≤ 30 Subgroup

The available clinical data repeatedly demonstrates that an improvement in ADAS-Cog associated with the neuroAD is achieved by approximately 12 weeks in the Baseline ADAS-Cog ≤ 30 Subgroup.

In the US Pivotal Study Baseline ADAS-Cog ≤ 30 Subgroup at 12 weeks, the Active group outperformed the Sham group in both ADAS-Cog and ADCS-CGIC measures at the 12-week time point:

1. Using ADAS-Cog, showing a difference of -1.61 or -1.79 for PE and PP, respectively (p-value = 0.077 and 0.049, respectively).

    a. Furthermore, more than 40% of the Active patients improved by -3 points or more at 12 weeks. More than double the number of Active subjects (31.8% PE, 31.7% PP) showed an improvement of -4 points or more than in the Sham group (15.4%).

2. Using ADCS-CGIC, showing a difference of -0.40 or -0.45 for PE and PP Populations, respectively (Wilcoxon test p-value = 0.10/0.07 for PE/PP respectively; Chi-square test p-value = 0.041/0.035 for PE/PP respectively).

    a. Furthermore, in the Baseline ADAS-Cog ≤ 30 Subgroup (PE), only 5 out of 42 (11.9%) subjects worsened in the Active group versus 14 out of 35 (40.0%) in the Sham group (p-value<0.01, two-sided Fisher's exact test).

3. When considering a post-hoc dual-end point analysis (combining subjects' performance on both ADAS-Cog and ADCS-CGIC), the Active arm of the Baseline ADAS-Cog ≤ 30 Subgroup outperforms the Sham arm, and this difference is statistically significant (Fisher's Exact test p-value = 0.0463). 64.3% of the Active group either improved or did not deteriorate both on ADAS-Cog and ADCS-CGIC compared to 42.9% of the Sham group. In addition, only 7.1% of the Active group reported worsening on both measures compared to 22.9% of the Sham group.

Two additional studies were conducted under a protocol highly similar to the US Pivotal Study by independent investigators in Korea (Korean Pilot and Pivotal Studies). As noted above, the independent investigators in these studies also concluded that the milder subset of patients with lower baseline severity was more likely to benefit based on the results of their Pilot Study.[23]

The Korean Pivotal Study was therefore limited to mild AD patients with baseline ADAS-Cog scores of 17-30. The results of the neuroAD US Pivotal Study were not yet available when the Korean Pivotal Study protocol was finalized; thus, the eligibility criteria were determined without reference to the US Pivotal Study results. In both of these studies, the Active group outperformed the Sham group in the Baseline ADAS-Cog ≤ 30 Subgroup by nearly two points at 12 weeks. These studies confirm that the Baseline ADAS-Cog ≤ 30 Subgroup identified in the US Pivotal Study is clinically meaningful.

Given the similarities across the protocols for the US Pivotal, Korean Pilot, and Korean Pivotal investigations, as well as the study populations, a combined meta-analysis between all studies was conducted. At 12 weeks, a WMD analysis demonstrated that the Active group outperformed the Sham group in the Baseline ADAS-Cog ≤ 30 Subgroup (-1.66, 95% CI: -3.03 to -0.29, p-value = 0.017).

Ten other supplemental studies showed a benefit of neuroAD intervention, when compared to baseline (in non-controlled studies) or when comparing Active to Sham (in controlled studies), at each time point.

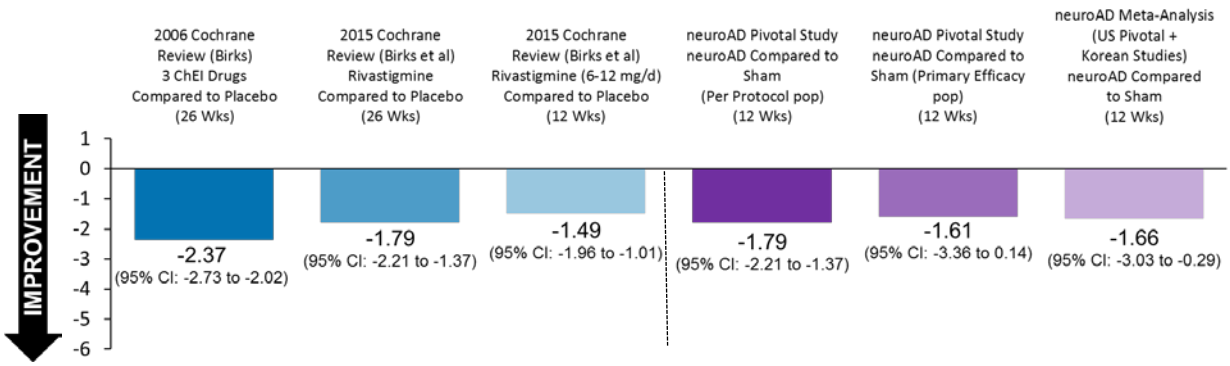
Thus, in totality, in the ADAS-Cog ≤ 30 Subgroup, the data consistently demonstrates a benefit for the neuroAD treated group over Sham, and nearly two points of improvement or more for the Active group compared to baseline on the ADAS-Cog scale. Note that approximately 80% of both Active and Sham subjects in the Baseline ADAS-Cog ≤ 30 Subgroup were already on stable AD medications (either ChEI or NMDA or both), and so the observed benefit is on top of the current SOC.

1.6.3 The Benefits Seen with neuroAD are Clinically Relevant

The magnitude of the benefit of the neuroAD Therapy System intervention is clinically meaningful, as measured by both ADAS-Cog and ADCS-CGIC scales, jointly and separately.

Regarding the ADAS-Cog, current approved ChEI drugs (the first line treatment) show an average ADAS-Cog improvement in the range of -2 points. For instance, in a 2006 Cochrane review regarding ChEl for mild to moderate Alzheimer's disease, the authors report that: "*The results of 10 randomized, double blind, placebo controlled trials demonstrate that treatment for 6 months, with donepezil, galantamine or rivastigmine at the recommended dose for people with mild, moderate or severe dementia due to Alzheimer's disease produced improvements in cognitive function, on average -2.37 points (95%CI -2.73 to -2.02, p<0.00001).*"[24] In addition, for rivastigmine specifically, a Cochrane review (2015)[25] calculates an ADAS-Cog average improvement of -1.49 (95% CI: -1.96 to -1.01) at a 12 week time point and -1.79 (95% CI: -2.21 to -1.37) at a 26 week time point. This is compared with -1.79 to -1.66 for the neuroAD Therapy System at 12 weeks (US Pivotal Study PP Baseline ADAS-Cog ≤ 30 Subgroup Population, and meta-analysis results, respectively). It should be noted that the observed improvement with the neuroAD is principally in a population of patients who are already receiving other treatments, but nonetheless shows a magnitude of benefit comparable to monotherapy in drug-naïve patients. A comparison of performance on ADAS-Cog between neuroAD and FDA-approved AD drugs is shown in the chart below.

Figure 10: ADAS-Cog Performance for Approved AD Drugs Compared to ADAS-Cog Performance for the neuroAD Baseline ADAS-Cog ≤ 30 Subgroup

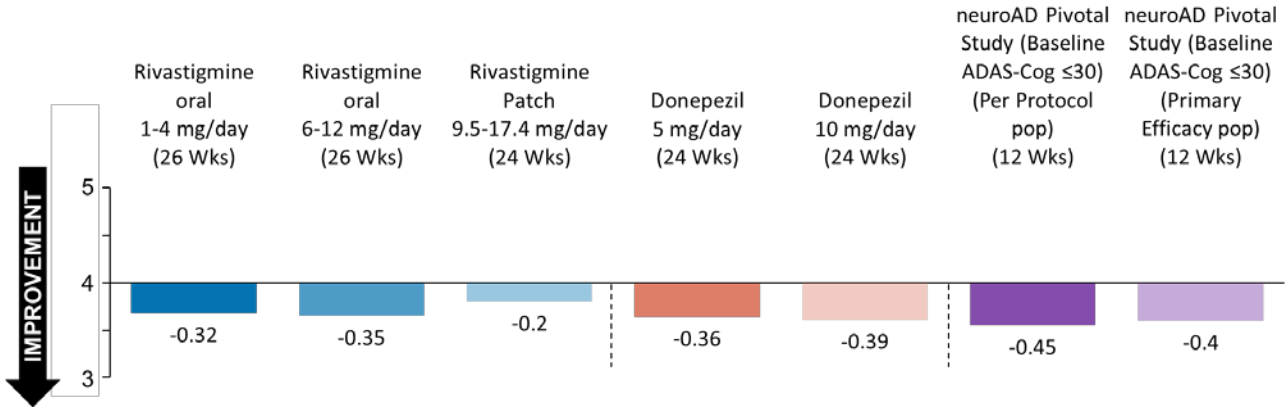


Furthermore, a survey of 200 US physicians (who actively treat a high volume of mild to moderate AD patients), was conducted in the US by a third party (sponsored by Neuronix). It provided additional support on the perception of clinical meaningfulness of new treatments, with 86% of physicians surveyed indicating that -2 points improvement on the ADAS-Cog scale combined with -0.5 point improvement on ADCS-CGIC after 12 weeks of treatment is clinically meaningful. It is worth noting that in the Baseline ADAS-Cog ≤ 30 Subgroup at 12 weeks, such results were observed. Moreover, many physicians (47%) reported that at least -1 point improvement on ADAS-Cog alone (or even no deterioration) is clinically meaningful. See **Appendix 4** for the report of the survey.

When considering the CGIC scale, ChEI drugs report an average improvement in the range of -0.2 to -0.39.[26] This compares well with -0.4 to -0.45 for the neuroAD Therapy System (US Pivotal results for subjects with baseline ADAS-Cog ≤30, for PE and PP Populations, respectively, at 12 weeks). Furthermore, only 12% of subjects worsened on the ADCS-CGIC scale in the Active group compared with 40% subjects in the Sham group (p-value < 0.01, two-sided Fisher's exact test). By its definition, the ADCS-CGIC scale is designed such that **any** improvement represents clinically meaningful change, and therefore these changes indicate a clinically meaningful improvement. A comparison of performance on CGIC between neuroAD and approved AD drugs is shown in the

chart below. The chart depicts the different outcomes for currently available, FDA-approved AD medications.

Figure 11: CGIC Performance for Approved AD Drugs Compared to CGIC Performance for neuroAD in the Baseline ADAS-Cog ≤ 30 Subgroup



Finally, Alzheimer's disease researchers are now calling[27] for FDA to reduce the regulatory bar that the Center for Drug Evaluation and Research (CDER) has traditionally required of dual assessment for Alzheimer's disease studies in both cognitive and functional (or global) scales, as they consider this requirement to be a barrier for introducing new treatment options to the market, given that drug studies continually fail to show improvement on both assessment tools. Although the study was not originally designed to assess a dual endpoint, in a post-hoc analysis, the neuroAD Pivotal Study has shown that Active patients outperform Sham when considering combined improvement on both cognitive and global assessment scales (ADAS-Cog and ADCS-CGIC) for the Baseline ADAS-Cog ≤ 30 Subgroup (p-value = 0.0463).

Thus, when comparing its benefits, the adjunctive neuroAD Therapy System outcomes are similar to currently-approved ChEI drugs that are approved as monotherapies, when considering either the ADAS-Cog scale or CGIC scale, and, importantly, the combination of the two scales.

1.6.4 The Benefits of neuroAD Outweigh the Risks, Supporting Clearance of the *De Novo* Request

A device is a candidate for the *de novo* pathway if the device does not fall within an existing classification regulation. This includes devices for which there is no legally marketed predicate device or, when compared to other legally marketed predicate devices, the device has a new intended use or different technological characteristics that raise different questions of safety and effectiveness. In addition, the following conditions should be satisfied:

1. The device is a low to moderate risk device.
2. The probable benefits outweigh the probable risks associated with the use of the device.
3. The probable risks to health associated with the use of the device can be mitigated by general controls alone, or a combination of general and special controls.

A reasonable assurance of safety and effectiveness can be achieved if all of the above conditions are satisfied. Other TMS devices that were first of a kind for major depressive disorder (MDD) and OCD were cleared according to the same *de novo* pathway.

Especially for low risk *de novo* systems and EAP-designated technologies, FDA recognizes that due to technology novelty, initial studies may show relatively small benefit, and that greater uncertainty regarding benefits and risks may be acceptable to patients for such novel devices. FDA's own risk-benefit guidance[28] recognizes that *"[i]t is not unusual for novel devices that address an unmet medical need to have relatively small probable benefits, and FDA may determine the novel device to be reasonably safe and effective even though the applicant demonstrates a relatively small probable benefit.*" Per the guidance, the lack of other treatments should be considered in this decision.

For neuroAD, both direct probable risks (e.g., side effects) as well as indirect probable risks (e.g., foregoing other treatments) are minimal, as the device has been demonstrated to be safe and can be used in conjunction with other approved therapies. Probable benefits clearly exist, as shown by improvements in both ADAS-Cog and ADCS-CGIC.

It is important to note that approximately 80% of subjects in both Active and Sham groups were on stable AD medications (ChEI, NMDA, or both), the current standard of care (SOC). Therefore, the benefit shown in the neuroAD clinical studies is on top of the SOC. In the US Pivotal Study PE Population, Active group subjects experienced benefit whether or not they were taking medication.

Given the extremely low risks of the device, even a modest benefit outweighing these risks would be sufficient to meet the statutory standard for clearance of the *de novo* request. However, the totality of the evidence demonstrates that the benefit provided by the device is on par with currently-approved, first line AD drugs, and therefore significantly outweighs its minimal risks.

The availability of this novel, low risk device treatment for mild to moderate AD is of critical importance to patients and their families given the lack of curative treatment options. Development of a complementary treatment modality that does not preclude other alternatives also supports current efforts to develop multidimensional treatment approaches. The neuroAD offers a treatment method, combining TMS with cognitive therapy, that works in an entirely different manner than existing drug therapies and can be added to those therapies without significant adverse effects. With each treatment option (both pharmacologic and non-pharmacologic) providing a meaningful benefit by itself, the possibility of combining multiple treatments together has the potential to dramatically improve the lives of both patients and caregivers.

As noted above, in an open letter published in 2018 by ResearchersAgainstAlzheimer's, leading AD researchers advocated that FDA not establish a threshold so high that it would interfere with the availability of new AD treatments,[29] recognizing that development in this area requires recognition of incremental improvement as clinically meaningful. This philosophy has led to movement away from the dual endpoint criteria for evaluation of AD treatments. Recent studies have been designed to detect relatively small differences in only one endpoint rather than two. This approach is consistent with FDA standards for approval of *de novo* requests, which require probable benefit that outweighs probable risk, rather than the more stringent standard that applies to higher risk devices. FDA's guidance on the EAP program also supports approval of safe devices that offer modest benefits, recognizing that patient access to safe, innovative therapies in areas of unmet need is critical. Patient and caregiver interviews demonstrating the need for additional treatments and the potential benefit of the neuroAD are included in **Appendix 5**.

Given the potential for a large proportion of the indicated population (i.e., patients with Baseline ADAS-Cog ≤ 30) to experience at least some degree of clinically meaningful benefit with very low potential risk, the data provides strong support that the neuroAD meets the applicable standard for FDA to grant the *de novo* request.

2.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale - Cognitive
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change
AE	Adverse Event
CDR	Clinical Dementia Rating
CGIC	Clinical Global Impression of Change
ChEI	Cholinesterase Inhibitors
CRO	Clinical Research Organization
EAP	Expedited Access Pathway
EC	Ethical Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
ICF	Informed Consent Form
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
MT	Motor Threshold
PE	Primary Efficacy (population)
PI	Principal Investigator
PP	Per-Protocol (population)
rTMS	Repetitive Transcranial Magnetic Stimulation (used interchangeably with TMS)
SAE	Serious Adverse Event
SOC	Standard Of Care
TMS	Transcranial Magnetic Stimulation

3.0 DISEASE BACKGROUND

3.1 Alzheimer's Disease

Alzheimer's disease (AD) is an acquired cognitive and behavioral impairment of sufficient severity that it markedly interferes with social and occupational functioning and is the most common cause of dementia.[30] AD is a neurodegenerative disorder characterized by the gradual onset and progression of dementia. AD is well established to be degenerative, progressive, and irreversible, as the disease interferes with the neuron-to-neuron communication at synapses and contributes to cell death.[31]

No treatment currently available for AD slows or stops the damage to neurons that causes AD symptoms and eventually makes the disease fatal.[32] Currently, there are 5.7 million people living with AD, 5.5 million of whom are age 65 years or older.[33] Those who suffer from AD experience a host of symptoms including: memory loss, problems in executive functions, challenges in planning or problem solving, confusion, trouble understanding verbal and spatial relationships, trouble speaking, and decreased or poor judgment. As the disease progresses, cognitive and functional abilities continue to deteriorate until the person requires assistance with even the most basic activities of daily living, such as bathing, dressing, eating, and using the bathroom. Those who progress into more severe stages of AD may become bed-bound and require 24 hour care. Individuals who have difficulty moving are more prone to infections, including pneumonia. AD-related pneumonia is a common contributing factor in the death of people with AD. Death certificates for individuals with AD often list acute conditions, such as pneumonia, as the primary cause of death rather than AD. Thus, while the Center for Disease Control and Prevention ("CDC") published that 110,561 people died from AD in 2015,[34] the actual number of deaths is thought to be much higher. The Alzheimer's Association estimated that approximately 700,000 people age 65 and older will die with AD in 2018, making it the third leading cause of death in the US, and the only disease among the ten leading causes of death that cannot be prevented, cured or even slowed.

3.2 AD Evaluation Scales

The most commonly used evaluation scales in AD research are described below.

- Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog)

ADAS intends to measure the severity of the most important symptoms of AD. Its subscale ADAS-Cog is the most popular cognitive testing instrument used in clinical trials of nootropics. It consists of 11 tasks measuring the disturbances of memory, language, praxis, attention and other cognitive abilities which are often referred to as the core symptoms of AD.

The total score ranges from 0-70 points and measures the number of mistakes counted in the test. A higher result represents greater cognitive dysfunction. AD patients deteriorate on average in the range of 4 to 7 points per annum, depending on the level of their dementia.[35]

ADAS-Cog is globally considered as the gold standard for evaluation of cognitive performance of Alzheimer's dementia, and was used as a primary endpoint in all approved cholinesterase inhibitor (ChEI) drug approval studies (donepezil, rivastigmine, galantamine and tacrine (which is no longer on the market)). However, there is no established or agreed-upon threshold as to what change in ADAS-Cog constitutes a clinically meaningful change.

A copy of the ADAS-Cog Administration and Scoring Manual is included in **Appendix 2**.

- ADCS-Clinical Global Impression of Change (ADCS-CGIC)

The Alzheimer's Disease Cooperative Study – Clinical Global Impression - Change scale (ADCS-CGIC) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past diagnosis with the patient. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating. Assessment is performed using a structured interview with both the patient and the caregiver.

The purpose of the baseline measurement of ADCS-CGIC is to set the reference for future comparison.

The 7-point scale is characterized as follows: 1-very much improved; 2-much improved; 3-minimally improved; 4-no change; 5-minimally worsened; 6-much worsened; or 7-very much worsened.

ADCS-CGIC has been used, in particular, in studies that led to the marketing approval of donepezil, galantamine, and memantine, and in later rivastigmine studies.

By definition, any change measured on the ADCS-CGIC scale is clinically meaningful.[36]

A copy of the ADCS-CGIC questionnaire is included in **Appendix 3**.

- Dual End-Point Assessment

FDA's Center for Drug Evaluation and Research (CDER) has traditionally required dual assessment for Alzheimer's disease studies in both cognitive and functional (or global) scales. At a 1992 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee meeting, the dual assessment strategy was endorsed again by the Advisory Committee, and for which both a cognitive outcome and a global assessment were required in order to demonstrate efficacy and clinical meaning.[37] With subsequent marketing approvals for tacrine and donepezil, the ADAS-Cog and CGIC became the most commonly used dual outcomes, and in an important sense, *de facto* outcomes and guidelines.[38]

In sum, the substantial majority of 12-week to 26-week phase 2 and 3 clinical trials for mild AD and for mild to moderate AD drugs have used the ADAS-Cog and the CGIC (with or without the inclusion of another functional scale, ADCS-ADL inventory scale) as co-primary outcomes, starting in the early 1990s and continuing to the present.

As noted above, Alzheimer's researchers are now calling[39] for a reduction of the regulatory bar of dual assessment for Alzheimer's studies in both cognitive and functional (or global) scales, as they consider this to be the barrier for introducing new treatment options to the market, given that drug studies continually fail to show improvement using this standard. CDER recently issued a draft guidance document proposing a single-endpoint threshold for approval of new drugs for early Alzheimer's disease.[40]

Nevertheless, in the context of AD clinical trials, in the presence of a statistically significant cognitive effect on the ADAS-Cog, and any statistically significant, positive effect on the CGIC, would be considered an indicator of clinical meaning. Such a statistically significant positive effect, regardless of effect size, means that a greater number of individual participants benefited from the Active treatment than from the Sham condition. As the CGIC is applied along with the demonstration of

cognitive benefit, any positive effect on the CGIC is, by definition, clinically meaningful, and an indicator of meaningful cognitive effect as well. Thus, the two scales are complementary.

3.3 Current Therapies and Unmet Need

3.3.1 Pharmacological Interventions

Currently available pharmacological treatments for AD have demonstrated a limited effect. The four approved drugs and one combination therapy currently on the market for treatment of AD temporarily improve symptoms by increasing the availability of neurotransmitters in the brain.[41]

Three of these drugs (rivastigmine, donepezil, and galantamine), all of which are cholinesterase inhibitors, are approved for treatment in mild to moderate AD. The effectiveness of these drugs varies from person to person. Moreover, patients have shown limited tolerability for these medications, thus further reducing their usefulness.[42]

In a 2006 Cochrane review[43] regarding cholinesterase inhibitors for mild to moderate Alzheimer's Disease, the authors report that: "The results of 10 randomized, double blind, placebo controlled trials demonstrate that treatment for 6 months, with donepezil, galantamine or rivastigmine at the recommended dose for people with mild, moderate or severe dementia due to Alzheimer's disease produced improvement in cognitive function, on average -2.37 points (95%CI -2.73 to -2.02, p<0.00001)."

In addition, a more recent Cochrane review in 2015[44] focused on Alzheimer's disease treatment using rivastigmine, which was one of the cholinesterase inhibitors included in the 2006 Cochrane review. In the 2015 Cochrane review of rivastigmine, the authors report that based on seven trials with 3,450 patients analyzed: *"After 26 weeks of treatment, rivastigmine compared to placebo was associated with better outcomes for cognitive function measured with ADAS-Cog score mean difference -1.79 (95%CI -2.21 to -1.37)."*

When considering the CGIC scale, the approved ChEI drugs show the following benefits, as measured by difference between treatment and placebo at the 26-week follow-up: donepezil: -0.36 and -0.39 (for 5mg/day and 10mg/day, respectively); rivastigmine-oral: -0.32 and -0.35 (for 1-4mg/day and 6-12 mg/day, respectively); rivastigmine-patch: -0.20.[45]

As may be expected, where available, results reported at 12 weeks for ChEI drugs were inferior to those reported at 26 weeks, on both ADAS-Cog and CGIC scales.

3.3.2 Non-Pharmacological Interventions

Non-pharmacological strategies (mainly nutritional supplements and life style changes) for delaying the progression of cognitive deficits and resulting functional impairment in AD have produced limited results.

There are currently no medical devices that have been cleared or approved by FDA for treatment of AD.

Alternative or supplemental treatments added to pharmacological interventions include psychosocial treatment and targeting cognition or cognitive training for AD in the mild to moderate stages of the disease in one-on-one, group training[46] or computer-based training.[47] Overall, a lesser effect is

considered to be obtained with cognitive training[48] alone compared with drug treatment.[49] A 2010 review of "Exercising the Brain" methods, including those for patients with dementia, concluded that the effectiveness of cognitive training interventions in AD remains equivocal.[50] Furthermore, a recent (2013) Cochrane review of cognitive training for treatment of AD[51] concluded that: *"Cognitive training was not associated with positive or negative effects in relation to any reported outcomes. The overall quality of the trials was low to moderate".* When combining the ten available studies into a meta-analysis, the results show a Standardized Mean Difference (SMD) improvement of 0.10 (non-significant; 95% CI: -0.21 to 0.40).

To summarize, there are currently no medical devices that have been cleared or approved by FDA for treatment of AD, and even currently available pharmacological treatments for AD have demonstrated a limited effect. Notably, no new types of drugs have been approved in the past 20 years, and no near-term approvals are anticipated based on ongoing studies. Failed clinical trials have unfortunately been commonplace in this treatment space since the 1990s, including at the latest stages of clinical research. As discussed in a 2014 Cleveland Clinic study,[52] the failure rate in clinical trials for AD drug candidates between 2002 and 2012 was 99.6% overall, with 98% of Phase III clinical trials failing. This trend continues today, and in the last few years Merck, Pfizer, Johnson & Johnson, Eli Lilly and Roche have all failed large Phase III trials in AD.[53] This trend may lead to long delays in the treatment development pipeline.[54] In an open letter published in 2018 by ResearchersAgainstAlzheimer's, leading AD researchers advocated that FDA not establish a threshold so high that it would interfere with the availability of new treatments,[55] recognizing that development in this area requires recognition of incremental improvement as clinically meaningful. Such an approach is necessary to build the broad platform upon which a multifaceted approach to treatment can be developed.

The lagging development of new treatment options is widely recognized by regulators, patients and caregivers, and physicians who treat AD. As noted by Commissioner Gottlieb,[56] making new treatment options for AD available to the public is a priority of FDA. The Agency also acknowledged the unmet need in AD treatment options by granting expedited access pathway ("EAP") status for the neuroAD Therapy System because the device "*may offer significant, clinically meaningful advantages over existing legally marketed alternatives; and the availability of the device may be in the best interest of patients (e.g. addresses an unmet medical need.)*." AD patients and their caregivers are also keenly aware of the need for new treatment options. As per the US Alzheimer's Association, none of the currently-approved drugs slows or stops the progression of the disease, and AD remains the only disease in the ten leading causes of death in the US that cannot be prevented, cured or even slowed down.[57] In a survey of US caregivers of AD patients sponsored by Neuronix (see **Appendix 4**), when asked whether they are satisfied with currently available treatment options, approximately two-thirds indicated that treatment could be improved or that they were not at all satisfied.

All can agree that finding a cure for Alzheimer's disease should be of the highest priority in the scientific community. However, unfortunately, a cure is not on the near-term horizon. Until such time as a cure can be found, the treatment paradigm is shifting towards a multifaceted approach for treating the symptoms of disease, using a combination of strategies (both pharmacologic and non-pharmacologic clinically based interventions). With each treatment option providing a meaningful benefit by itself, the possibility of combining multiple treatments together (adjunctive therapies) has the potential to improve the lives of both patients and caregivers.

Within this treatment landscape, neuroAD was designed as an adjunctive treatment, using well accepted and safe TMS therapy, coupled with computer-based adaptive cognitive training, to provide a clinically significant benefit in these patients. neuroAD offers physicians the opportunity to take a multifaceted approach to treat AD patients, and offers patients the opportunity for additional benefit with minimal increased risk.

4.0 DEVICE DESCRIPTION

4.1 Background / Rationale for the Device

Transcranial magnetic stimulation (TMS) is a well-known technology that allows for discrete non-invasive probing for diagnostic purposes and modulation of cortical excitability and functions.[58] TMS, if applied repetitively (rTMS), produces an electromagnetic field in the brain that induces a modulation in brain cortical excitability.[59] TMS has been studied extensively since being introduced in 1985, and safety guidelines for using TMS were originally published by the US National Institute of Health ("NIH") in 1996 and were later adopted by the International Federation of Clinical Neurophysiology ("IFCN") in 1999. The primary side effects reported for TMS include transient headache, neck pain, local pain, tooth ache, paresthesia.[60] While a potential risk of seizure is associated with TMS therapy, *"[o]nly a few cases of TMS induced seizures have been reported so far out of hundreds of thousands examined subjects . . ."*[61]

High-frequency rTMS has been evaluated for use in various psychiatric and neurological conditions such as depression, mania, obsessive–compulsive disorder, posttraumatic stress disorder, schizophrenia, and Parkinson's disease.[62] Although the exact biological mechanism explaining the effects of rTMS on the brain is still unknown, it has been suggested to involve an increase in synaptic plasticity.[63] TMS treatment is cleared in the U.S. for treatment of refractory depression,[64] migraine headache with aura,[65] and was recently cleared for the treatment of Obsessive Compulsive Disorder (OCD).[66] It is estimated that TMS has been used in several million treatments in the US,[67] showing that TMS is a practical technology from which patients have benefited to-date.

Long-term potentiation ("LTP") is a long-lasting enhancement in signal transmission between two neurons that results from stimulating them synchronously. It is one of several phenomena underlying synaptic plasticity, the ability of chemical synapses to change their strength.[68] More than a decade ago, a working hypothesis was put forward, suggesting that high-frequency rTMS, similar to LTP, enhances the efficiency of synaptic cortical activity, whereas low-frequency rTMS reduces it.[69] Data suggesting a differential antidepressant response to rTMS, depending on baseline glucose metabolism, supported this hypothesis. Based on a meta-analysis of previous studies examining the effect of rTMS on cognition, an enhancement in attention, executive function, learning, and memory was found.[70] In addition, active rTMS was reported to show statistically significant improvements in cognitive function in elderly patients with refractory depression[71] and similarly procedural memory improved following rTMS treatment of patients with major depression.[72] A recent study confirms that five daily sessions of high frequency rTMS over the left and then the right dorsolateral prefrontal cortex (DLPFC) improves cognitive function in patients with mild to moderate AD.[73] Moreover, a recent review on TMS and AD concludes that TMS may have therapeutic utility in AD.[74] Cognitive improvement was observed in AD patients subjected to both cognitive training (performing an action naming task) and rTMS (applied to the left and right DLPFC) simultaneously. In that study, patient performance was recorded during rTMS stimulation and was found to improve (relative to Sham rTMS)[75]. In another study of the same research group, rTMS of the DLPFC induced an improvement only in the percentage of correct responses of auditory sentence comprehension.[76]

In light of these early findings, the neuroAD Therapy System was developed to provide an additional treatment option for patients with mild to moderate AD. The device has been under clinical investigation for approximately 10 years, with the first-in-man ("FIM") study taking place in 2009. Since the FIM study, the device has been investigated under several clinical trials throughout the world. The neuroAD Therapy System received the European Conformity ("CE") mark in 2012, and is

approved and distributed in Europe, Australia, and Israel. In 2016, the FDA granted EAP status for the neuroAD Therapy System, recognizing that its intended use would address an unmet need, and that it could offer potential benefits to patients.

neuroAD was designed as an adjunctive treatment to provide a safe, clinically significant benefit in patients over and above the Standard of Care (SOC). It does not require patients to discontinue use of other treatments, allowing patients to continue taking their prescribed AD drugs.

4.2 Intended Use/Indications for Use

The neuroAD Therapy System is intended for neuro-stimulation concurrently combined with cognitive training. neuroAD is indicated for the treatment of mild to moderate dementia of the Alzheimer's type in patients with a baseline ADAS-Cog score up to 30. neuroAD may be used in conjunction with other pharmacological and non-pharmacological therapies.

4.3 Technological Features

The neuroAD Therapy System is a non-invasive tool for the stimulation of cortical neurons for the treatment of mild to moderate AD patients with baseline ADAS-Cog score ≤30. The device is a computerized, electronic-based medical device that produces and delivers non-invasive, magnetic stimulation using brief duration (~380 µsec) rapidly alternating, or pulsed, magnetic fields to induce electrical currents directed at spatially discrete regions of the cerebral cortex. This method of cortical stimulation by application of brief magnetic pulses to the head is known as TMS or rTMS. TMS is hypothesized to induce Long Term Potentiation ("LTP") which is associated with learning and memory processes, thus making the spatially discrete regions of the cerebral cortex more receptive to cognitive training. Concurrent with the TMS administration, the neuroAD Therapy System also administers adaptive computer-based cognitive training exercises targeted to the same region of the cerebral cortex that is being stimulated. The device is used by prescription only under the supervision of a licensed physician. Treatments may be performed in both inpatient and outpatient settings.

The neuroAD Therapy System is an integrated system consisting of a combination of hardware, software and accessories. As stated above, the neuroAD Therapy System is composed of 2 units:

- The neuroAD Base Unit – controls the TMS and the cognitive training.
- The neuroAD Navigation Unit – directs the operator on positioning the TMS-administrating coil on the spatially discrete regions of the cerebral cortex (i.e., treatment region).

The units are electronically and mechanically independent from each other, and are separately computerized.

Figure 12: System Diagram and Main Units

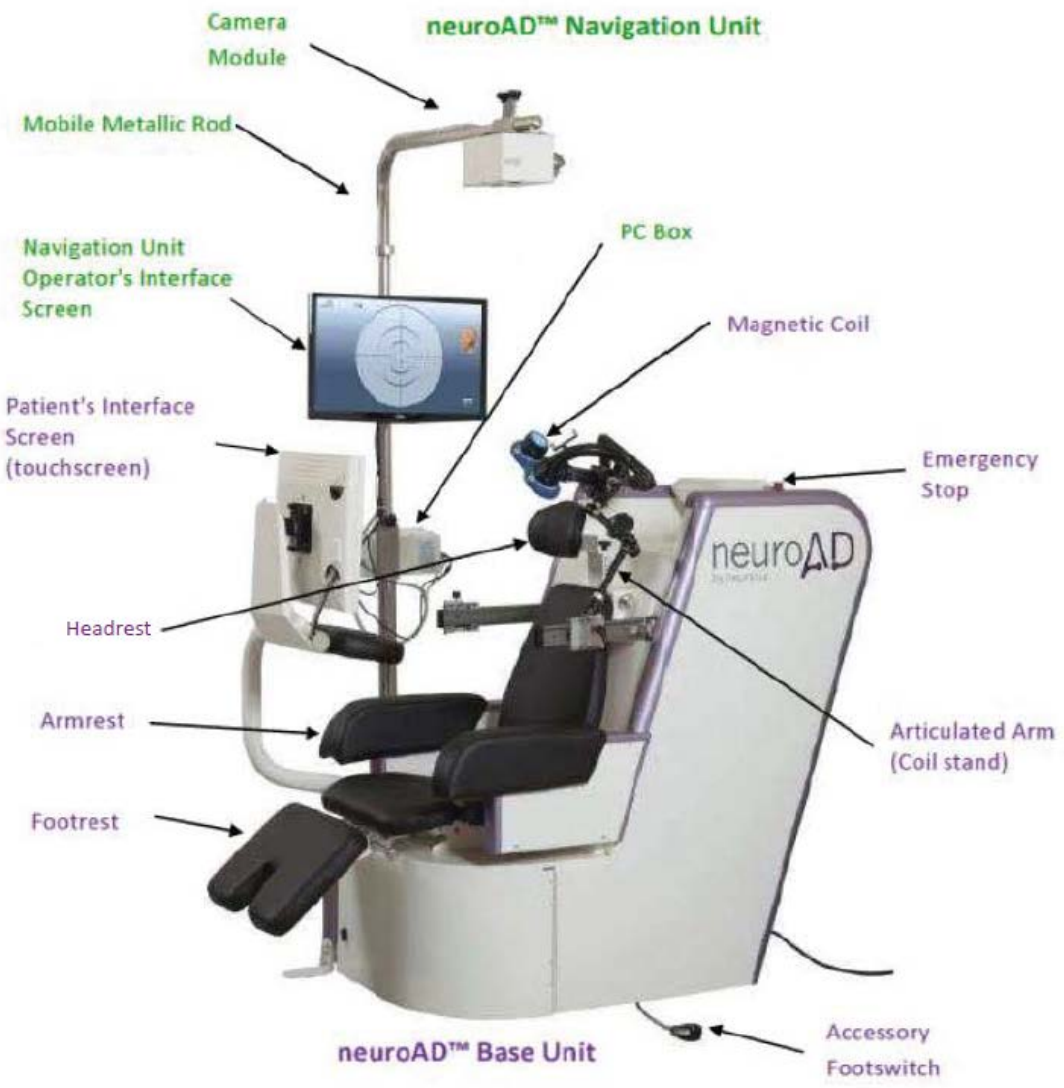
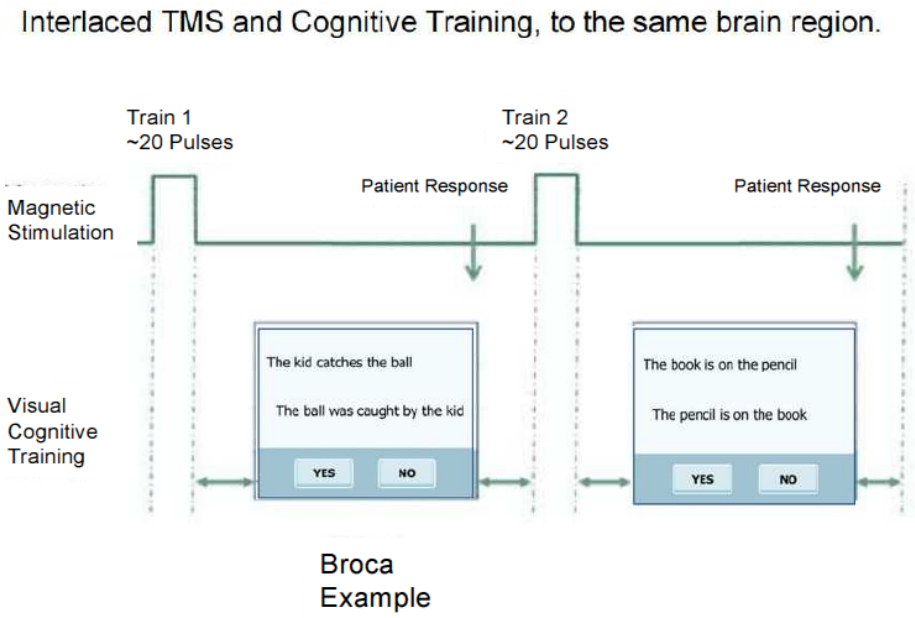


Figure 13: Example – Treatment with TMS and Cognitive Training on One Brain Region



4.3.1 Safety Considerations

(b) (4)

[redacted]

Table 1: Comparison of neuroAD to TMS Systems/Guidelines

(b) (4)

[redacted]

4.4 Principles of Operation

The treatment protocol consists of six weeks of five daily one-hour sessions per week. Each treatment session includes concurrent application of TMS and tailored cognitive exercises, designed to accommodate the specific discrete region of the cerebral cortex that is being stimulated by TMS. Overall six spatially discrete regions of the cerebral cortex are treated (i.e., Broca, Wernicke, Dorsolateral Prefrontal Cortex Left & Right, and Parietal Cortex Left & Right). During each daily session, three alternate spatially discrete regions are treated, applying 1300 pulses of magnetic stimulation (at frequency of 10Hz) for all regions together, synchronized with four different cognitive training paradigms (exercises). On average, the net total time for the 4 paradigms is approximately 30 minutes, depending on the length of the different paradigms. The overall procedure takes approximately 45-60 minutes, depending on the operator and operator-patient interaction. As discussed above, the biological mechanism explaining the effects of high-frequency repetitive TMS (rTMS) on the brain has been suggested to involve an increase in synaptic plasticity.[80] Consequently, it is believed that TMS may "prime the brain" to be more receptive to cognitive training. TMS treatment paradigms for other illnesses have used a similar approach of combining

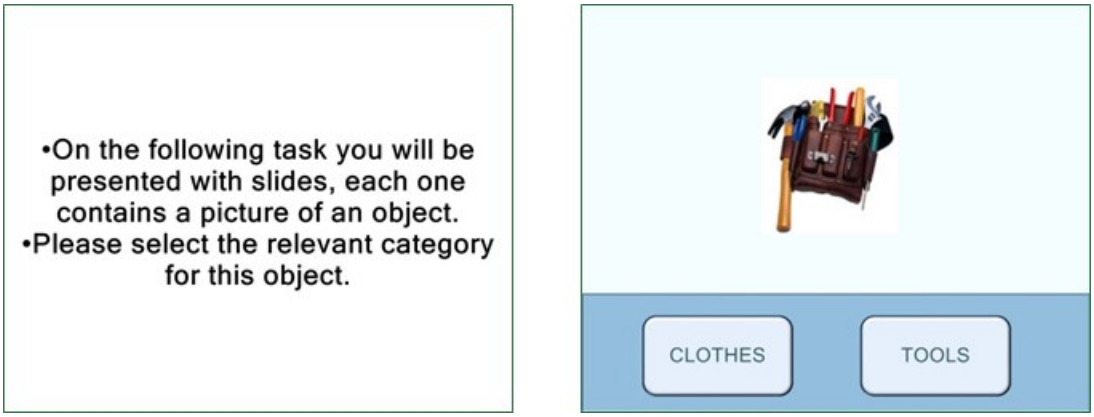
TMS with environmental stimulus that provoke a response in the targeted area of the brain in order to achieve greater efficacy. Some examples of this approach include TMS treatment of OCD,[81] alcoholism[82] and other addiction studies,[83] as well as in treatment of Post-Traumatic Stress Disorder ("PTSD").[84]

TMS intensity is based on the patient's daily Motor Threshold (MT) as determined by a standard procedure (Schutter et al. 2006).[85] As part of this standard procedure, single TMS pulses are administered to the patient's motor cortex, while the Operator monitors the patient for motor reaction. Once the MT is determined for the specific patient, on the specific treatment day, the intervention stimulation power is determined relative to that MT. The treated regions of the cerebral cortex are stimulated by TMS intensity in the range of 90-110% of MT. Before starting the treatment, the Operator adjusts the treatment power per region, relative to the previously established MT, according to the following recommendations: Broca – 90% of MT, Wernicke and dorso lateral left and right – 100% and parietal left and right – 110%.

Once the system is set, the Operator continues to the actual treatment. The neuroAD Base Unit Software presents the treatment sequence for a specific treatment day, as determined by the treatment algorithm. The Operator navigates the magnetic coil to the specific target brain region by loosening the main screw and maneuvering the Articulated Arm. The magnetic coil is in the exact point, when indicated by a big green circle in the middle of the target ("Bull's-eye"), and while touching the patient's head. When the Magnetic Coil is positioned accurately, the Operator locks the magnetic coil in position and starts the treatment stimulation and cognitive training paradigm, which are managed automatically by the Base Unit Software.

Each cognitive training paradigm starts with presenting the patient with simple instructions on the upcoming cognitive training exercise. The operator confirms the patient understands the instructions, and if needed, provides a few example questions using the neuroAD User Interface. Next, the Operator starts the treatment and continuously monitors the Magnetic Coil location on the neuroAD Navigation Unit Operator Interface Screen. An example cognitive training task is provided below in **Figure 14**.

Figure 14: Patient Touchscreen (Showing Example of Categories Task)



The cognitive training paradigm and TMS stimulation stop automatically upon paradigm completion, and the software user interface guides the operator on the next treatment area / paradigm (the Operator can stop the cognitive training paradigm and TMS stimulation before the end of the

paradigm if required to do so). Once four paradigms are completed, the treatment session for that day ends.

(b) (4)

[redacted]

5.0 PRECLINICAL TESTING

The neuroAD Therapy System complies with all relevant recognized standards (as well as TMS safety guidelines as described above), in particular FDA's guidance document, "*Guidance for Industry and FDA Staff – Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems*" (July 26, 2011).[86] The neuroAD Therapy System is not sold sterile, nor is it intended to be sterilized by the user. Cleaning instructions for the device are provided in the Operator Manual.

A summary of the non-clinical performance testing conducted for the neuroAD is included in **Table 2** below.

Table 2: neuroAD Therapy System Performance Testing

Bench Test Type	Applicable Standard	Device Under Test	Acceptance
Electrical Safety	IEC 60601-1: 2005 + CORR. 1: 2006 + CORR. 2:2007 + AM1:2012 - Medical electrical equipment-Part 1: General requirements for basic safety and essential performance	neuroAD Therapy System neuroAD Base Unit neuroAD Navigation Unit	Device met acceptance criteria per IEC 60601-1
EMC	IEC 60601-1-2:2007 Ed. 3.0 - Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic compatibility – Requirements and tests	neuroAD Therapy System: 1. neuroAD Base Unit 2. neuroAD Navigation Unit	Device met acceptance criteria per IEC 60601-1-2
RFID Immunity	IEC 60601-1-2:2014 Ed 4.0 - Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic disturbances – Requirements and tests	neuroAD Therapy System: 1. neuroAD Base Unit 2. neuroAD Navigation Unit	Device met acceptance criteria per IEC 60601-1-2
(b) (4)	[redacted]	[redacted]	[redacted]

Bench Test Type	Applicable Standard	Device Under Test	Acceptance
(b) (4)			

6.0 CLINICAL EVIDENCE IN SUPPORT OF NEUROAD

6.1 Introduction

During FDA's review of the *de novo* request, Neuronix has submitted to FDA data for a total of 374 subjects (Active and Sham).

The primary evidence of device effectiveness and safety comes from the US Pivotal Study (NRX-US4), a prospective, randomized, multi-center, double-blind, sham-controlled investigation in 130 subjects.

In addition, two studies were conducted in Korea by independent investigators (the studies were not sponsored by Neuronix). The Korean Pilot Study was conducted under a very similar protocol as the US Pivotal Study and recruited subjects with mild to moderate AD. Based on the findings of the Korean Pilot Study, the investigators, independent of Neuronix, concluded that milder patients were the most likely to respond to the neuroAD System treatment, as reported in the publication of that study.[87] To confirm this hypothesis, the investigators ran the Korean Pivotal Study, which was conducted under a protocol very similar to the US Pivotal Study, except that study enrollment was limited to AD patients with a baseline ADAS-Cog 17-30.

Seven supplemental investigations, conducted in both clinical and commercial use settings, are provided as further evidence of device safety and efficacy. Three additional investigations that used scales other than ADAS-Cog are also discussed separately.

In addition to clinical data, the company collected supportive data from other sources. For example, survey data from US physicians who treat AD patients, as well as another survey conducted among AD patients' caregivers/family members, is provided to support the clinical meaningfulness of the device performance and the unmet medical need.

For ease of review, the table below summarizes the evidence submitted in support of the *de novo* request for the neuroAD.

Table 3: Evidence Submitted in *De Novo* Request for neuroAD

Topic	Description
Clinical Data	
US Pivotal Study (NRX-US4) (N=130)	• Primary investigation conducted in the US (9 sites) and in Israel (1 site) • Mild to moderate AD patients, including patients with ADAS-Cog above and below 30 • Subgroup analysis conducted in subjects with baseline ADAS-Cog ≤30

Topic	Description
Korean Studies (Pilot (N=26) and Pivotal (N=22))	• 2 investigations (Pilot and Pivotal) that were conducted under protocols very similar to the US Pivotal Study • Korean Pilot Study included mild to moderate AD patients, including patients with ADAS-Cog above and below 30 • Korean Pivotal Study was limited to mild AD patients with baseline ADAS-Cog ≤30
Meta-Analyses and Combined Analyses of Studies Under Similar Protocol	• Meta-analysis and combined analyses of US Pivotal and Korean Pivotal and Pilot Studies conducted under similar protocols
Supplemental Investigations (N=167)	• 7 investigations where subjects underwent neuroAD Therapy System treatment and were evaluated using ADAS-Cog • Studies include: o Assaf 1 (Open label study, Israel), o Assaf 2 (double-blind, sham controlled, Israel), o Assaf 3 (double-blind, sham controlled, Israel), o Harvard (double-blind, 3-arm, sham controlled, US), o NeuroCare (naturalistic follow-up, commercial clinic, Israel), o Nantes (Open label study, commercial clinic, France), and o Italy (double-blind, 3-arm, sham controlled, Italy).
Other Investigations (N=29)	• 3 investigations where subjects underwent neuroAD Therapy System treatment outside of the US (“OUS”), but were evaluated using scales other than ADAS-Cog • Studies include: o UK (naturalistic follow-up, commercial clinic), o Orsay (naturalistic follow-up, commercial clinic, France), and o Thailand (double-blind, 2-arm, clinical study, Thailand)
Stakeholder Input Data	
Patient Caregiver/Family Member Survey (N=150)	Company conducted survey investigating patient caregiver/family member views on new treatments for AD.
Physician Survey (N=200)	Third-party survey to investigate what US neurologists and psychiatrists believe to be clinically significant improvement on AD cognitive/behavioral scales.

All studies targeted a similar population of AD patients, and included six-week daily 1-hour sessions (5 days / week) with the neuroAD Therapy System. Studies varied primarily in regard to: follow-up time frames and evaluation scales; one study included some power setting variation (10% to 20% higher stimulation relative to MT); and other studies included a few maintenance sessions (post 6 weeks).

Below are summaries of the US Pivotal Study and the Korean studies, which the company primarily relies upon because they were conducted under similar protocols. Pooled meta-analysis of the US Pivotal Study and Korean studies is justified, and these assessments are included after the discussion of the Korean studies.

Note, the seven supplemental investigations that assessed ADAS-Cog and the three additional investigations that used scales other than ADAS-Cog are also summarized below.

Study publications are included in the references in **Appendix 6**.

6.2 US Pivotal Study (NRX-US4)

6.2.1 US Pivotal Study Design and Objective

The study design was a prospective, randomized, multi-center, double-blind, sham-controlled investigation. The design of the study was discussed with FDA in pre-submission interactions prior to initiation. During the final pre-submission interaction, FDA confirmed that the protocol addressed the agency's prior comments. See **Appendix 1** for the full protocol.

The study was conducted at ten clinical centers, which included 9 US sites and one site in Israel. As discussed with FDA, the first two patients at each of the sites were run-in/roll-in patients who received the active treatment as is customary with medical device studies and were therefore only included in safety analyses. The remaining patients recruited at each of the sites were randomly assigned by IVRS to either:

- Active group – neuroAD Therapy System treatment, TMS stimulation and cognitive training, or
- Sham/control group – sham TMS and pseudo cognitive training

The recruited subjects were mild to moderate Alzheimer's patients, with MMSE scores from 18-26.

<u>Study Objectives</u>

Primary Objectives

- To evaluate the efficacy of the neuroAD Therapy System in the improvement of mild to moderate Alzheimer patients' cognitive function compared with Sham after 6 weeks of treatment using ADAS-Cog score after 6 weeks of treatment; and
- Demonstrate device safety.

Secondary Objectives

- To demonstrate device efficacy using ADCS-CGIC after 6 weeks of treatment;
- To demonstrate efficacy using ADAS-Cog score after an additional 6 weeks of follow-up; and
- To demonstrate efficacy using ADCS-CGIC after an additional 6 weeks of follow-up.

<u>Study Population</u>

The study population was limited to mild to moderate Alzheimer's disease subjects that met all inclusion criteria and none of the exclusion criteria below.

Inclusion Criteria:

a) Male or female age 60-90 years;
b) Patients diagnosed with mild or moderate stage of Alzheimer's disease, according to the DSM-IV criteria;

c) MMSE score 18 to 26;
d) ADAS-Cog above 17;
e) Physical clearance for study participation as evaluated by the clinician;
f) Spouse, family member or professional caregiver agree and capable of taking care for the participation of the patient in the study (answering questions regarding the patient's condition and assuming responsibility for medication);
g) Agreement to participate in approximately 15 weeks during the study;
h) Normal to near-normal vision and hearing with correction as needed (e.g., corrective lenses, hearing aid);
i) Fluent in English or Hebrew;
j) Minimum of 8th grade education; and
k) If medicated for AD, then use of cholinesterase inhibitors, Memantine or Ginkgo-biloba for at least 3 months and on stable dose for at least 60 days prior to screening and during the course of study (including follow-up period).

Exclusion Criteria:

a) CDR 0, 0.5 or 3;
b) Severe agitation;
c) Mental retardation;
d) Patient lacking capacity to consent to study participation (this condition may be removed in accordance with local State regulations and IRB approval);
e) Unstable medical condition;
f) Use of benzodiazepines or barbiturates 2 weeks prior to screening;
g) Pharmacological immunosuppression;
h) Participation in a clinical trial with any investigational agent within 6 months prior to study enrollment;
i) History of Epileptic Seizures or Epilepsy;
j) Contraindication for performing MRI scanning;
k) Contraindication for receiving TMS treatment according to a TMS questionnaire;
l) Pregnant women and women who have the ability to become pregnant unless they are on an acceptable method of contraception during the study;
m) Patients with depression, bipolar disorder or psychotic disorders or any other neurological or psychiatric condition (whether now or in the past), which the Investigator finds as interfering with the study;
n) Alcoholism or drug addiction as defined by DSM-IV within last 5 years (addicted more than one year and or in remission less than 3 years) or severe sleep deprivation;
o) Patients with metal implants in the head, (i.e. cochlear implants, implanted brain stimulators and neurostimulators, aneurysm clips) with the exception of metal implants in mouth;
p) Patients with personal history of either any clinically defined medical disorder (which the Investigator finds as interfering with the study) or any clinically defined neurological/psychiatric disorder (other than AD), including (but not limited to): stroke, brain lesions, substance abuse, vitamin B12 deficiency, abnormal thyroid function, cerebrovascular condition, other neurodegenerative disease, head trauma, multiple sclerosis; or personal history of previous neurosurgery or head trauma that resulted in loss of consciousness (unless the investigator confirms the disorder to be irrelevant to the study);
q) Patients with any signs or symptoms of increased intracranial pressure, as determined in a neurological exam;
r) Cardiac pacemakers;
s) Implanted medication pumps;
t) Intracardiac lines;
u) Significant heart disease;
v) Currently taking medication that lower the seizure threshold;

w) Patients on which TMS Motor Threshold cannot be found; and
x) Patients who underwent TMS treatment in the past.

Study Treatment Visits

- Approximately 1 hour session, five days per week for six weeks for up to 30 visits.
- All subjects were assessed at the beginning of each visit for adverse events or change in medical condition.
- All subjects were asked to use earplugs at the beginning of the treatment session, regardless of their group assignment.

Active group (#1)

Each active treatment session started with evaluating the TMS Motor Threshold to determine stimulation intensity. Daily stimulation was performed on up to 3 different brain regions (out of six). Each subject received 1300 TMS pulses (at a frequency of 10Hz) per day for all stimulated brain areas together. (b) (4) [redacted].

Sham group (#2)

Sham treatments were administered on the same neuroAD System as the Active treatment and in the same treatment room. Procedures followed a similar time frame as the active treatment and included Sham treatment of TMS (sound recording, no actual stimulation) and a pseudo cognitive training administered via the same user interface (Patient Screen). The Operator moved the TMS Coil during the Sham procedure as in the Active intervention to define the positioning of the coil. Instead of cognitive training, Sham group participants were engaged in a visual perceptual task, which presented pictures of objects and required the patient to report like or dislike. In addition, Sham group participants watched short nature (or other) movies without a demand for any response.

Randomization and Blinding

The first two subjects recruited at each site were considered run-in/roll-in subjects (not randomized) and were treated with the Active neuroAD Therapy System treatment. The remaining subjects recruited at each of the sites were centrally randomly assigned into one of the two study groups using the Interactive Voice Response System (IVRS).

Randomization:

Following the MRI scan, every recruited subject was centrally randomly assigned by IVRS into one of two groups:

- Treatment (Active) group (#1) – neuroAD Therapy System treatment (TMS stimulation combined with cognitive training); or
- Control (Sham) group (#2) – sham TMS stimulation and sham cognitive training.

The following information was entered into the IVRS prior to receiving the subject's group allocation:

- Subject's 6-digit study identification number;
- Confirmation subject meets all inclusion/exclusion criteria;
- Confirmation subject provided signed informed consent;
- Subject's date of birth; and
- Subject's gender.

Originally subjects were centrally randomized using a 1:1 ratio of Active (treatment) and Sham (control) groups, with a block size of four stratified per site. Following a software error that was reported to FDA, it was determined that some of the subjects in the Active group may have been administered cognitive training at a lower level of difficulty than optimal. As a result, the protocol was amended, and the following modifications were applied to the study sample size and randomization plan:

- Sample size was increased to ensure at least 50 subjects in each of the treatment arms (excluding "roll-in" patients), per the original statistical plan.
- Subjects randomized after the protocol was amended were randomized centrally using a ratio of Active to Sham of 2:1.

This software error has been addressed technically and is not expected to occur in the future.

Blinding

The following involved parties were blinded to the subjects' group assignment until the end of the study: Investigators, ADAS-Cog & ADCS-CGIC raters, subjects, caregivers, sponsor's team, and the clinical research organization ("CRO") management team.

In order to administer the correct treatment and provide proper monitoring, the following parties were unblinded to the subjects' group assignment: neuroAD Operators (members of the sites' teams), the CRO monitors, and the CRO IVRS team. No other parties were unblinded during the course of the study.

To assure proper blinding throughout the study, only the subject and operator were present in the treatment room during the procedure; source worksheets were clearly marked and kept out of reach of unauthorized personnel. In addition, the eCRF was password protected and an audit trail was maintained. Blinding regarding treatment information and subjects' group assignment was maintained throughout the study until database lock.

Blinding Confirmation

To confirm the blinding of the subject and caregiver was maintained, both the subject and caregiver were presented (separately) with the following question after the completion of first week of Active or Sham treatment (end of fifth Active/Sham treatment sessions, respectively):

- Subject: "Do you know if the treatment that you received today was an actual treatment or a placebo treatment?"
- Caregiver: "Do you know if the treatment the patient received today was an actual treatment or a placebo treatment?"
- Possible responses were: "Actual Treatment", "Placebo" or "Not sure / cannot tell".

To assure the ADAS-Cog and ADCS-CGIC raters remained blinded to the subject's group assignment, both raters were presented (separately) with the following question after completion of six weeks of active/sham treatment, and prior to first follow-up:

- "Do you know if the treatment the patient received was an actual treatment or a placebo treatment?"
- Possible responses were: "Actual Treatment", "Placebo" or "Not sure / cannot tell".

Study Evaluations and Visit Schedule

The study included the following evaluation scales:

- Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog)

ADAS intends to measure the severity of the most important symptoms of AD. Its subscale ADAS-Cog is the most popular cognitive testing instrument used in clinical trials of nootropics. It consists of 11 tasks measuring the disturbances of memory, language, praxis, attention and other cognitive abilities which are often referred to as the core symptoms of AD.

The total score ranges from 0-70 points and measures the number of mistakes counted in the test. A higher result represents greater cognitive dysfunction. AD patients deteriorate on average in the range of 4 to 7 points per annum, depending on the level of their dementia.[88]

A copy of the ADAS-Cog Administration and Scoring Manual is included in **Appendix 2**. In commercial use, the company plans to use a 3rd party vendor to train and certify users in administration of the ADAS-Cog instrument.

- ADCS-Clinical Global Impression of Change (ADCS-CGIC)

The Alzheimer's Disease Cooperative Study – Clinical Global Impression - Change scale (ADCS-CGIC) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past diagnosis with the patient. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating. Assessment is performed using a structured interview with both the patient and the caregiver.

The purpose of the baseline measurement of ADCS-CGIC is to set the reference for future comparison.

The 7-point scale is characterized as follows: 1-very much improved; 2-much improved; 3-minimally improved; 4-no change; 5-minimally worsened; 6-much worsened; or 7-very much worsened.

A copy of the ADCS-CGIC questionnaire is included in **Appendix 3**.

Visits Schedule

Screening Visit:

The screening window was up to 21 days before first treatment administration.

The following were collected or performed before any study-specific procedures were performed:

- Informed Consent Form;
- Complete physical examination, neuropsychological assessment, current medications that subject is using, and medical and surgical history;
- Ensure that all inclusion/exclusion criteria are met;
- Cognitive Dementia Rating (CDR);
- Mini Mental State Examination (MMSE);
- Safety TMS screening questionnaire;[89] and
- Participants were instructed not to be engaged in any other experiment and/or new therapy treatment during their participation in the study.

Only patients who met all eligibility criteria were enrolled and continued to the Baseline visit.

Baseline Visit:

The baseline window was up to 14 days before first treatment administration. The following procedures were conducted during the Baseline visit:

- ADCS-CGIC and ADAS-Cog

The ADCS-CGI-C and ADAS-Cog were performed by two different, independent raters, each of whom was blinded to the other's ratings. Patients who were not scored within the inclusion criteria of ADAS-Cog (> 17) were not referred to the Motor Threshold measurement and MRI procedure and were considered screening failures. Reason for exclusion was recorded in the study screening log.

- TMS Motor Threshold Measurement

An initial measurement of TMS motor threshold was performed to determine the MT and to confirm the patient's eligibility to receive TMS intervention. The subject was seated comfortably on the neuroAD Therapy System chair and the TMS coil was placed over the motor cortex. Standard procedure was followed.[90] Subjects were requested to place their hands on the device hand rest with the palms facing up for optimal scalp location for induction of visible contraction of finger muscles. A single-pulse TMS was applied at decreasing (or increasing) intensities over these sites to determine the motor threshold, defined as the minimal intensity required for inducing six visible motor responses out of 12. If the subject's Motor Threshold was not identified, he/she was removed from the study as a screen failure. TMS Motor Threshold measurement was performed on all study subjects prior to randomization.

- MRI Scan

All subjects underwent a structural MRI scan to identify excluded disorders including non-Alzheimer's brain pathology (analysis provided by investigator) and mark brain regions to be treated. No contrast media was used for the MRI scan. MRI region marking was performed by a qualified blinded professional. Though considered part of baseline visit, the MRI scan was allowed to be scheduled for a different date to accommodate site and patient schedule constraints but was required to be performed within a week of other baseline activities.

Patients who did not meet all of the eligibility criteria, including the MT threshold and brain scan criteria, were not randomized and were excluded from the study as screen failures.

Subjects were considered enrolled once they completed all screening and baseline activities including the baseline MRI scan.

Randomization

Following the MRI scan, every recruited subject (except for the run-in/roll-in subjects) was centrally randomly assigned by IVRS into one of two groups:

- Active (Treatment) group (#1) – neuroAD Therapy System treatment (TMS stimulation combined with cognitive training); or
- Sham (Control) group (#2) – sham TMS stimulation and sham cognitive training.

Treatment Visits

The basic agenda of the treatment visits (visits numbers 3 to 32) is described below:

- Approximately one hour session, five days per week for six weeks, overall up to 30 visits.
- All subjects were assessed at the beginning of each visit for adverse events or change in medical condition.
- All subjects were asked to use earplugs at the beginning of the treatment session, regardless of their group assignment.
- Both the Active and Sham groups followed same treatment visits schedule.

Post Treatment Visits

The ADAS-Cog and ADCS-CGIC raters were blinded to each other, and to the patient's treatment group assignment.

- Visit 33 (Week 7)

  The following assessments performed at this visit:

  - ADAS-Cog
  - ADCS-CGIC
  - Adverse Events assessment

- Visit 34 (Week 12)

  The following assessments performed at this visit:

  - ADAS-Cog
  - ADCS-CGIC
  - Adverse Events assessment

  Following visit 34 at week 12, each subject completed the course of the study.

<u>Study Procedure Matrix</u>

Table 4 below shows the study procedure matrix.

Table 4: Schedule of Activities, US Pivotal Study

Item	Screening	Baseline		Active/Sham Treatment Phase						Follow-Up	
Visit Number	**1**	**2**	**R**	**3-7**	**8-12**	**13-17**	**18-22**	**23-27**	**28-32**	**33**	**34**
Scheduled Week	**-21 to day -1**	**-14 to day -4**		**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 12**
Informed consent	X										
Medical History & Demographics	X										
Physical Exam	X										
Concomitant Medications	X			X	X	X	X	X	X	X	X
MMSE	X										
ADAS-Cog (Blinded Rater)		X								X	X
ADCS-CGIC (Blinded Rater)		X								X	X
CDR	X										
TMS Safety Questionnaire	X										
TMS Motor Threshold Measurement		X									
MRI		X (3 workings days turnaround)									
Randomization			X								
TMS Motor Threshold Measurement – daily (Active group only)				X	X	X	X	X	X		
neuroAD Treatment (Daily) (Group 1&2)				X	X	X	X	X	X		
Adverse Events		X		X	X	X	X	X	X	X	X
Inclusion & Exclusion Criteria	X	X (Review)									
Study Deviation	X	X		X	X	X	X	X	X	X	X
Study Exit Group 1											X
Study Exit Group 2											X
Treatment Group 1 – neuroAD System Active (real) Treatment. Patient #1-#2 assigned to the treatment group.											
Treatment Group 2 – neuroAD System Sham Treatment.											

<u>Study Endpoints</u>

Safety Endpoint:

- Adverse Events (AEs) including serious AEs (SAEs) that occurred at any time during the trial or follow up.

Primary Efficacy Endpoint:

- Change from baseline to week 7 in ADAS-Cog score.

Secondary Efficacy Endpoints:

- Change from baseline to week 7 in ADCS-CGIC.
- Change from baseline to week 12 in ADCS-CGIC.
- Change from baseline to week 12 in ADAS-Cog.

Statistical Methods Planned in the Protocol:

Statistical Plan

The statistical plan was designed and executed by a third party statistical vendor. The detailed statistical plan was designed and signed prior to study completion and breaking the blind. The statistical vendor had no access to the data prior to finalization of the statistical plan.

Sample Size

The total number of subjects in this trial was calculated to be up to 120 subjects (50 per arm, plus up to 20 roll-in patients receiving active treatment), to achieve over 90% power to demonstrate superiority of Active group to the Sham on change from baseline to end of treatment on ADAS-Cog.

As noted above, due to a software error, a concern was raised that some of the subjects received some of the cognitive training at a non-optimal difficulty level; hence, it was decided that these subjects will be excluded from the efficacy analyses. Consequently, up to 30 additional patients were added to the trial and the randomization rate was changed to a ratio of Active to Sham of 2:1, to have at least 50 valid randomized subjects in each study arm. Thus, the sample size was increased to be up to 150 subjects.

Handling of Missing Data

Per the pre-specified statistical plan, missing data for the primary and secondary endpoints was to have been imputed using multiple imputation methodology. This imputation was carried out and yielded results very similar to those obtained based on the non-imputed data, hence the results described in this document are based on observed (non-imputed) data only.

Changes during the Course of the Study:

Changes in the Conduct of the Study or Planned Analyses

Protocol Amendment #1:

Subjects' recruitment for this study was initiated in October 2013, under protocol version 200 dated July 2013. Thirty nine subjects were recruited under protocol version 200; of them, 14 were run-in subjects.

On April 2014, the study protocol was amended to provide for clarifications and additions, following previous interactions with the FDA. The protocol amendment included the following key modifications:

- Addition of ADCS-CGIC evaluation at week 7, to provide additional efficacy data.
- Addition of exclusion criteria to exclude subjects who underwent TMS treatment in the past, to maintain blinding.
- Change to subject withdrawal criteria to define a minimum required treatment sessions, to support modifications in the statistical plan as per previous interactions with the FDA.
- Additional clarification that ADAS-Cog and ADCS-CGIC raters should be blinded to each other.
- Updated list of expected adverse events, based on literature review.
- Prolongation of time window for baseline visit from up to 7 days prior to first treatment to up to 14 days prior to first treatment, to accommodate for sites and subjects schedule constraints.
- Prolongation of study duration.
- Addition of blinding questions.
- Other minor clarifications.

Protocol Amendment #2:

During the study a software error was detected. The software error implied that under specific conditions, some of the cognitive training exercise levels did not progress as planned per the pre-specified algorithm. The software error could affect only subjects in the Active group (#1). As a consequence, the following steps were taken:

- Sample size was increased to ensure at least 50 subjects in each of the treatment arms (excluding “roll-in” patients).
- Subjects randomized after protocol amendment were randomized centrally using a ratio of Active to Sham of 2:1.
- System software was updated to ensure this error did not repeat.

Changes in Planned Analysis

The statistical analysis was performed according to the Statistical Analysis Plan. In addition, in order to further evaluate the results observed in the Pivotal Study, additional analyses were conducted. The results of those additional analyses are provided below in **Sections 6.2.2.6** and **6.2.2.7**.

Changes in the Device

System software was updated following the discovery of the software error, as previously described. No other changes were made to the device during the conduct of the study.

Study Conduct and Monitoring

This study was conducted in compliance with the protocol following IRB/Ethics Committee approval and according to Good Clinical Practice (GCP) standards and principals originating in the Declaration of Helsinki. The study was monitored by a dedicated study team from the third party CRO. Although the Sponsor was responsible for site initiation visits, when available a representative from the CRO attended the visit to provide additional training on study records, Electronic Data Capture (“EDC”) system, and other study procedures. In case a representative from the CRO did not

attend the initiation visit, a separate visit (either on-site or teleconference) was performed. The CRO performed routine Interim Monitoring Visits (monitoring 100% of the data), study Close-Out Visits and management of study records. The CRO was also responsible for Data Management for this study. The EDC System was implemented in this study using Medidata Solutions eCRF, which complies with US 21 CFR parts 312 and 812, US 21 CFR part 11, Annex 11, and US-EU Safe Harbor requirements.

Medical Committee:

The medical committee, comprised of three independent doctors (two neurologists and a clinical neuropsychologist), provided independent medical support for the study, including review of Serious Adverse Event reports, and providing the study investigators with support on medical issues and questions. The medical committee also performed blinded review of protocol deviations and adverse events at the end of the study and prior to study unblinding.

Clinical Centers:

Ten clinical centers participated in the study; each one had a local Principal Investigator (PI) with overall responsibility for the study at the site, two raters who performed the assessment scales (ADAS-Cog, ADCS-CGIC), a study coordinator, and at least two Operators who operated the neuroAD Therapy System during procedures (lead Operator and back-up Operator). At some of the sites the study coordinator also served as an Operator of the neuroAD Therapy System.

It is important to note that the two raters who performed the assessment scales (ADAS-Cog & ADCS-CGIC) were independent from study staff that met the subjects throughout the study. As detailed above, the raters were blinded to the subject's group assignment and also to each other.

The study team at each of the clinical centers was appointed by the local PI.

Please see below a full list of participating clinical centers and Principal Investigators:

Table 5: Participating Centers and Principal Investigators, US Pivotal Study

Site #	Site Name	Principal Investigator
101	Lou-Ruvo Center for Brain Health, Cleveland Clinic, Las Vegas, NV	Charles Bernick, MD, MPH
102	Banner Sun Health Research Institute, Sun City, AZ	Marwan Sabbagh, MD
103	NYU Langone Medical Center, New York, NY	Steven H. Ferris, PhD Stella Karantzoulis, PhD
104	Palm Beach Neurology and Premiere Research Institute, West Palm Beach, FL	Carl Sadowsky, MD
105	Cleveland Clinic, Cleveland, Ohio	Babak Tousi, MD
106	Beth Israel Deaconess Medical Center, Harvard, Boston, MA	Alvaro Pascual-Leone, MD, PhD
107	Miami Jewish Health Systems, Miami, FL	Marc Agronin, MD
108	ATP Clinical Research, Costa Mesa, CA	Gustavo Alva, MD
109	Roskamp Institute, Sarasota, FL	Andrew P. Keegan, MD
201	Asaf-Harofe Hospital, Beer-Yakov, Israel	Carmel Armon, MD

6.2.2 US Pivotal Study Results

6.2.2.1 Study Subjects

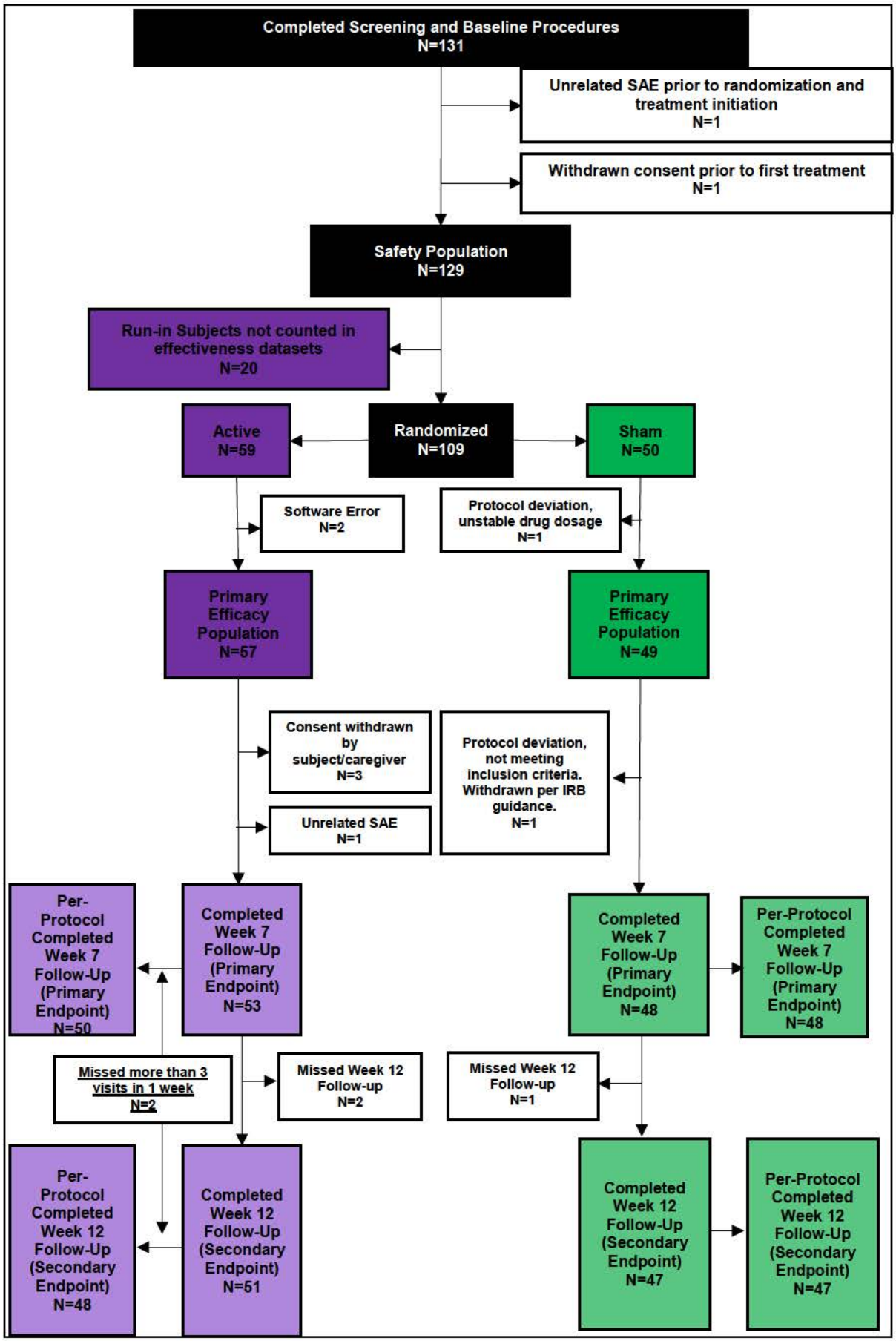
6.2.2.1.1 Disposition of Subjects

131 subjects completed screening and baseline procedures and were found eligible to participate in the study. One subject experienced an unrelated SAE that required hospitalization prior to randomization and treatment initiation (upper respiratory infection and cervical fracture due to a fall), and therefore was withdrawn from the study before actually entering the study.

Overall, 130 subjects were enrolled into the study. Of them, 20 subjects were considered as run-in/roll-in subjects and are included only in the safety analyses, and 110 subjects were randomized to receive either Active or Sham treatment.

A subject disposition flowchart is shown in **Figure 15** below.

Figure 15: Subject Disposition Flowchart, US Pivotal Study



6.2.2.1.2 Subject Disposition by Analysis Population

Subject disposition by analysis population is presented below.

Safety Population:

129 subjects out of the 130 enrolled (99.2%) were included in the Safety Analysis Population, including the 20 run-in subjects. One subject was excluded from the safety analysis as the subject withdrew consent post-randomization and prior to first treatment session administration (subject did not receive any Active or Sham treatment).

Primary Efficacy Analysis Population:

The Primary Efficacy (PE) Population is comprised of randomized subjects who had at least one baseline measurement on the primary efficacy endpoint ADAS-Cog and who participated in at least one post-baseline treatment visit (Active or Sham).

Included were subjects with no major entry violations as determined by blinded review. Also, as described above, subjects that may have been affected due to the software error were excluded from the PE Population in a manner that was blind to their outcome (but were included in the Safety Population).

Roll-in subjects were not included in the PE Population.

Overall 106 subjects were included in the PE Population (96.3% of the randomized subjects). Four subjects were excluded from the PE Population for the following reasons:

- Two subjects that may have been affected by the software error
- One subject for whom treatment was not initiated
- One subject who had major entry violation – increase in AD drug dosage (an increasing dose of AD drug may bias the results in favor of the investigational device)

Per-Protocol Population:

The Per-Protocol (PP) Population is a subset of the PE Population which consists of subjects who had no major protocol violations likely to affect outcome, and who (as defined in the protocol):

- Had at least 24 treatment visits of the planned treatments; and
- Did not miss more than 2 visits in any week of the planned six weeks of treatment; and
- Missed more than one session in no more than 2 weeks of treatment, of the planned six weeks of treatment.

Overall 98 subjects were included in the PP Population. All subjects that were excluded from the PP Population were excluded for not meeting the minimum required visits as set forth above. The reasons for not meeting the minimum number of visits are detailed below:

- One subject death (see description below); and
- Three subjects withdrew consent (two subjects withdrew consent after one treatment session, and one subject withdrew consent after 7 treatment sessions for an undisclosed reason);
- One subject was withdrawn for not meeting the baseline ADAS-Cog eligibility criteria; and

- Three subjects missed three treatment sessions in the same week.

6.2.2.1.3 Enrollment By Site

Table 6 below presents the enrollment by site out of the overall 130 subjects recruited into the study.

Table 6: Enrollment by Site, US Pivotal Study

Center	Enrollment
101	8
102	9
103	6
104	31
105	19
106	8
107	18
108	13
109	6
201	12
All	130

6.2.2.2 Demographics and Baseline Characteristics

The following demographics and baseline characteristics of the subjects are presented for the Safety Population (129/130 subjects enrolled). As shown in the tables below, there were no significant differences in baseline demographic characteristics between the Active and Sham groups.

Table 7: Gender by Study Group, US Pivotal Study

Study Group	Gender				All		P-Value
	Male		Female				
	N	%	N	%	N	%	
Active Group	41	51.9	38	48.1	79	100.0	0.499
Sham Group	29	58.0	21	42.0	50	100.0	
All	70	54.3	59	45.7	129	100.0	

More men (54.3%) participated in the study than women, though with no significant difference between groups (p=0.587), and in both study groups, the level of education of participants was mostly ‘completed college’ (55.8%).

Table 8: Comparison of Age, BMI, Time from AD Diagnosis and MMSE, US Pivotal Study

Parameter	Study Group	Mean	Std	Min	Median	Max	N	P-Value
Age [Years]	Active Group	76.9	6.8	61.6	77.3	89.1	79	0.850
	Sham Group	76.7	7.1	61.0	76.7	91.2	50	
	All	76.8	6.9	61.0	76.9	91.2	129	
BMI [Kg/M^2]	Active Group	25.9	5.4	17.5	24.6	44.6	77	0.912
	Sham Group	25.7	4.9	17.5	25.2	39.3	50	
	All	25.8	5.1	17.5	25.0	44.6	127	
Time from AD Diagnosis [Years]	Active Group	1.7	2.1	0.0	1.1	10.7	79	NS
	Sham Group	1.8	1.6	0.0	1.4	7.2	50	
	All	1.8	1.9	0.0	1.2	10.7	129	
MMSE Score	Active Group	21.7	2.4	18	22.0	26	79	0.322
	Sham Group	21.3	2.6	18	22.0	25	50	
	All	21.5	2.5	18	22.0	26	129	

The Global Clinical Dementia Rating (CDR) was mild (score of 1) for nearly all subjects (96.9%) participating in the study, which aligns with the eligibility criterion excluding any potential subjects with normal (0), very mild (0.5) or severe (3) scores.

With regard to other demographic characteristics:

- Race was similar between groups (p=0.736), with the majority of subjects in both groups being Caucasian.
- The highest level of education was also similar between groups (p=0.137 for the difference between the proportion of subjects who completed college).
- The proportion of subjects using medication was very similar (p=0.749) between groups, approximately 80% of subjects.

Table 9: Comparison of ADAS-Cog Baseline Score between Study Groups by AD Severity*, US Pivotal Study

AD Severity (MMSE)	Study Group	Mean	Std	Min	Median	Max	N	P-Value
Mild	Active Group	22.1	3.6	17.0	21.3	32.3	49	0.643
	Sham Group	22.8	4.4	16.7	21.3	36.7	30	
	All	22.4	3.9	16.7	21.3	36.7	79	
Moderate	Active Group	26.1	5.6	16.0	25.0	39.0	30	0.738
	Sham Group	26.7	8.3	17.7	24.0	40.3	20	
	All	26.3	6.7	16.0	24.8	40.3	50	
All	Active Group	23.6	4.8	16.0	22.3	39.0	79	0.929
	Sham Group	24.4	6.5	16.7	21.7	40.3	50	
	All	23.9	5.5	16.0	22.0	40.3	129	

* AD severity was determined within the study protocol as Mild: 21≤MMSE≤26; Moderate: 18≤MMSE≤20.

No statistical significance was noted between study arms with regard to Baseline ADAS-Cog in both the mild and moderate AD subgroups.

The average ADAS-Cog at baseline was 23.9 for all subjects (above), and the average TMS Motor Threshold as measured at baseline was 75.0 (below). There was no statistically significant difference between groups on either measure.

Table 10: Baseline Motor Threshold by Study Group, US Pivotal Study

Study Group	Mean	Std	Min	Median	Max	N	P-Value
Active Group	75.5	13.1	44.0	75.5	99.0	78	0.702
Sham Group	74.2	12.7	24.0	77.0	97.0	50	
All	75.0	12.9	24.0	76.0	99.0	128	

As can be seen from the tables above, the differences between groups were small and not statistically significant. No significant differences between groups were noted on other demographics and baseline characteristics, or in physician examinations and medical history.

6.2.2.3 Treatment Compliance

Overall subjects' compliance was excellent, with more than 90% of the subjects participating in the study completing at least 28 treatment sessions (Active or Sham) or more, out of the required 30 treatment sessions.

Out of the 129 subjects included in the Safety Population, 8 subjects (6.2%) did not meet the minimum number of treatment visits as defined by the study protocol:

- Three subjects completed the six week treatment plan but did not participate in the minimum required treatment visits (Active or Sham), which was considered a protocol deviation
- Three subjects withdrew consent and did not complete the six week treatment plan
- One subject was withdrawn from the study and did not complete the six week treatment plan for not meeting inclusion-exclusion criteria
- One subject died during the course of the six week treatment plan (unrelated to treatment – see below)

Frequency distribution of compliance in the PE Population is presented below:

Table 11: Compliance by Treatment Group, US Pivotal Study (PE Population)

Treatment Group	1		7		14		20		26		27		28		29		30		All	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Active	2	3.5	1	1.8	1	1.8	0	0	1	1.8	2	3.5	9	15.8	17	29.8	24	42.1	57	100.0
Sham	0	0	0	0	0	0	1	2.0	0	0	0	0	11	22.4	11	22.4	26	53.1	49	100.0
All	2	1.9	1	0.9	1	0.9	1	0.9	1	0.9	2	1.9	20	18.9	28	26.4	50	47.2	106	100.0

*Note: Percentages shown in the table are not cumulative.

As shown in **Table 11** above, 42.1% and 53.1% of subjects in the Active group and Sham group, respectively, completed the full series of 30 treatment sessions. An additional 29.8% and 22.4% of subjects in the Active group and Sham group, respectively, missed only one treatment session and completed 29 treatment sessions.

Overall, 98 out of 106 (92.5%) subjects participated in 28 sessions or more, presenting a high treatment compliance in both study groups.

Other than the subjects discussed above who did not complete the minimum required treatments, a limited number of subjects missed treatment visits (Active or Sham), typically due to vacation, concomitant medical conditions, or technical error. In the case of technical error, these issues typically were technical malfunctions that prevented operation of the device, but that did not present safety concerns for either the operator or the patient.

6.2.2.4 Protocol Deviations

There were several minor protocol deviations, as shown in the table below, none of which affected the study.

Table 12: Protocol Deviations, US Pivotal Study

Deviation Type	Number	Excluded from Analyses?	Comments
Did not meet inclusion criterion #4 – ADAS-Cog above 17	1	Yes	Withdrawn from study
Did not meet inclusion criterion #11 – Stable dose of AD drugs	1	Yes	Excluded from efficacy analysis
Different ADCS-CGIC raters at baseline, week 7, and week 12	3	No	
Inconsistency in test order: Screening and Baseline procedures performed on same day; ADAS-Cog test performed after entire Screening process	15	No	
Different ADAS-Cog raters at baseline, week 7, and week 12	4	No	
ADAS-Cog rater had access to randomization information for subject but indicated no knowledge of assignment at time of evaluation	1	No	
ICF was not signed by the caregiver accompanying the enrolled subject	1	No	Resolved during study
Subject wrote on the ICF form but did not sign ICF form	1	No	Resolved during study
Consenting investigator failed to document that prospective study subject demonstrated the capacity to consent	2	No	Resolved during study

6.2.2.5 Safety Evaluation

6.2.2.5.1 Adverse Events

Adverse Events (AEs) are presented for the Safety Population, which included run-in subjects (N=129).

Overall, 94 Adverse Events (AEs) were reported in the study. Of them, 70 AEs were of mild severity, 22 of moderate severity, and one was severe. The distribution of the severity of the AEs was similar in both study groups, with the single AE rated as 'Severe' occurring to a subject in the Active group (further details below).

Table 13: AEs by Severity/Intensity and Study Group, US Pivotal Study

Severity/Intensity	Study Group					
	Active Group (N=79)		Sham Group (N=50)		Any	
	# of patients	# of events	# of patients	# of events	# of patients	# of events
Any	32 (41%)	63	16 (32%)	31	48 (37%)	94
Mild AE	26 (33%)	49	10 (20%)	21	36 (28%)	70
Moderate AE	9 (11%)	12	7 (14%)	10	16 (12%)	22
Severe AE	1 (1%)	1	0 (0%)	0	1 (1%)	1
Unknown	1 (1%)	1	0 (0%)	0	1 (1%)	1

Adverse events were categorized regarding relationship to the study procedure and relationship to the investigational device. As shown in **Table 14** below, most of the AEs reported in the study were found to be not related or unlikely to be related to study procedures, as determined by the site investigator. Nine subjects in the Active group and two subjects in the Sham group (overall 9% of study subjects) reported AEs that were found to be possibly or probably related to study procedures.

Table 14: AEs by Relationship to Study Procedure and Study Group, US Pivotal Study

Relationship to Study Procedure	Study Group		
	Active Group N=79	Sham Group N=50	Any
Any	63; 32 (41%)	31; 16 (32%)	94; 48 (37%)
Not Related	42; 26 (33%)	24; 13 (26%)	66; 39 (30%)
Unlikely	8; 6 (8%)	3; 2 (4%)	11; 8 (6%)
Possible	10; 7 (9%)	4; 2 (4%)	14; 9 (7%)
Probable	3; 2 (3%)	0; 0 (0%)	3; 2 (2%)
Definite	0; 0 (0%)	0; 0 (0%)	0; 0 (0%)

Similarly, with respect to relationship to the study device, as shown in **Table 15** below, most of the AEs reported in the study were found to be not related or unlikely to be related to study device, as determined by the site's investigator. 11 subjects in the Active group and two subjects in the Sham group (overall 10% of study subjects) reported AEs which were found to be possibly or probably related to the study device.

All AEs possibly or probably related to the study device were expected and mild in nature.

Table 15: AEs by Relationship to Study Device and Study Group, US Pivotal Study

Relationship to Study Device	Study Group		
	Active Group N=79 (Events, Subjects, % Subjects)	Sham Group N=50 (Events, Subjects, % Subjects)	Any (Events, Subjects, % Subjects)
Any	63; 32 (41%)	31; 16 (32%)	94; 48 (37%)
Not Related	43; 27 (34%)	25; 13 (26%)	68; 40 (31%)
Unlikely	5; 5 (6%)	2; 1 (2%)	7; 6 (5%)
Possible	8; 5 (6%)	4; 2 (4%)	12; 7 (5%)
Probable	5; 4 (5%)	0; 0 (0%)	5; 4 (3%)
Definite	2; 2 (3%)	0; 0 (0%)	2; 2 (2%)

11 subjects in the Active group reported a total of 15 AEs that were found to be possibly, probably or definitely related to the investigational device. Two subjects in the Sham group also reported events

that were possibly, probably, or definitely related to the study device. All potentially related AEs were mild in nature and resolved on their own or with slight adjustment of the treatment (adjusting treatment intensity by adjusting the TMS Motor Threshold) or administration of nonprescription pain medication, such as Tylenol. Potentially related AEs were expected AEs that are often associated with TMS such as headache, neck pain, skin discomfort or muscle twitching. For some subjects, events persisted through multiple treatment sessions but severity was mild, did not require discontinuation, and the events were managed and overcome by adjusting/decreasing the treatment intensity (MT%).

It is important to note that these AEs were all transient, occurred during treatment and with no further side effects or other impact on subjects' daily life.

One death occurred in the study, which was unrelated to the study procedure or treatment, as discussed below. No unanticipated adverse device effects occurred during the investigation.

6.2.2.5.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

There were only four SAEs in the study, none of which were related to the study procedure or device. Three occurred in the Active group and one in the Sham group: death, cervical fracture, urinary retention and asthenia. A narrative of each case is provided below.

Death:

An 83 year old female, randomized into the Active group. The SAE occurred during the six week treatment course. Subject started treatments on October 13, 2014.

Event Description:

On November 3, 2014, the subject's caregiver contacted the site, stating the subject would miss her scheduled visit due to subject feeling tired.

The following day, on November 4, 2014, the subject's caregiver contacted the site again, reporting the subject had stomach issues on November 3, met with a physician and was prescribed with enema. Later that day, on the evening of November 3, the subject was found deceased in the bathroom. Autopsy was not performed.

The last study treatment visit took place on Thursday, October 30, 2014. The treatment session scheduled for Friday, October 31, 2014 was cancelled in advance due to subject and caregiver travelling arrangements for the weekend.

The event was assessed as an unexpected SAE, not related to the study, by the site investigator, medical committee and sponsor.

Cervical Fracture:

An 85 year old female, in the non-randomized Active group. The SAE occurred post-screening and baseline evaluations and prior to randomization and first treatment session.

Event Description:

While scheduled to be randomized into the study, on March 5, 2015, the subject experienced an upper respiratory infection and was referred by her primary care provider to inpatient hospitalization support. As the subject was preparing to leave her home to go to the hospital, she accidentally tripped and fell, injuring her neck. Injury resulted in a non-displaced fracture of the cervical spine that was treated with a hard cervical collar. Subject was hospitalized.

The subject's participation in the study was discontinued. The event was resolved on June 25, 2015. Subject did not receive any active or sham treatment

The event was assessed as an unexpected SAE, not related to the study, by the site investigator, medical committee and sponsor.

Urinary Retention:

An 87 year old male, randomized into the Sham group. Subject had history of BPH and urinary retention. SAE occurred during the six week treatment course. Subject started treatments on October 22, 2014.

Event Description:

On November 19th, 2014, the subject presented to the hospital with suprapubic burning and pressure. A Foley catheter was placed. Subject was found to have UA positive for just nitrites. Given Ceftriaxone and admitted overnight. Event resolved on November 20th.

Subject missed one study visit on November 20, 2014, due to hospitalization.

The event was assessed as an SAE, not related to the study, by the site investigator, medical committee and sponsor.

Asthenia

An 83 year old male, randomized into the Active group. Subject had history of coronary artery bypass graft since July 2014. SAE occurred during the six week treatment course. Subject started treatments on April 20, 2015.

Event Description:

On April 24, 2015, the subject arrived at study session number 5 disheveled and slow to respond. The site team discussed with the caregiver, and the subject was taken to the emergency room. No study procedures were performed on April 24, 2015.

Subject was hospitalized for generalized weakness. Subject found to be in rapid atrial fibrillation, have slightly low potassium, and mildly dehydrated. Normal EEG, CXR with mild atelectasis, cardiomegaly, head CT with no new findings. Subject was monitored, rehydrated, and discharged on April 30, 2015.

Subject missed four study sessions on April 24-30, 2015, due to hospitalization. Subject resumed study sessions on April 31, 2015.

The event was assessed as an unexpected SAE, not related to the study, by the site investigator, medical committee and sponsor.

6.2.2.5.3 Discussion of AEs and SAEs

Thirteen subjects reported potentially related AEs during the study, of which eleven subjects were in the Active group and two subjects were in the Sham group. All potentially related events were mild and resolved within the scope of the study (most AEs resolved on the same day of occurrence with either minor adjustments or no action taken).

All potentially related AEs were anticipated AEs, which are commonly associated with TMS administration, mainly headache (7/13) and skin discomfort (3/13).

Comparing to previously reported TMS studies for the treatment of Major Depressive Disorder[91,92] the rate of potentially related AEs reported in this study is relatively low (11 events for 79 Active subjects in the study (14%), compared with 99 events for 165 subjects reported for the Neuronetics' MDD pivotal study (60%) and 37 events for 101 subjects reported in Brainsway's MDD study (37%)), and of mild severity.

Overall four SAEs were reported during the study, of which one was a death. None of the SAEs occurred during a treatment session. All SAEs were determined by the treating PI, study Medical Committee and the sponsor to be unrelated to the study procedure or device.

6.2.2.5.4 Safety Conclusions

The treatment was well tolerated by participating subjects. A relatively similar percentage of Active group subjects (41%) and Sham group subjects (32%) experienced adverse events. In both groups, most adverse events were mild in severity. The single severe event (death) occurred in the Active group and was determined to be unrelated to the study device or study procedure. Given the age of the study population, it was not unusual that an unrelated patient death occurred during the study.

In the Active group, 50 of 63 adverse events reported were determined to be not related or unlikely related to the study procedure (10 events possibly related, 3 events probably related, and no events definitely related). Similarly, 48 of the 63 adverse events in the Active group were determined to be unrelated or unlikely related to the study device (8 events possibly related, 5 events probably related, and 2 events definitely related). Both adverse events in the Active group that were definitely device related were headaches and resolved.

All adverse events that were possibly, probably, or definitely related to the study procedure or study device were mild in severity and resolved within approximately 1 week and often the same day. The most commonly reported related adverse events were headache, skin discomfort, and neck pain.

Two serious adverse events were reported in the Active group and one in the Sham group. In the Active group, these events included one case of asthenia, which resolved in 6 days and the other was the death that is discussed above. Neither event was related to the study procedure or device. In the Sham group, one serious event (urinary retention) was reported and was also considered unrelated.

The adverse event rate was relatively low compared to other previously cleared TMS applications. The most significant risk of TMS reported in literature and guidance[93,94,95] is inducement of seizures. No seizures were reported in this study.

Thus, the study demonstrated a highly favorable safety profile of the neuroAD Therapy System, with no evidence of significant risk to patients. In addition to a low rate of adverse events, the study also found a high rate of treatment compliance (93% of subjects attended ≥ 26 out of 30 sessions) and few subjects withdrew from the study, both of which support that the treatment is well tolerated.

6.2.2.6 Efficacy Evaluation

As noted above, the efficacy of the neuroAD Therapy System was evaluated through the Cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) and the Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC). Results are reported here for the 101 (53 Active, 48 Sham) PE Population study subjects with available data at week 7 and week 12, as well as for the PP Population.

6.2.2.6.1 All Subjects

(i) Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog)

As detailed above, the ADAS-Cog scale consists of 11 items. Scores for each item are calculated per the subject's incorrect answers and added together for a maximum of 70 points. A higher ADAS-Cog score indicates greater cognitive impairment. Thus, in reporting mean change at follow-up compared to baseline, negative numbers indicate improvement.

In this study, the primary efficacy analysis was performed on the PE Population, evaluating change in ADAS-Cog score at week 7 compared with Baseline. The analysis of the primary endpoint revealed minimal mean change in ADAS-Cog at 7 weeks in the Active group (mean change of 0.07) compared to the Sham group (-1.38). This difference was not statistically significant. The mean scores were 23.63 and 23.70 at baseline and week 7, respectively, in the Active group as compared to mean scores of 24.39 and 23.01 at baseline and week 7, respectively, in the Sham group. Similar results were obtained for the PP Population (0.04 and -1.38, respectively, non-significant).

Therefore, the original primary endpoint assessing mean change in ADAS-Cog at 7 weeks was not achieved in the overall Pivotal Study Population.

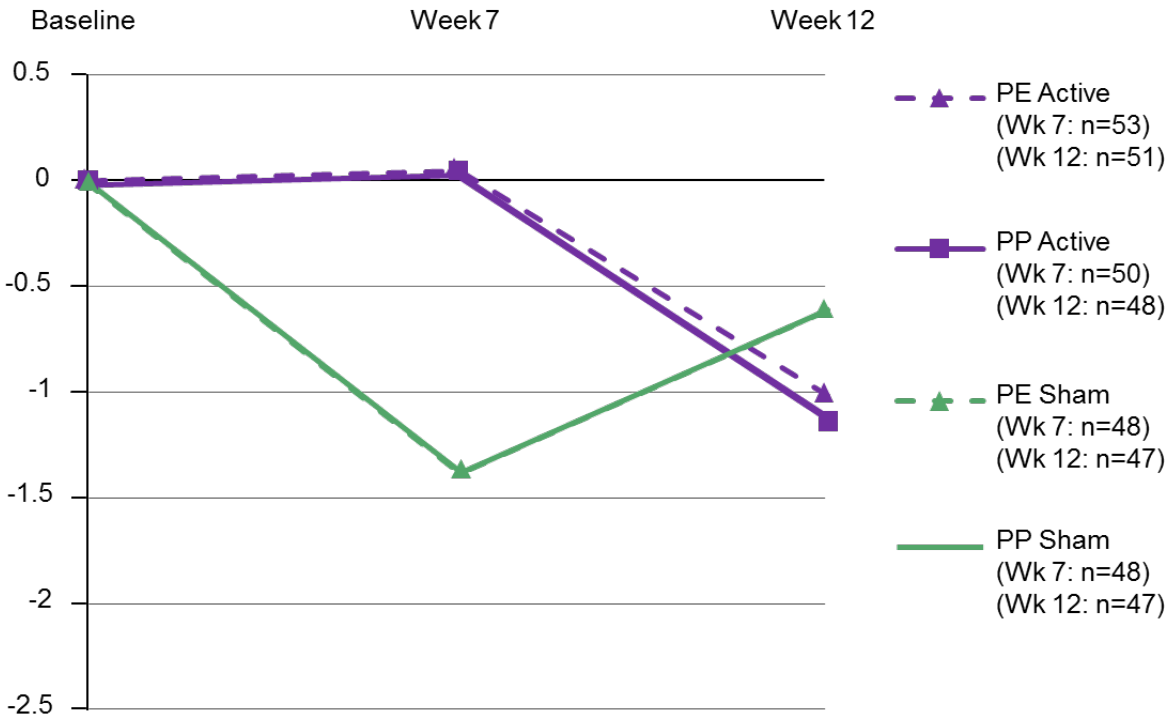
Although week 7 was the pre-specified time point for evaluation of the primary endpoint of the study, the results observed at week 7 were notably different than those observed in the study at the longer-term follow-up at week 12. By week 12, which was a pre-specified secondary endpoint of the study, improvement had dropped off in the Sham group and the Active group had continued to improve. Specifically, mean change in the Active group (PE Population) had increased to -1.03, while mean change in the Sham group, conversely, had decreased to -0.61 (difference was not statistically significant). Similar, though slightly stronger, results were reported in the PP Population (Active group mean change of -1.13). Given these results, it appears that more time was required for the placebo effect to lessen in the Sham group than originally anticipated. A delayed effect of TMS treatment has also been reported in other investigations, with maximum effect observed after cessation of treatment.[96, 97]

The improvement in the Active group and deterioration in the Sham group over time is illustrated in **Figure 3** and reported in **Table 2**. Please note that negative numbers indicate improvement (*e.g.,* larger negative mean changes represent larger improvements).

Table 16: Mean Change in ADAS-Cog from Baseline to Weeks 7 and 12, US Pivotal Study (All Patients)

ADAS-Cog Change PE Population		**n**	**Mean**	**Std**	**Min**	**Median**	**Max**	**P value**
ADAS Cog Change FU-1 (Week 7)	*Active*	53	0.07	3.97	-9.00	-0.33	14.00	
	Sham	48	-1.38	4.62	-16.67	-1.17	10.67	
								0.094
ADAS Cog Change FU-2 (Week 12)	*Active*	51	-1.03	4.85	-11.67	-1.33	10.67	
	Sham	47	-0.61	3.96	-10.67	-1.00	8.00	
								0.639
ADAS-Cog Change PP Population		**N**	**Mean**	**Std**	**Min**	**Median**	**Max**	
ADAS Cog Change FU-1 (Week 7)	*Active*	50	0.04	4.05	-9.00	-0.33	14.00	
	Sham	48	-1.38	4.62	-16.67	-1.17	10.67	
								0.110
ADAS Cog Change FU-2 (Week 12)	*Active*	48	-1.13	4.80	-11.67	-1.33	10.67	
	Sham	47	-0.61	3.96	-10.67	-1.00	8.00	
								0.565

Figure 16: Mean Change in ADAS-Cog from Baseline to Weeks 7 and 12, US Pivotal Study (All Patients)



*Note that negative numbers indicate improvement

(ii) The Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC)

The Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC) is an interview-based global measure of change that involves both patient and caregiver, incorporating domains of cognition, behavior and social and daily functioning, assessed to enable the clinician to quantify the degree of change that may have occurred in the patient from baseline.[98]

At 7 weeks, similar results were observed for the Active and Sham groups (4.04 and 4.06, respectively; difference non-significant).

At 12 weeks, the Active group improved (mean score 3.84), and the Sham group deteriorated (mean score 4.19); the difference was -0.35 and -0.38 favoring Active (for PE and PP Populations, respectively), and the results were marginally statistically significant (Wilcoxon test p-value = 0.11 and 0.09; post-hoc Chi-square test p-value for the distribution= 0.037 and 0.031; for PE and PP Populations, respectively).

Furthermore, when examining the percentage of patients who showed deterioration on the ADCS-CGIC scale, there was a significant difference between Active (8/50 deteriorated, 16%) and Sham (18/43 deteriorated, 42%); the difference was statistically significant (post-hoc two-sided Fisher's exact test, p-value = 0.01).

Table 17: Mean ADCS-CGIC Score by Visit and Study Group, US Pivotal Study

Analysis Population / Visit / Study Group			ADCS-CGIC Score						Chi-square Test	Wilxocon Test
			Mean	Std	Min	Median	Max	N		
PE Population	7 Weeks	Active Group	4.04	0.94	1.00	4.00	6.00	53		
		Sham Group	4.06	1.00	2.00	4.00	6.00	48	0.775	0.959
	12 Weeks	Active Group	3.84	1.00	1.00	4.00	6.00	50		
		Sham Group	4.19	1.05	2.00	4.00	6.00	43	0.037	0.115
PP Population	7 Weeks	Active Group	4.04	0.97	1.00	4.00	6.00	50		
		Sham Group	4.06	1.00	2.00	4.00	6.00	48	0.808	0.976
	12 Weeks	Ative Group	3.81	1.01	1.00	4.00	6.00	47		
		Sham Group	4.19	1.05	2.00	4.00	6.00	43	0.031	0.092

Figure 17: Mean ADCS-CGIC, US Pivotal Study (PE Population)

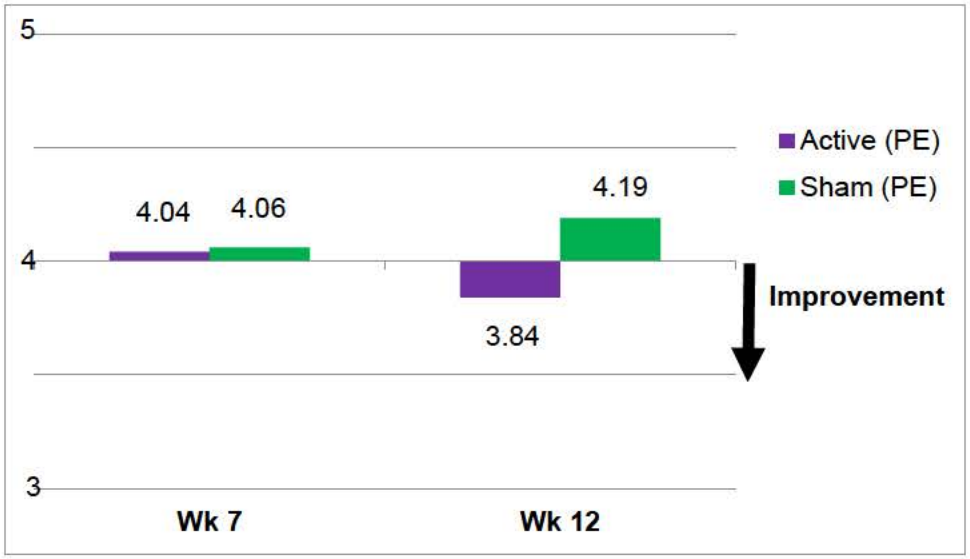
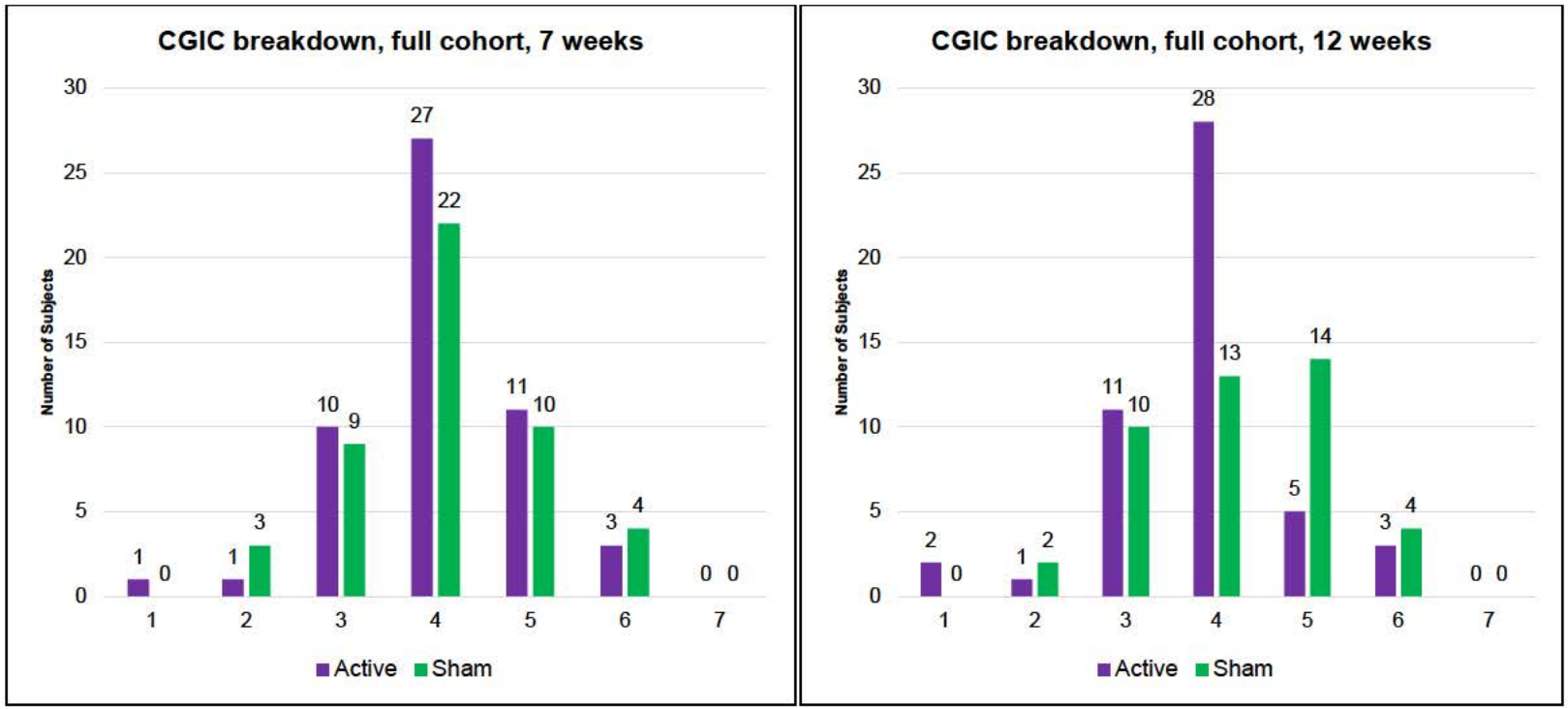


Table 18: ADCS-CGIC Score by Visit and Study Group, US Pivotal Study

Analysis Population and Cut-Off/ Visit / Study Group			1		2		3		4		5		6		All		P-Value
			N	%	N	%	N	%	N	%	N	%	N	%	N	%	
PE Population	7 Weeks	Active Group	1	1.9	1	1.9	10	18.9	27	50.9	11	20.8	3	5.7	53	100.0	
		Sham Group	0	0	3	6.3	9	18.8	22	45.8	10	20.8	4	8.3	48	100.0	0.775
	12 Weeks	Active Group	2	4.0	1	2.0	11	22.0	28	56.0	5	10.0	3	6.0	50	100.0	
		Sham Group	0	0	2	4.7	10	23.3	13	30.2	14	32.6	4	9.3	43	100.0	0.037

Figure 18: Distribution of ADCS-CGIC Scores at 7 and 12 Weeks, US Pivotal Study (PE Population)



6.2.2.6.2 Outcomes for the Baseline ADAS-Cog ≤ 30 Subgroup (i.e., Indicated Population)

As it is commonly known from the literature that baseline ADAS-Cog interacts with treatment outcome,[99] the Statistical Analysis Plan (SAP) prospectively included baseline ADAS-Cog as a covariate to assess interaction with efficacy outcome. This analysis revealed a statistically significant interaction between treatment group outcome at 7 weeks and baseline ADAS-Cog score (p-value = 0.029). This interaction was even more pronounced at 12 weeks (p-value = 0.0072).

This strong interaction indicates a non-homogeneous effect across different baseline values. Although a specific cut-off for baseline ADAS-Cog was not pre-specified, a cut-off of 30 was selected based on published literature. For example, Rutherford et al.[100] conducted a TMS intervention study on AD patients, and concluded that patients with baseline ADAS-Cog ≤ 30 responded better to the intervention than patients with baseline ADAS-Cog > 30. Ito et al.[101] performed a meta-analysis on 52 AD studies (including approximately 20,000 AD patients) and found that baseline ADAS-Cog is a significant covariate affecting the rate of disease progression, and that more demented patients (e.g., patients with baseline ADAS-Cog > 30) deteriorate faster than less affected patients (e.g., patients with baseline ADAS-Cog ≤ 30). Importantly, the subgroup of subjects with baseline ADAS-Cog ≤ 30 represents the vast majority of the study population (85% of the study cohort) (**Table 19**).

Table 19: Baseline ADAS-Cog ≤ 30 Subgroup, US Pivotal Study

	Active (n=53)	Sham (n=48)
Baseline ADAS-Cog ≤30	45	40
Baseline ADAS-Cog >30	8	8

As discussed in more detail in **Section 6.3**, the investigators of the Korean studies, who independently investigated the neuroAD device for use in Alzheimer's disease, similarly concluded that milder Alzheimer's disease patients respond more favorably to the neuroAD treatment. Following the Korean Pilot Study, which used the same inclusion/exclusion criteria as the US Pivotal Study, the investigators restricted their Pivotal Study to subjects with baseline ADAS-Cog 17-30, which is identical to the proposed indicated subgroup population from the US Pivotal Study (referred to as the "Baseline ADAS-Cog ≤30 Subgroup"). Notably, the determination that milder Alzheimer's disease patients respond more favorably to the neuroAD treatment and the decision to restrict the Korean Pivotal Study population to subjects with baseline ADAS-Cog up to 30, were made independent of Neuronix and before the US Pivotal Study results were available. Thus, this study can serve as an independent confirmatory study to validate the Baseline ADAS-Cog ≤ 30 Subgroup.

(i) ADAS-Cog Outcomes for the Baseline ADAS-Cog ≤ 30 Subgroup

Analyzing the data among subjects with baseline ADAS-Cog scores ≤30 at 7 weeks showed that both Active and Sham groups improved, with a small and non-significant difference (Active = -0.61 and -0.70 for PE and PP, respectively; Sham = -1.08 for PE and PP).

At 12 weeks in the Baseline ADAS-Cog ≤ 30 Subgroup, the Active group continued to improve while the Sham group deteriorated towards baseline (Active = -1.92 and -2.11 for PE and PP, respectively; Sham = -0.32 for PE and PP). In terms of between-group difference for mean change in ADAS-Cog at 12 weeks, the Active group significantly outperformed the Sham group in the PP Population

(difference -1.79, p-value = 0.049) and neared statistical significance in the PE Population (difference -1.61, p-value =0.07).

The results observed in the Baseline ADAS-Cog ≤ 30 Subgroup at weeks 7 and 12 are displayed in **Figure 19** below.

Figure 19: Mean Change in ADAS-Cog from Baseline to Weeks 7 and 12, US Pivotal Study (Baseline ADAS-Cog ≤30 Subgroup)

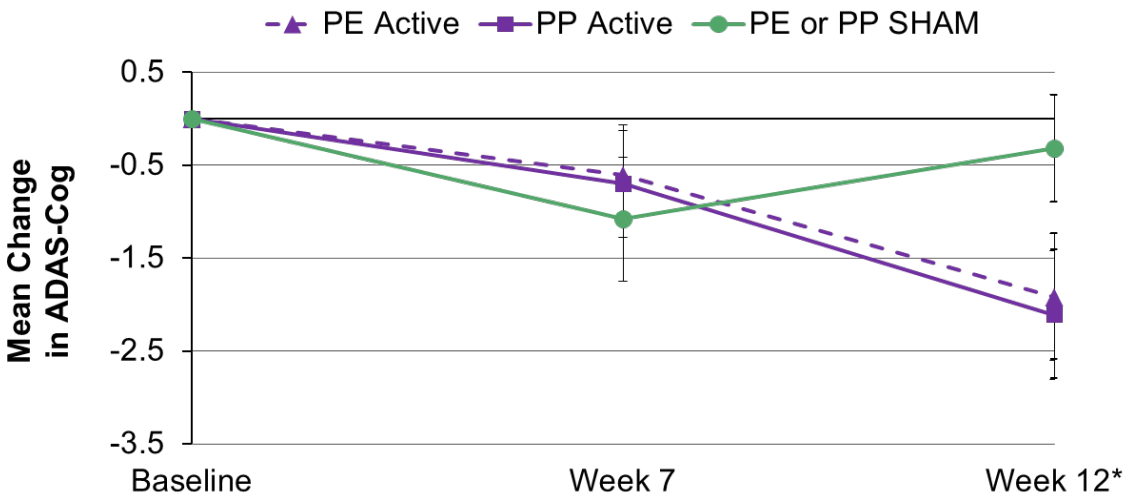


Table 20: Mean Change in ADAS-Cog from Baseline to Weeks 7 and 12, US Pivotal Study (ADAS-Cog Baseline ≤30 Subgroup)

ADAS-Cog Change (Baseline ADAS-Cog ≤ 30) PE Population		n	Mean	Std	Min	Median	Max	P value
ADAS Cog Change FU-1 (Week 7)	*Active*	45	-0.61	3.13	-9.00	-0.67	4.64	
	Sham	40	-1.08	3.81	-9.67	-0.83	10.67	
								0.536
ADAS Cog Change FU-2 (Week 12)	*Active*	44	-1.92	4.27	-11.67	-2.00	8.00	
	Sham	39	-0.32	3.87	-8.67	-1.00	8.00	
								0.077
ADAS-Cog Change (Baseline ADAS-Cog ≤ 30) PP Population		**N**	**Mean**	**Std**	**Min**	**Median**	**Max**	
ADAS Cog Change FU-1 (Week 7)	*Active*	42	-0.7	3.17	-9.00	-0,83	4.67	
	Sham	40	-1.08	3.81	-9.67	-0.83	10.67	
								0.620
ADAS Cog Change FU-2 (Week 12)	*Active*	41	-2.11	4.12	-11.67	-2	6	
	Sham	39	-0.32	3.87	-8.67	-1	8	
								0.049

It should also be noted that at 12 weeks, all ADAS-Cog thresholds below 30 demonstrate positive effects for the neuroAD device (**Table 21**).

Table 21: Observed Mean Difference in ADAS-Cog by Baseline ADAS-Cog Score at Week 12, US Pivotal Study

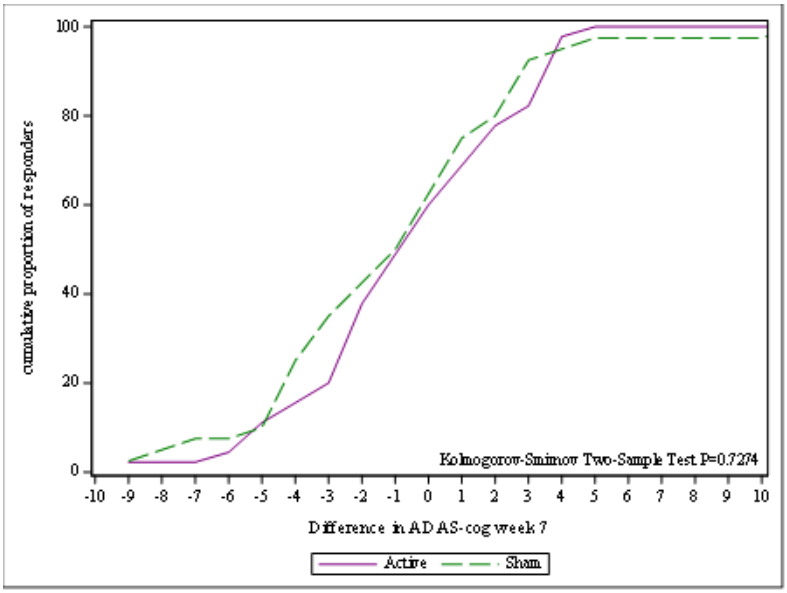
Baseline ADAS-Cog	≤ 18	≤ 20	≤ 25	≤ 30	≤ 35	≤ 40	≤ 45
Mean difference (Active-Sham) (95% CI)	-3.78 (-7.26, -0.31)	-1.64 (-4.96, 1.68)	-1.46 (-3.40, 0.47)	-1.61 (-3.39, 0.17)	-0.95 (-2.68, 0.78)	-0.35 (-2.13, 1.43)	-0.42 (-2.19, 1.35)
n (Active/Sham)	7/2	14/13	37/34	44/39	50/42	51/46	51/47

(ii) ADAS-Cog Responder Analyses for the Baseline ADAS-Cog ≤ 30 Subgroup

The data was also analyzed using an S-curve plot that tracks along a continuum the percentage of patients achieving at least that degree of change in ADAS-Cog, for the Baseline ADAS-Cog ≤ 30 Subgroup.

As shown in **Figure 20** below, at 7 weeks there is an apparent overlap between Active and Sham subjects in the Baseline ADAS-Cog ≤ 30 Subgroup.

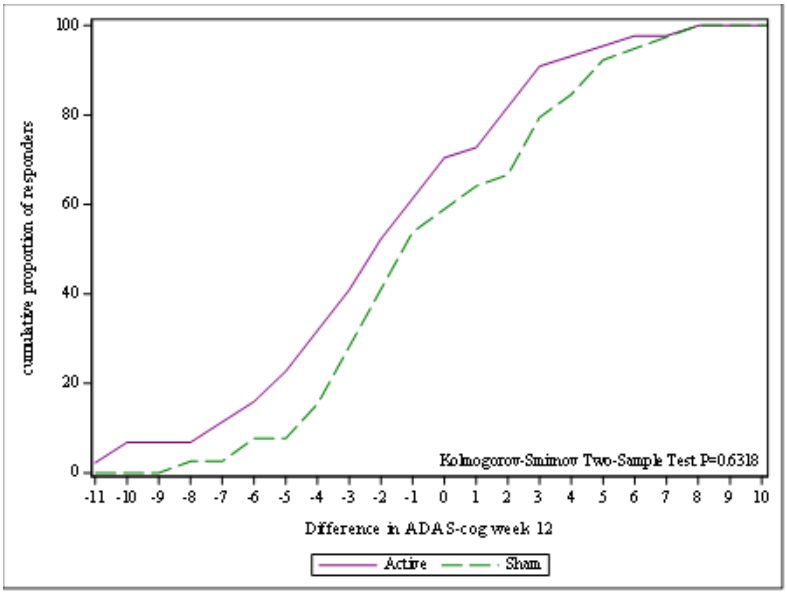
Figure 20: ADAS-Cog S-Curve Analysis at Week 7, US Pivotal Study (PE Population with Baseline ADAS-Cog ≤30)



However, at 12 weeks, which was the pre-specified secondary endpoint, there is a clear separation in the Baseline ADAS-Cog ≤ 30 Subgroup favoring the Active group, for all potential ADAS-Cog change thresholds. The S-curve analysis, although not pre-specified, is typically performed in Alzheimer's drug studies and therefore was performed to illustrate magnitude of effect across a range of thresholds for improvement and deterioration. It is clear that in the Baseline ADAS-Cog ≤ 30 Subgroup for every threshold selected, the Active group outperforms the Sham group.

The separation is in both the X-axis (implying that for the same responders' percentile, there is a difference between -1 to -2 ADAS-Cog points favoring Active) and in the Y-axis (implying that for a specific threshold determined, more Active patients will reach that threshold than Sham).

Figure 21: ADAS-Cog S-Curve Analysis at Week 12, US Pivotal Study (PE Population with Baseline ADAS-Cog ≤30)



Clearly, as shown in **Table 22,** in the Baseline ADAS-Cog ≤30 Subgroup more than 70% of the Active subjects show ether improvement or no deterioration (ADAS-Cog-change ≤ 0) at 12 weeks. Interestingly, about one-third of Active subjects show improvement of at least -3 to -4 points. In addition, more than double the number of Active subjects (31.8% PE, 31.7% PP) in the Baseline ADAS-Cog ≤ 30 Subgroup showed an improvement of ≤ -4 points on ADAS-Cog than in the Sham group (15.4%).

Table 22: ADAS-Cog Responder Analyses at Week 12, US Pivotal Study (Baseline ADAS-Cog≤30 Subgroup)

	Improvement or No Deterioration ***(ADAS-Cog-change ≤ 0)***	**At Least 3-Point Improvement** ***(ADAS-Cog-change ≤ -3)***	**At Least 4-Point Improvement** ***(ADAS-Cog-change ≤ -4)***
	PE Population		
Active	70.5% (31/44)	40.9% (18/44)	31.8% (14/44)
Sham	59.0% (23/39)	28.2% (11/39)	15.4% (6/39)
	PP Population		
Active	70.7% (29/41)	41.5% (17/41)	31.7% (13/41)
Sham	59.0% (23/39)	28.2% (11/39)	15.4% (6/39)

Overall, it is evident that 31% of Active patients improve by at least -4 points (compared with 11.8-58% for a typical ChEI),[102] 40% improve by at least -3 points, and 70% either improve or do not deteriorate (compared with 34.5-87% for a typical ChEI).

(iii) Clinical Global Impression of Change (ADCS-CGIC) for the Baseline ADAS-Cog ≤ 30 Subgroup

In terms of ADCS-CGIC in the Baseline ADAS-Cog ≤ 30 Subgroup (PE and the PP Populations), the Active group reported a lower (i.e., improved) mean ADCS-CGIC score than the Sham group at each time point.

At 7 weeks, the Active group in the Baseline ADAS-Cog ≤ 30 Subgroup improved, and the Sham group deteriorated (mean scores of 3.98 for PE/PP and 4.05 for PE/PP, respectively; difference non-significant).

At 12 weeks, the Active group in the Baseline ADAS-Cog ≤ 30 Subgroup continued to improve (mean score 3.74/3.69 for PE/PP, respectively), and the Sham group continued to deteriorate further (mean score 4.14 for both PE/PP). Thus, the Active group outperformed the Sham group on average by -0.40 in the PE Population or -0.45 in the PP Population, and results were statistically significant (Wilcoxon test p-value = 0.10/0.07 for PE/PP respectively; Chi-square test p-value = 0.041/0.035 for PE/PP respectively).

Figure 22: ADCS-CGIC Score by Visit and Study Group, US Pivotal Study (Baseline ADAS-Cog ≤30 Subgroup)

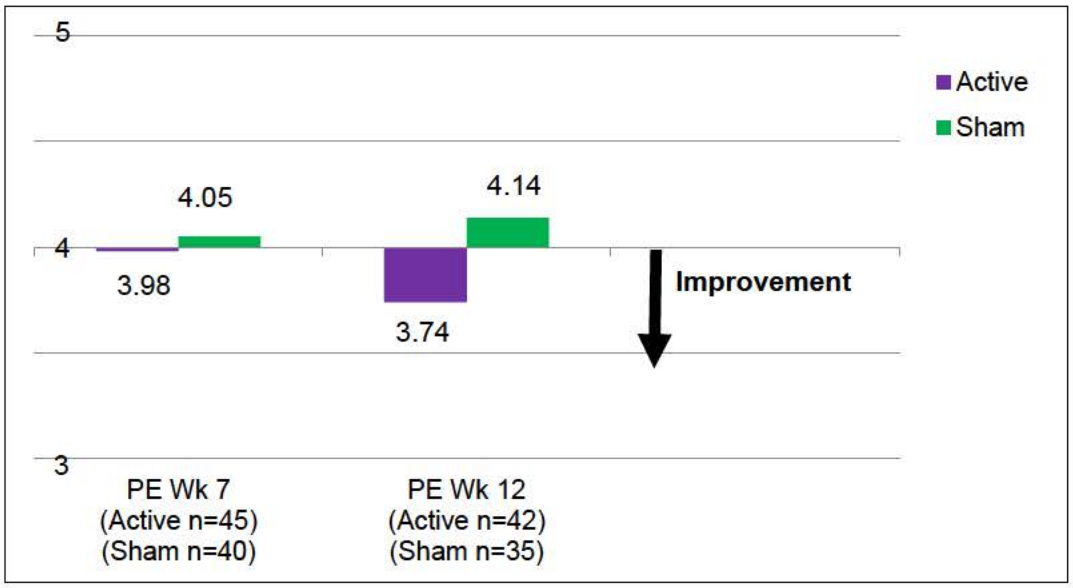


Table 23 presents the mean ADCS-CGIC scores by visit and study group.

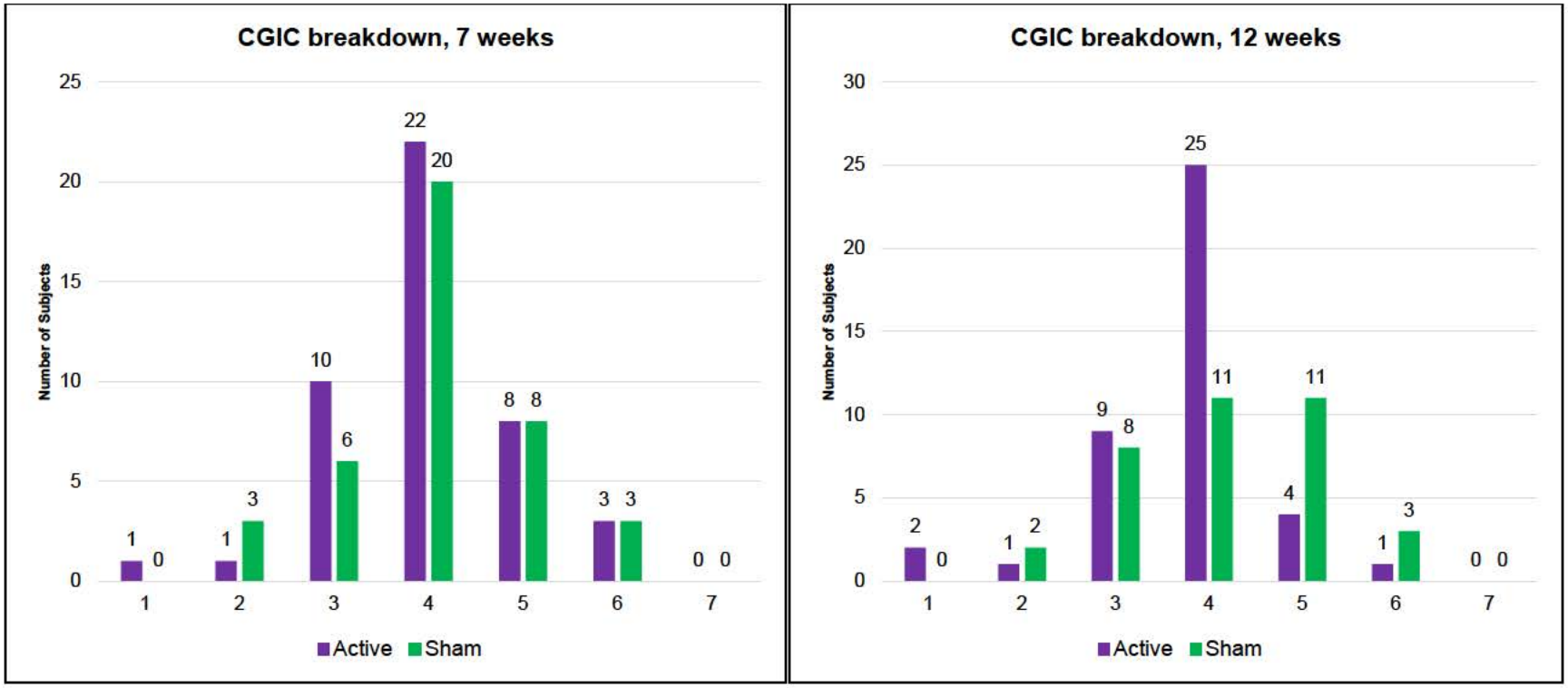
Table 23: Mean ADCS-CGIC Score by Visit and Study Group, US Pivotal Study (PE Population with Baseline ADAS-Cog ≤30)

Analysis Population / Visit / Study Group			ADCS-CGIC Score						Chi-square Test	Wilcoxon Test
			Mean	Std	Min	Median	Max	N		
PE, Baseline ADAS-Cog ≤30	7 Weeks	Active Group	3.98	0.99	1.00	4.00	6.00	45		
		Sham Group	4.05	0.99	2.00	4.00	6.00	40	0.729	0.703
	12 Weeks	Active Group	3.74	0.94	1.00	4.00	6.00	42		
		Sham Group	4.14	1.06	2.00	4.00	6.00	35	0.041	0.100

Table 24: ADCS-CGIC Score by Visit and Study Group, US Pivotal Study (PE Population with Baseline ADAS-Cog ≤30)

Analysis Population and Cut-Off/ Visit / Study Group			1		2		3		4		5		6		All		P-Value*
			N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Efficacy, Baseline ADAS-Cog ≤30	7 Weeks	Active Group	1	2.2	1	2.2	10	22.2	22	48.9	8	17.8	3	6.7	45	100.0	
		Sham Group	0	0	3	7.5	6	15.0	20	50.0	8	20.0	3	7.5	40	100.0	0.729
	12 Weeks	Active Group	2	4.8	1	2.4	9	21.4	25	59.5	4	9.5	1	2.4	42	100.0	
		Sham Group	0	0	2	5.7	8	22.9	11	31.4	11	31.4	3	8.6	35	100.0	0.041

Figure 23: Distribution of ADCS-CGIC Scores at 7 and 12 Weeks, US Pivotal Study (PE Population with Baseline ADAS-Cog ≤30)



Furthermore, among the Baseline ADAS-Cog ≤ 30 Subgroup subjects, only 5 out of 42 (11.9%) subjects worsened on the ADCS-CGIC scale in the Active group versus 14 out of 35 (40.0%) subjects in the Sham group. This difference was statistically significant (p<0.01, two-sided Fisher's exact test).

(iv) Dual Endpoint Analysis (ADAS-Cog and ADCS-CGIC) for the Baseline ADAS-Cog ≤ 30 Subgroup

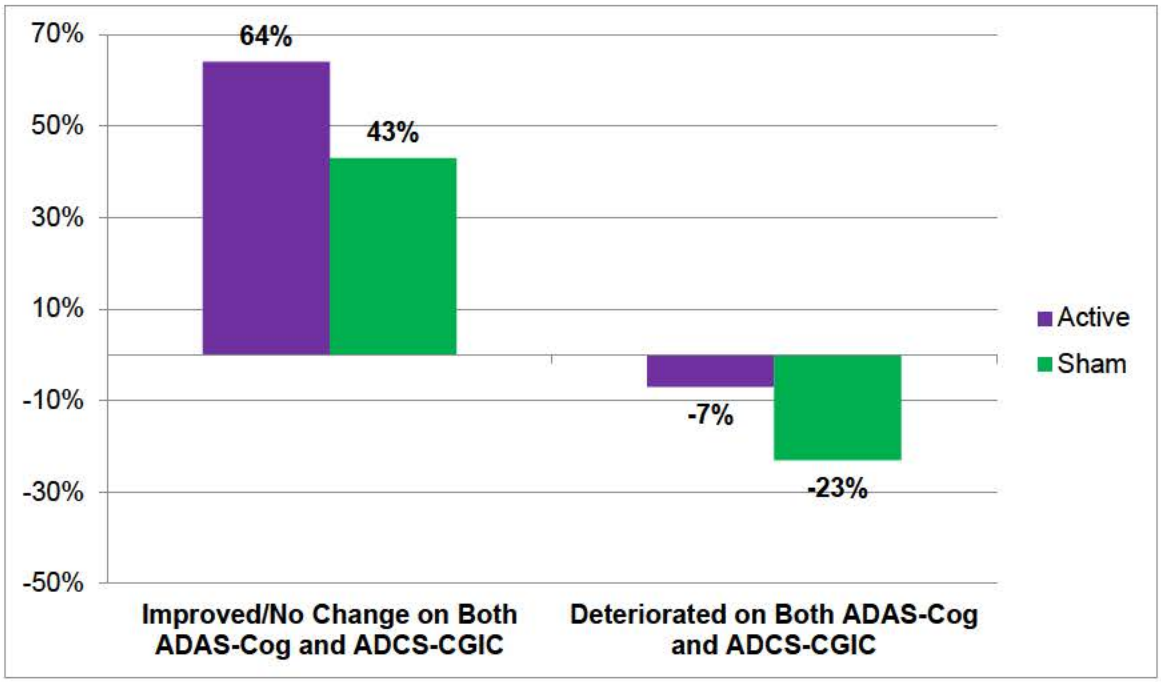
Table 25 below shows the proportion of responders as measured on both the ADAS-Cog and ADCS-CGIC scales (responders defined as those improved or not changed, ADAS-Cog change ≤ 0, 1 ≤ ADCS-CGIC ≤ 4) in the Baseline ADAS-Cog ≤ 30 Subgroup post-hoc analysis. Although the study was not originally designed to assess a dual endpoint, evaluation of both outcomes is informative given the limitations of the ADAS-Cog alone.

In the Baseline ADAS-Cog ≤ 30 Subgroup, there is no difference in dual-outcome responders at 7 weeks. However, when considering the 12-week outcome, it shows a distinct separation on both outcomes between the Active (64% responders) and Sham (42% responders) groups. Similarly, when considering percentage of patients deteriorating on both measures, only 7.1% of Active patients deteriorated compared with 22.9% of Sham patients. The differences in response on the post-hoc dual endpoints are statistically significant (p-value = 0.0463, Fisher Exact test).

Table 25: ADAS-Cog and ADCS-CGIC Combined Responder Rate at 12 Weeks, US Pivotal Study (Baseline ADAS-Cog ≤30 Subgroup)

			ADAS-Cog outcome	
			Improvement/No Change (≤0)	**Deterioration (>0)**
Active Group	**ADCS-CGIC**	Improvement/No Change (≤4)	27 / 64.3%	10 / 23.8%
		Deterioration (>4)	2 / 4.8%	3 / 7.1%
Sham Group	**ADCS-CGIC**	Improvement/No Change (≤4)	15 / 42.9%	6 / 17.1%
		Deterioration (>4)	6 / 17.1%	8 / 22.9%

Figure 24: ADAS-Cog and ADCS-CGIC Combined Responder Rate at 12 Weeks, US Pivotal Study (Baseline ADAS-Cog ≤30 Subgroup)



(v) Summary of Outcomes for Baseline ADAS-Cog ≤ 30 Subgroup

Thus, in summary, the effectiveness analyses in the Baseline ADAS-Cog ≤ 30 group show the following:

- Although the pre-specified primary endpoint of the study (ADAS-Cog improvement at 7 weeks compared to baseline) was not met, there was evidence of increasing improvement over time, with 12-week results improved in the Active group compared to 7-week results, while the Sham group deteriorated over this time period. A delayed effect is possible for TMS treatments and has been reported in other investigations.
- There was clear evidence of a relationship between baseline ADAS-Cog and outcome, with patients with a baseline ADAS-Cog ≤30 performing better than those with a baseline ADAS-Cog > 30. This baseline variable (although not the specific threshold) was pre-specified as a covariate. The specific threshold of 30 was selected based on literature and is consistent with the need for patients to be able to engage with the cognitive training as part of the neuroAD treatment.
- Benefit in both ADAS-Cog (difference of -1.61 and -1.79 points favoring the Active group for PE and PP Populations, respectively, p = 0.07 and p = 0.049) and ADCS-CGIC (difference of -0.4 and -0.45 points favoring the Active group for PE and PP, respectively, Chi-square p = 0.041 and p = 0.035) was shown at 12 weeks for patients with a baseline ADAS-Cog ≤ 30.
- For the selected subgroup of subjects with baseline ADAS-Cog ≤ 30, regardless of the ADAS-Cog cut-off selected, the Active group outperforms the Sham at 12 weeks, with over 40% of patients showing at least a 3-point improvement and more than 70% showing either improvement or no deterioration (change ≤ 0) at 12 weeks compared to baseline. Only 11% of Active group patients showed deterioration, compared to 40% of Sham group patients.

- In a post-hoc dual-endpoint analysis, 64.3% of patients either improved or did not change on both ADAS-Cog and ADCS-CGIC endpoints (defined as a score of ≤ 0 on ADAS-Cog and ≤ 4 on ADCS-CGI-C). The magnitude of benefit on each scale is consistent, and the evidence of benefit in two scales further supports the positive treatment effect (Fisher's Exact Test, p = 0.0463).

6.2.2.6.3 Baseline ADAS-Cog ≤30 Subgroup - Clinical Considerations

As previously described, based on the available clinical data, the company elected to limit the indicated population to those who showed greater and more consistent benefit, and with less variability in the outcomes.

Moreover, as evidenced by all clinical data sources, the Baseline ADAS-Cog >30 Subgroup consistently represents a small minority of the patient population. Approximately 15% of subjects in the US Pivotal Study had Baseline ADAS-Cog >30, which is consistent with other investigations and real-world data sources reported by the company.

(i) Analysis of Cognitive Training Progression

(b) (4)

Figure 25: Cognitive Training Progression – Standard Mean Difference, US Pivotal Study

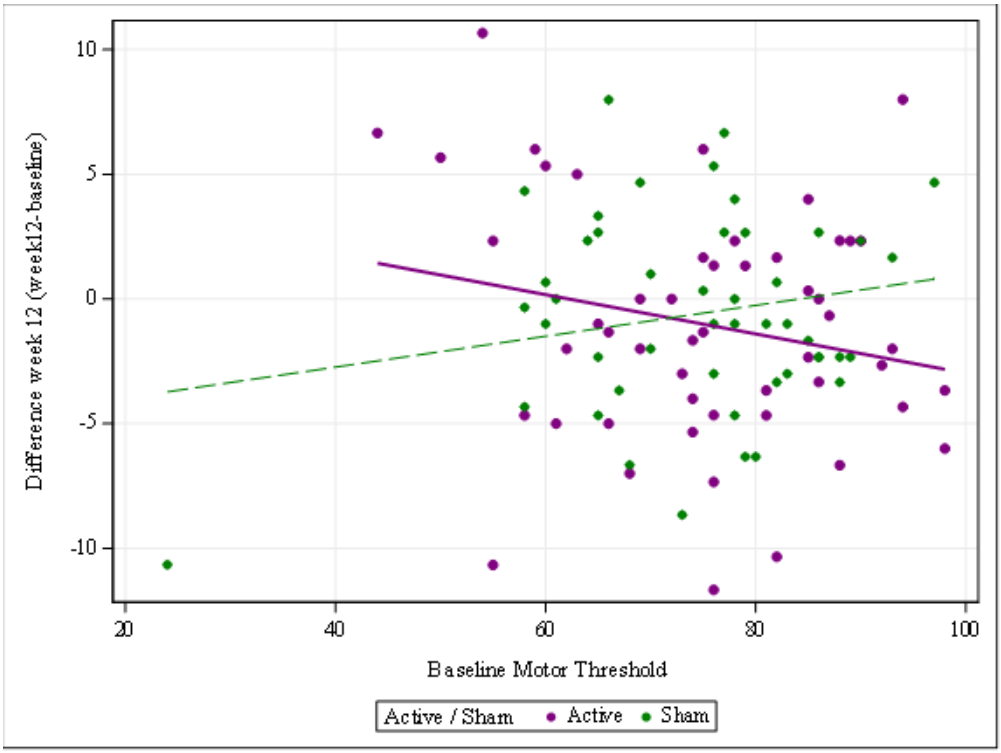
(ii) Analysis of Baseline Motor Threshold

The increased evidence base for the correlation between motor cortex excitability and Alzheimer's disease severity may provide an explanation for the aforementioned findings of difference in reaction to treatment based on Baseline ADAS-Cog. Studies have shown that higher motor cortex excitability resulting in a lower Motor Threshold (MT) for TMS highly correlates with disease severity and progression of the disease.[103],[104],[105,106] Furthermore, as the safety guidelines require that the TMS power be set relative to the measured MT (in the range of 90% to 110% of MT), a lower MT implies an application of lower absolute TMS power.

Due to the literature suggesting a correlation between disease severity, treatment response, and motor threshold, the interaction between treatment group and Baseline TMS Motor Threshold (MT) in this study was examined as a post-hoc covariate. The post-hoc covariate analysis found significant interaction between treatment group and baseline TMS Motor Threshold (p-value = 0.014 and p-value = 0.048, for 7 weeks and 12 weeks ADAS-Cog outcomes, respectively).

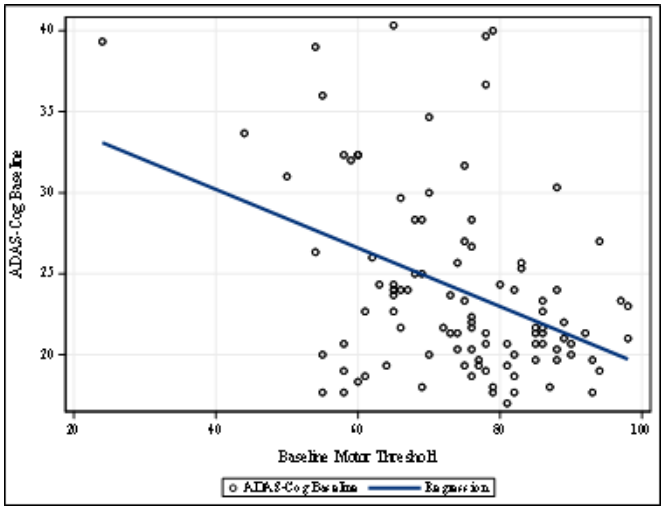
As can be seen from the graphs below, there are two opposite trends representing the two study groups: for the Active group, the higher the baseline TMS Motor Threshold, the greater the improvement on ADAS-Cog (represented by negative numbers), while for the Sham group, the higher the Baseline TMS Motor Threshold the greater the deterioration on ADAS-Cog.

Figure 26: ADAS-Cog Change at Week 12 by Baseline TMS Motor Threshold, US Pivotal Study (PE Population)



Furthermore, the company also investigated the correlation between baseline ADAS-Cog and Motor Threshold for all patients included in the Pivotal Study. A scatter plot of the correlation is provided below in **Figure 27**. In general, there is a significant interaction ($p < 0.001$) with a moderate correlation factor ($r=-0.405$), and patients with lower ADAS-Cog scores are clustered towards higher Motor Threshold values. The moderate correlation coefficient is likely due to the small number of patients with a baseline ADAS-Cog>30 and the variability observed among these patients, which is discussed in more detail below.

Figure 27: Correlation between Baseline ADAS-Cog and Motor Threshold, US Pivotal Study



This data further supports the discussion above, that patients with lower ADAS-Cog values at baseline (and higher baseline Motor Thresholds) were observed to have greater improvement on the ADAS-Cog scale.

Thus, the analysis of the data related to cognitive training performance and baseline Motor Threshold (which guides the TMS power setting) also supports the cut-off of 30. The maximum level of performance of patients on the neuroAD Cognitive Paradigms was different between the two groups (subjects with baseline ADAS-Cog ≤ 30 and subjects with baseline ADAS-Cog > 30), indicating more severe patients could not engage with and progress through the cognitive training paradigm as well as less severe patients. In addition, analyses showed that patients with lower ADAS-Cog values at baseline had higher baseline Motor Thresholds and therefore higher TMS power settings, which implies higher magnetic field stimulation strength. Thus, more seriously affected patients are potentially less likely to benefit from both the cognitive training and TMS components of neuroAD treatment.

6.2.2.6.4 Individual Subject Responses

Waterfall plots were generated illustrating the change in ADAS-Cog from baseline for all US Pivotal Study subjects at week 7 (**Figure 28**) and week 12 (**Figure 29**). These graphs show Active and Sham subjects separately and distinguish between Baseline ADAS-Cog ≤30 (n=85) and Baseline ADAS-Cog >30 subjects (n=16).

As shown in the waterfall plots, overall the difference between the Active group and Sham group increases from week 7 to week 12, and by week 12, the majority of Active subjects with Baseline ADAS-Cog ≤30 improve, while the Sham subjects with Baseline ADAS-Cog ≤30 split equally between improvement and deterioration.

With respect to the Baseline ADAS-Cog >30 group, as shown in **Figure 28** and **Figure 29**, Active group subjects with Baseline ADAS-Cog >30 were distributed between outcomes representing deterioration, no change, and improvement compared to baseline at week 7 and week 12. That said,

many of the subjects with Baseline ADAS-Cog >30, both in the Active and the Sham groups, are found at the extreme left and right ends of the x-axis, representing an amplified magnitude of change. This distribution distinctly differs from the Baseline ADAS-Cog ≤30 group, which shows fewer outcomes at the extremes of the range. It is important to note the small number of patients with Baseline ADAS-Cog >30 (8 Active, 8 Sham), which limits the ability to draw clear conclusions regarding this subpopulation.

Figure 28: Waterfall Plot at Week 7, US Pivotal Study (PE Population)

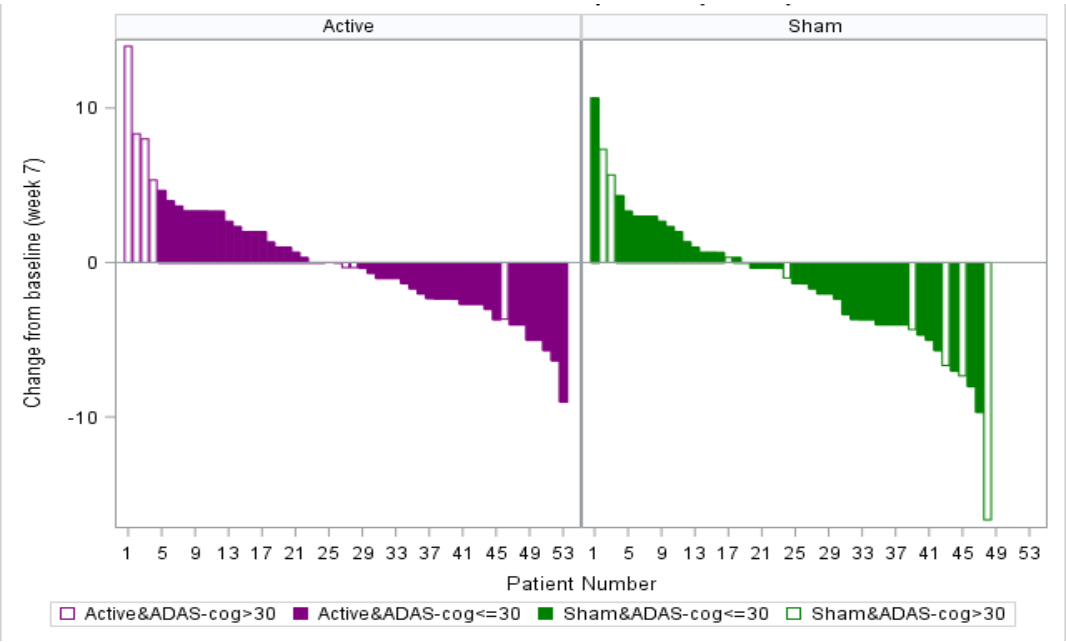
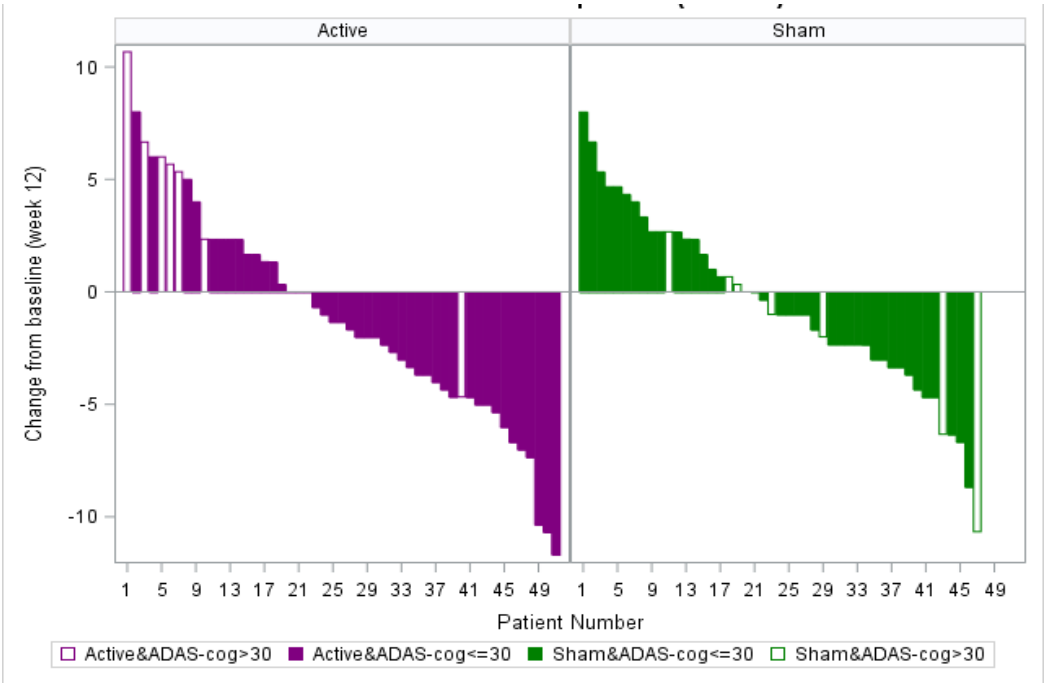
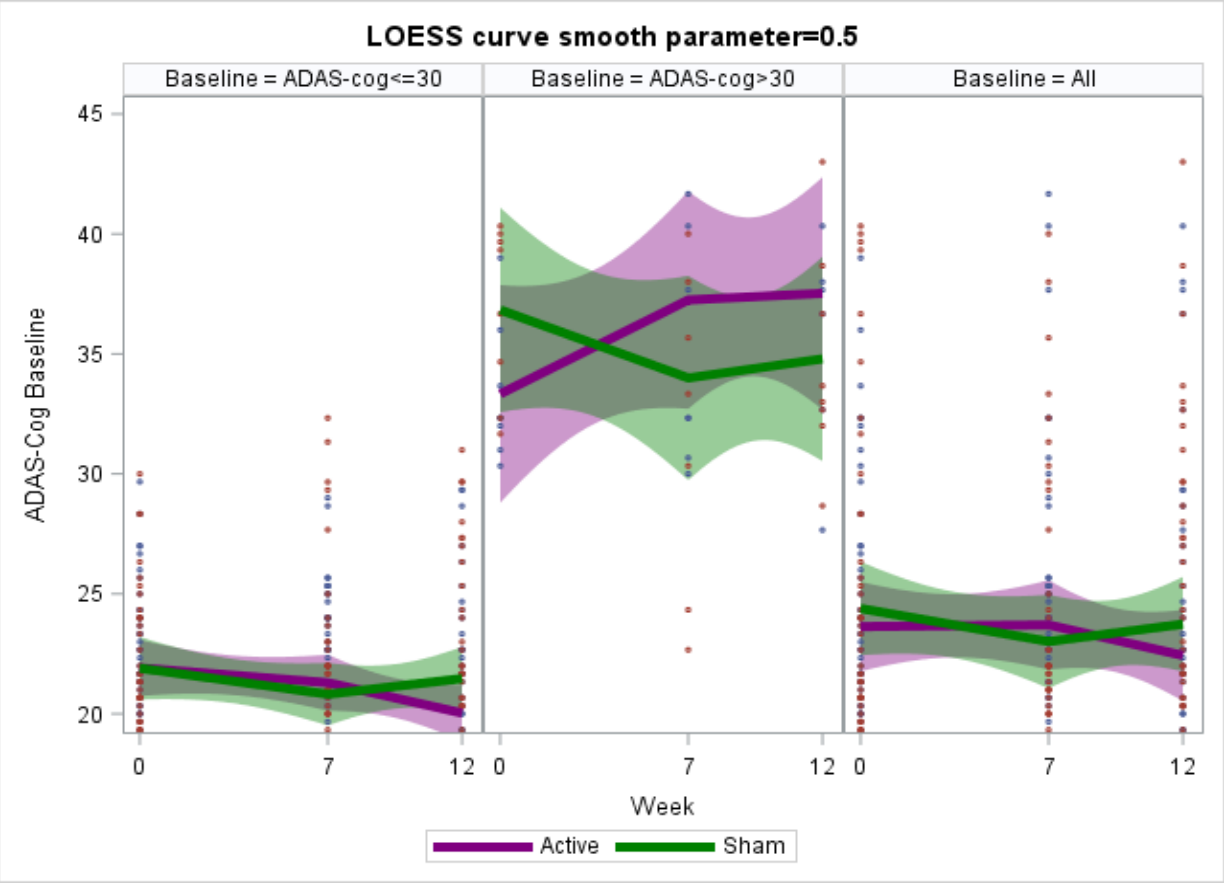


Figure 29: Waterfall Plot at Week 12, US Pivotal Study (PE Population)



To evaluate the variability and the statistical impact of the Baseline ADAS-Cog ≤30 and Baseline ADAS-Cog >30 Subgroup on the overall results, the sponsor produced line plots ("Spaghetti Plots") for individual patients in each of the populations of interest, then applied local weighted smoothing ("LOESS"). The LOESS line plots below demonstrate that the outcomes for the Baseline ADAS-Cog >30 group, in both study arms, were more variable than the outcomes for Baseline ADAS-Cog ≤30 group and the all subjects group. This variation is represented graphically as the shaded area surrounding each line. The area for subjects with Baseline ADAS-Cog >30 is approximately three times wider than the corresponding area for Baseline ADAS-Cog ≤30, demonstrating the impact of this small group on the overall population results.

Figure 30: LOESS Line Plot, US Pivotal Study (PE Population)



Considering the aforementioned ADAS-Cog results observed for the subgroup of subjects with baseline ADAS-Cog>30, it was noted that no statistically significant difference was found between the groups with respect to the ADCS-CGIC scores of these subjects at either 7 or 12 weeks. However, in the PE Population subgroup of subjects with baseline ADAS-Cog >30, it should be noted that at 12 weeks, 3 out of 8 (37.5%) and 4 out of 8 (50%) worsening subjects were reported in the Active group and Sham group respectively. The absence of any clear signal of worsening on ADCS-CGIC among this set of patients suggests a wide degree of variability in this small cohort, particularly when compared to the ADAS-Cog results.

Finally, the divergent results on the two scales (ADAS-Cog and ADCS-CGIC) further demonstrate the variability in the outcomes of the group of subjects with Baseline ADAS-Cog >30, and serve as further evidence that clear conclusions cannot be drawn from the performance of this subpopulation.

For the baseline ADAS-Cog >30 group (PE), looking at those subjects who responded (defined as either improvement or no change) on both scales simultaneously, there are small differences between Active and Sham groups at either 7 weeks or 12 weeks, all of which are nonsignificant. This further highlights the variability in outcomes in the Baseline ADAS-Cog >30 group.

Table 26: ADAS-Cog and ADCS-CGIC Post-Hoc Combined Responder Analysis at 7 and 12 Weeks, US Pivotal Study (PE Population, Baseline ADAS-Cog > 30)

		Week 7			Week 12		
		Diff ADAS-Cog ≤0	**ADCS-CGIC = 1-4**	**Both**	**Diff ADAS-Cog ≤0**	**ADCS-CGIC = 1-4**	**Both**
Baseline ADAS-Cog >30	**Total Sample Size**	16	16	16	15	16	15
	Active	4/8= 50.0%	5/8= 62.5%	4/8= 50.0%	1/7= 14.3%	5/8= 62.5%	1/7= 14.3%
	Sham	5/8= 62.5%	5/8= 62.5%	3/8= 37.5%	5/8= 62.5%	4/8= 50.0%	2/8= 25.0%
	P-value	>0.99	>0.99	>0.99	0.1189	>0.99	>0.99

6.2.2.6.5 Blinding Analysis

At the end of the first week of Active or Sham treatment, subjects and caregivers were asked the following questions to confirm blinding:

- Subject: "Do you know if the treatment that you received today was an actual treatment or a placebo treatment?"
- Caregiver: "Do you know if the treatment the patient received today was an actual treatment or a placebo treatment?"

The results of this assessment are reported below:

Table 27: Analysis of Treatment Masking (Subject Perspective) by Study Group, US Pivotal Study (Safety Population)

Study Group	**Treatment the Subject Believes He Is Receiving**								**All**	
	Actual Treatment		**Placebo**		**Not Sure / Cannot Tell**		**Missing**			
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Active Group	28	38.4	4	5.5	36	49.3	5	6.8	73	100.0
Sham Group	16	32.7	2	4.1	31	63.3	0	0.0	49	100.0
All	44	36.1	6	4.9	67	54.9	5	4.1	122	100.0

Table 28: Analysis of Treatment Masking (Caregiver Perspective) by Study Group, US Pivotal Study (Safety Population)

Study Group	Treatment the Caregiver Knows the Subject Is Receiving								All	
	Actual Treatment		Placebo		Not Sure / Cannot Tell		Missing			
	N	%	N	%	N	%	N	%	N	%
Active Group	12	16.4	3	4.1	41	56.2	17	23.3	73	100.0
Sham Group	7	14.3	5	10.2	29	59.2	8	16.3	49	100.0
All	19	15.6	8	6.6	70	57.4	25	20.5	122	100.0

At the end of six weeks of Active or Sham treatment, and prior to first follow-up visit, both ADAS-Cog and ADCS-CGIC raters were asked the following question to confirm blinding:

- "Do you know if the treatment the patient received was an actual treatment or a placebo treatment?"

The results of this assessment are reported below:

Table 29: Analysis of Treatment Masking (ADAS-Cog Rater Perspective) by Study Group, US Pivotal Study (Safety Population)

Study Group	Treatment the ADAS-Cog Rater Knows the Subject Is Receiving								All	
	Actual Treatment		Placebo		Not Sure / Cannot Tell		Missing			
	N	%	N	%	N	%	N	%	N	%
Active Group	0	0.0	1	1.6	43	67.2	20	31.3	64	100.0
Sham Group	1	2.3	2	4.5	31	70.5	10	22.7	44	100.0
All	1	0.9	3	2.8	74	68.5	30	27.8	108	100.0

Table 30: Analysis of Treatment Masking (ADCS-CGIC Rater Perspective) by Study Group, US Pivotal Study (Safety Population)

Study Group	Treatment the ADCS-CGIC Rater Knows the Subject Is Receiving								All	
	Actual Treatment		Placebo		Not Sure / Cannot Tell		Missing			
	N	%	N	%	N	%	N	%	N	%
Active Group	2	3.1	0	0.0	42	65.6	20	31.3	64	100.0
Sham Group	0	0.0	0	0.0	34	77.3	10	22.7	44	100.0
All	2	1.9	0	0.0	76	70.4	30	27.8	108	100.0

As can be seen from the tables above, the blinding to treatment group assignment was maintained across all parties, with the majority of all respondents indicating they were not sure of the treatment received.

No significant difference was found between study groups on any of the blinding questions, With p-values of 0.597, 0.431, 0.391 and 0.431 for subject, caregiver, ADAS-Cog rater and ADCS-CGIC rater respectively, as tested by Fisher's exact test.

6.2.2.7 Additional Statistical Analyses

6.2.2.7.1 Covariate Analysis

As outlined in the protocol and SAP, the possible effects of covariates were tested by assessing the interaction term in the following model: Change = $\text{ADAS-Cog}_{\text{Baseline}}$ + Covariate + Group + Covariate x Group. The model was tested on raw values due to a normal distribution of the efficacy endpoints.

The covariate analysis showed no significant impact on the change of ADAS-Cog from baseline to week 7 or week 12, on any of the following variables with the exception of Baseline TMS Motor Threshold (as previously explained).

The following covariates were tested:

- Global CDR
- Age
- Gender
- Ethnicity
- Race
- BMI
- Nicotine use
- Center
- Disease Severity (mild vs. moderate, based on MMSE)
- Level of Education
- Hand dominance
- Medicated for AD
- Time since AD diagnosis to treatment
- Number of missed treatment visits
- Baseline TMS Motor Threshold value (%)[3]

6.2.2.7.2 Treatment by Center

Poolability of sites with at least 12 subjects was evaluated. Sites with fewer than 12 subjects were combined into an "other" category and analyzed as a single (combined) group. To test poolability, the effect of site was tested on the primary efficacy endpoint. As the site-by-group interaction provided a p-value of 0.15 or greater, (for both 7-week and 12-week outcomes) the sites were deemed poolable, and all analyses were carried out using the entire sample.

[3] Not pre-specified in the SAP

6.2.2.7.3 Examination of Subgroups

Several additional post hoc analyses were performed to examine different subgroups within study population:

Mild vs. Moderate Disease Severity as Defined by MMSE

Study protocol defined Disease Severity by MMSE score:

- Mild: 21≤MMSE≤26
- Moderate: 18≤MMSE≤20

  Covariate analysis found no effect of disease severity as defined by MMSE on the ADAS-Cog Change from baseline to Follow-up (p=0.526 and p=0.770 for week 7 and week 12 respectively).

- Medicated vs. Non-Medicated Subjects

  Interestingly, only approximately 20% of study subjects were not medicated for AD when enrolled into the study. Examining the Non-Medicated sub-population in this study vs. the Medicated population found no significant difference in gender, age, time from AD diagnosis and ADAS-Cog change. However, those who were not previously medicated for AD still demonstrated a notable change following neuroAD Therapy System treatment.

6.2.2.7.4 Compliance and Relationship to Response

Further analysis examined whether change in ADAS-Cog from baseline to week 7 depends on compliance, which was defined as the number of attended visits.

Table 31 below demonstrates that most of the subjects participating in the study attended at least 28 treatment visits in both groups. Hence, due to the low numbers of non-compliant subjects, meaningful analysis of relationship between compliance and response could not be performed.

Table 31: Compliance by Treatment Group, US Pivotal Study (PE Population)

Treatment Group	1		7		14		20		26		27		28		29		30		All	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Active	2	3.5	1	1.8	1	1.8	0	0	1	1.8	2	3.5	9	15.8	17	29.8	24	42.1	57	100.0
Sham	0	0	0	0	0	0	1	2.0	0	0	0	0	11	22.4	11	22.4	26	53.1	49	100.0
All	2	1.9	1	0.9	1	0.9	1	0.9	1	0.9	2	1.9	20	18.9	28	26.4	50	47.2	106	100.0

Linear regression similar to that described in the primary analysis, but with additional covariates of compliance and its interactions was fit. The model included two significant interactions – the first is between Baseline ADAS-Cog and treatment group, and the second is between Baseline ADAS-Cog and compliance. Since the sample was divided into categories based on the two variables, the samples within each subgroup became small, and therefore did not provide sufficient data for meaningful analysis.

6.2.2.7.5 Treatment – Disease Interactions

No relationship was found between response to treatment and concomitant medications or concurrent medical condition other than AD.

6.2.3 Pivotal Study Conclusions

The results of the US Pivotal Study support the following conclusions:

- The safety profile of the neuroAD Therapy System treatment is highly favorable. No serious device-related events have been observed.
- The neuroAD Therapy System treatment is well tolerated by patients, with a high degree of compliance with the treatment schedule. Over 90% of subjects attended at least 90% of sessions.
- Although the pre-specified primary endpoint of the study (ADAS-Cog improvement at 7 weeks compared to baseline) was not met, there was evidence of increasing improvement over time, with 12-week results improved in the Active group compared to 7-week results, while the Sham group deteriorated over this time period.
- There was clear evidence of a relationship between baseline ADAS-Cog and outcome based on a pre-specified covariate analysis of baseline ADAS-Cog that revealed a statistically significant interaction at 7 weeks (p-value = 0.029) and 12 weeks (p-value = 0.0072) . Based on additional post-hoc analyses it was determined that patients with a baseline ADAS-Cog ≤30 are more likely to benefit than those with a baseline ADAS-Cog > 30. The specific threshold of 30 was selected based on literature and is consistent with the need for patients to be able to engage with the cognitive training as part of the neuroAD treatment, as well as their higher motor threshold values.
- The Korean Pilot and Pivotal Studies provide independent confirmatory evidence of the clinical meaningfulness of the Baseline ADAS-Cog ≤ 30 Subgroup. The investigators for the Korean studies concluded that milder patients respond more favorably to the neuroAD treatment and subsequently restricted the Korean Pivotal Study population to subjects with baseline ADAS-Cog up to 30. These decisions were made independent of Neuronix and before the US Pivotal Study results were available.
- Benefits in both ADAS-Cog (difference of -1.61 and -1.79 points favoring the Active group for PE and PP Populations, respectively, p = 0.07 and p = 0.049) and ADCS-CGIC (difference of -0.4 and -0.45 points favoring the Active group for PE and PP, respectively, Chi-square p = 0.041 and p = 0.035) were shown at the secondary assessment time point of 12 weeks for patients with a baseline ADAS-Cog ≤ 30.
- For the selected subgroup of subjects with baseline ADAS-Cog ≤ 30, regardless of the ADAS-Cog cut-off selected, the Active group outperforms the Sham at the 12-week time point, with over 40% of patients showing at least a 3-point improvement at 12 weeks compared to baseline. Only 11% of Active group patients showed deterioration, compared to 40% of Sham group patients.
- In a post-hoc dual-endpoint analysis, 64.3% of Active patients either improved or did not change on both ADAS-Cog and ADCS-CGIC endpoints (defined as a score of ≤ 0 on ADAS-Cog and ≤ 4 on ADCS-CGI-C). The magnitude of benefit on each scale is consistent, and the evidence of benefit in two scales further supports the positive treatment effect (Fisher's Exact Test, p = 0.0463).
- Although most patients in the study were receiving concomitant medications for their Alzheimer's disease, there was evidence of benefit in patients with or without medication. There did not appear to be any increase in adverse events when the neuroAD Therapy System was added to medication.

Thus, there is evidence that the indicated population (i.e., baseline ADAS-Cog ≤30) benefits from the device in a clinically meaningful way. These conclusions may be derived from the ADAS-Cog and ADCS-CGIC outcomes individually as well as collectively. As will be shown below, the degree of improvement associated with neuroAD is on par with currently-approved ChEI drugs (when using either ADAS-Cog or CGIC evaluations). Additional evidence supporting these conclusions is provided in other studies, as discussed below.

The availability of the neuroAD Therapy System would offer a low risk option to add to medication in patients with mild to moderate Alzheimer's disease. The favorable benefit/risk profile supports the availability of this new treatment modality.

6.3 Korean Studies

Two independent studies using the neuroAD Therapy System were conducted in Korea by independent investigators (that is, the studies were not sponsored by Neuronix). The Korean Pilot Study was conducted under a highly similar protocol as the US Pivotal Study[4] and recruited mild to moderate AD subjects (including subjects with baseline ADAS-Cog scores greater than and less than 30). Based on the findings of the Korean Pilot Study, the investigators, independent of Neuronix, concluded that milder patients were the most likely to respond to the neuroAD Therapy System treatment, as outlined in the publication for this study.[107]

To confirm this hypothesis, the investigators ran the Korean Pivotal Study, which was conducted under a protocol similar to the US Pivotal Study, except that study enrollment was limited to mild AD patients that had baseline ADAS-Cog between 17 and 30.

Both the Korean Pilot and Korean Pivotal Studies used the same treatment procedure as the neuroAD US Pivotal Study as well as follow-up assessments at 7 and 12 weeks following treatment initiation. The results of the Korean Pilot Study are presented below, followed by the results of the Korean Pivotal Study. Lastly, a meta-analysis of three studies pooled together (US Pivotal, Korean Pilot and Korean Pivotal) is presented.

6.3.1 Korean Pilot Study

6.3.1.1 Korean Pilot Study Protocol

The Korean Pilot Study[108] was a double-blind, sham-controlled study, conducted at Chungnam National University Hospital, Daejeon, Korea. The study was approved and supervised by the local Ethical committee. All participants provided written informed consent prior to participation in any study procedure.

Subjects were randomized into Active and Sham groups in a 2:1 ratio. Overall, 27 subjects were recruited into this study (18 Active, 9 Sham).

The study followed a highly similar protocol to the US Pivotal Study (NRX-US4) protocol.

[4] The main difference between the Korean studies and the US Pivotal was that the Korean studies used additional assessment scales.

Main Entry Criteria:

Male and female subjects who were diagnosed with mild to moderate AD, with MMSE 18-26, CDR=1 or 2, and baseline ADAS-Cog>17 were included in the study. Subjects were excluded if they had a history of epilepsy, severe agitation, unstable medical condition, etc. Subjects who were taking Cholinesterase inhibitors or Memantine were required to be on a stable dose for at least 2 months prior to study participation.

Study Procedures:

After providing informed consent, subjects were randomized to receive either Active or Sham treatment. All subjects had a structural MRI scan to allow for localization of the treatment brain regions.

Both Active and Sham subjects followed the same treatment schedule of 6 weeks, 5 days per week (overall 30 sessions), approximately 45-60 minutes per session. In each treatment session, 1300 pulses were administrated for 3 alternate brain regions.

Subjects were followed at week 7, and week 12. No maintenance treatment sessions were performed.

6.3.1.2 Korean Pilot Study Results

Results:

Twenty-six (26) subjects completed the study, as 1 subject from the Sham group dropped out of the study due to headaches.

Safety:

No Serious Adverse Events were reported. No AEs were reported other than the headache in a Sham subject described above.

Efficacy:

In terms of change in ADAS-Cog for all subjects, the Active group improved by -4.28 points at 7 weeks, compared to -1.75 points for the Sham group, with -2.52 points difference. At week 12, although the Active group continued to improve (-5.39), the Sham group also showed some improvement (-2.88), and the between-group difference was -2.51.

For the ADCS-CGIC, at 7 weeks, an average improvement of -1.6 points was observed for the Active arm, compared with -0.5 points for the Sham arm (-1.1 difference). At 12 weeks, similar results were obtained but the between-group difference did not reach statistical significance.

When the results are analyzed by baseline characteristics, the Principal Investigator concluded that the treatment was found to be more effective for milder patients. Analyzing the Baseline ADAS-Cog ≤ 30 Subgroup, a meaningful difference within the Active group was seen in patients with a baseline ADAS-Cog score ≤ 30 at 7 weeks (-4.57 for Active (n=14) versus -2.14 for Sham (n=7), (difference of -2.43) and at 12 weeks (-5.70 for Active vs. -4.00 for Sham, difference of -1.70).

Figure 31: Mean Change in ADAS-Cog, Korean Pilot Study (Baseline ADAS-Cog ≤ 30)

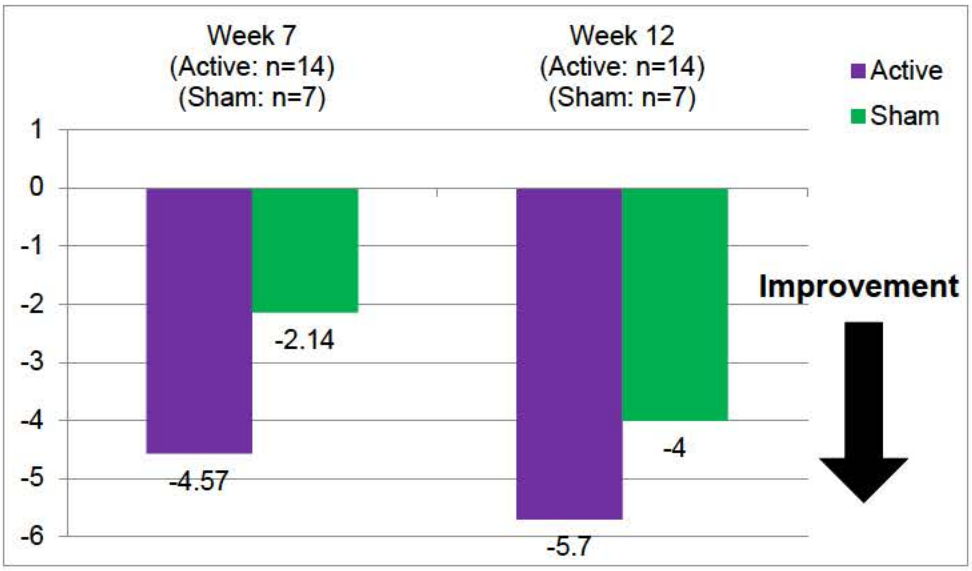


Table 32: Mean Change in ADAS-Cog, Korean Pilot Study (Baseline ADAS-Cog ≤ 30)

ADAS-Cog Change (Baseline ADAS-Cog ≤ 30)		n	Mean	Std	Min	Median	Max	P value (T-test_
ADAS Cog Change FU-1 (Week 7)	Active	14	-4.57	5.81	-20.00	-4.00	6.00	
	Sham	7	-2.14	3.67	-7.00	-2.00	3.00	
								0.3287
ADAS Cog Change FU-2 (Week 12)	Active	14	-5.79	6.02	-21.00	-5.00	1.00	
	Sham	7	-4.00	2.16	-7.00	-3.00	-2.00	
								0.335

6.3.2 Korean Pivotal Study

Following the Korean Pilot Study, the investigators conducted the Korean Pivotal Study, where patient enrollment was limited to the milder population with baseline ADAS-Cog ≤30, which was determined to be more likely to benefit from neuroAD therapy, based on the outcome of the Korean Pilot Study.

6.3.2.1 Korean Pivotal Study Protocol

This was a double-blind, sham-controlled study, conducted at Chungnam National University Hospital, Daejeon, Korea to support Korean-FDA (K-FDA) approval. The study was approved and supervised by the local Ethical committee. All participants provided written informed consent prior to participation in any study procedure. Note that the study was placed on hold based on a

determination by the K-FDA that it wishes to receive the US FDA's decision prior to continuation of the Korean Pivotal Study, and rendering its decision.

The study follows a similar protocol to the Korean Pilot investigation but focuses on the milder AD population with baseline ADAS-Cog 17-30.

Subjects were randomized into Active and Sham groups in a 1:1 ratio. Overall, 22 subjects were recruited into this study (11 Active, 11 Sham).

Main Entry Criteria:

Male and female subjects who are diagnosed with mild to moderate AD, with MMSE 21-26, CDR=1, and baseline 17<ADAS-Cog≤30 were included in the study. Subjects were excluded if they had a history of epilepsy, severe agitation, or unstable medical condition. Subjects who were taking cholinesterase inhibitors or memantine were required to be on a stable dose for at least 2 months prior to study participation. Note that the entry criteria specified the same baseline ADAS-Cog upper threshold as is proposed for the Baseline ADAS-Cog ≤ 30 Subgroup from the US Pivotal Study.

Study Procedures:

After providing informed consent, subjects were randomized to receive either Active or Sham treatment. All subjects had a structural MRI scan to allow localization of the treatment brain regions.

Both Active and Sham subjects followed the same treatment schedule of 6 weeks, 5 days per week (overall 30 sessions), approximately 45-60 minutes per session. In each treatment session, 1300 pulses were administrated for 3 alternate brain regions.

Subjects were followed at week 7 and week 12.

6.3.2.2 Korean Pivotal Study Results

Results:

22 subjects were recruited into this study, 11 were randomized to the Active group and 11 were randomized to the Sham group.

As noted above, the study is on hold; interim results are provided below.

Safety:

No Serious Adverse Events were reported or documented in the study.

One Active patient had a skin rash (allergy) AE. The patient changed from the rivastigmine patch to donepezil 5mg. The event was mild and believed to be unrelated to neuroAD. There were no AEs reported in the Sham group.

Efficacy:

In this study, the Active group reported mean change in ADAS-Cog of -3.09 points at 7 weeks and -3.64 points at 12 weeks. These results compare favorably to the Sham group, which reported a mean change in ADAS-Cog of -0.55 points at 7 weeks and -1.91 points at 12 weeks. The between-

group difference for mean change in ADAS-Cog was statistically significant at the 7-week follow-up visit (p=0.0340). In addition, the Active group reported increased improvement between the first and second follow-up visit. Although the between-group difference at 12 weeks was -1.7 points, it did not maintain statistical significance, likely due to the small sample size.

Figure 32: Mean Change in ADAS-Cog, Korean Pivotal Study (Baseline ADAS-Cog ≤ 30)

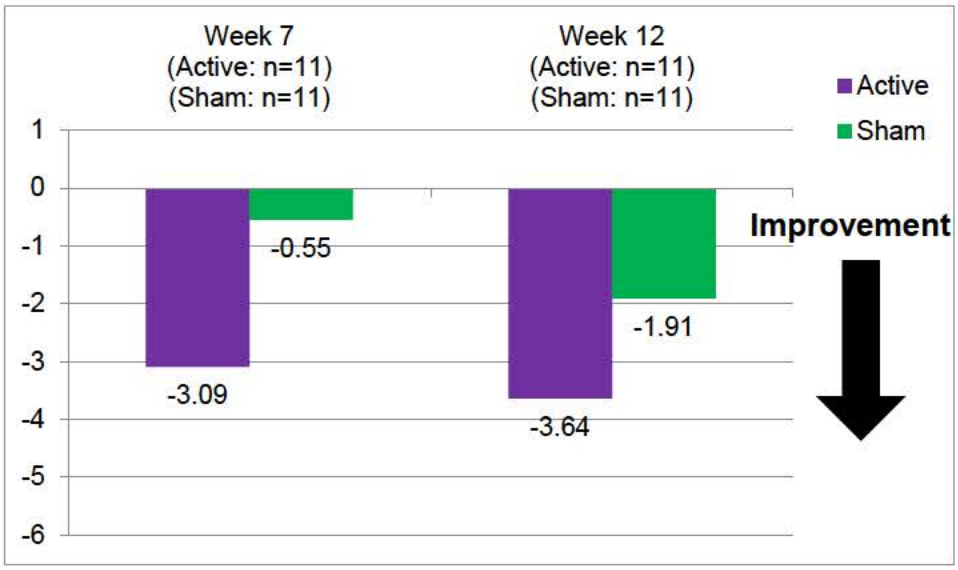


Table 33: Mean Change in ADAS-Cog, Korean Pivotal Study (Baseline ADAS-Cog ≤ 30)

ADAS-Cog Change		n	Mean	Std	Min	Median	Max	P-value (T-test)
ADAS Cog Change FU-1 (Week 7)	Active	11	-3.09	2.77	-7.00	-3.00	3.00	
	Sham	11	-0.55	2.46	-5.00	0.00	3.00	
								0.0340
ADAS Cog Change FU-2 (Week 12)	Active	11	-3.64	2.98	-9.00	-4.00	2.00	
	Sham	11	-1.91	3.73	-9.00	-3.00	4.00	
								0.2437

6.3.3 Conclusions

The Korean Pilot and Pivotal Studies support the results observed in the neuroAD Pivotal Study, and confirms that the neuroAD Therapy System provides clinically meaningful benefit in patients whose baseline ADAS-Cog score is ≤30 points. In addition, no serious related adverse events were reported in either Korean study.

In sum, the independent investigators in Korea determined based on the results of the Korean Pilot Study that the proposed subgroup identified in the US Pivotal Study (patients with baseline ADAS-Cog ≤ 30) are the patients most likely to benefit from treatment. In particular, the Korean Pivotal

Study can serve as an independent validation for the Baseline ADAS-Cog ≤ 30 Subgroup (i.e., the indicated population) selection which emerged from the US Pivotal Study.

6.3.4 Analyses of US Pivotal Study and Korean Studies

As described above, the 2 Korean studies were conducted under protocols that were very similar to the US Pivotal Study. As the studies had similar protocols with comparable subject populations, a combined meta-analysis between the US Pivotal and Korean studies was conducted, as well as additional analyses to assess the combined data.

The question has arisen regarding the Korean study investigators' decision to restrict the Korean Pivotal Study to milder patients following the Korean Pilot is that the effect size is smaller when the analysis is restricted to the Baseline ADAS-Cog ≤30 Subgroup. Specifically, the company notes that in the Korean Pilot Study full analysis set, the effect size at 7 and 12 weeks is -2.52 points and -2.51, respectively, favoring the Active group, while the Baseline ADAS-Cog ≤30 Subgroup leads to an effect size at 7 and 12 weeks of -2.43 points and -1.70 points, respectively, favoring the Active group. However, this effect is largely driven by the single subject in the Sham group with a baseline ADAS-Cog >30, who reported deterioration from baseline at both at 7 weeks (+1.0) and at 12 weeks (+5.0).

As shown in the table below, Active subjects in the Baseline ADAS-Cog ≤30 Subgroup performed better than their counterparts at 7 weeks (mean change -4.57 and -3.25, respectively) and at 12 weeks (mean change -5.79 and -4.0, respectively). By contrast, the change in the Sham group when analyzing the Baseline ADAS-Cog ≤30 Subgroup is driven by 1 subject who had a baseline ADAS-Cog >30 and performed poorly. Thus, while restricting the intended population to milder patients yields an apparent smaller effect size, it is clinically reasonable to do so.

6.3.4.1 Comparison of Trends in the Korean Studies versus US Pivotal Study

There are some differences in the ADAS-Cog results over time between the Korean and US studies. Specifically, the mean between-group difference increased in the US Pivotal Study at 12 weeks compared to 7 weeks, but decreased in the Korean studies during that same period. However, the change in mean between-group difference from 7 weeks to 12 weeks across these studies does not reach significance (p-value = 0.156, NS>0.10). This difference between the studies is likely due, in part, to variability in the Sham group's performance across the studies and the greater magnitude of improvement reported by the Active subjects in the Korean studies at 7 weeks. The compounding effect of these two factors, along with other variables such as the relatively small sample sizes in the individual Korean studies per treatment group, likely contributed to the observed differences over time. Nonetheless, the mean between-group difference at 12 weeks was nearly identical across all 3 studies (US Pivotal: -1.61 favoring Active group; Korean Pilot: -1.7 favoring Active group; Korean Pivotal: -1.73 favoring Active group). Moreover, while there were differences in how the Sham group performed across the studies, the Active group consistently improved from 7 weeks to 12 weeks across all three studies.

6.3.4.2 Meta-Analysis of ADAS-Cog Outcomes

As explained above, since the US Pivotal had an almost identical study design as the 2 Korean studies, meta-analysis for the combined outcomes of the studies was performed. Below are presented the results for the Baseline ADAS-Cog ≤ 30 Subgroup.

The statistical analysis and graphical presentation were performed using Stata version 12.1 (Stata Corp., College Station, TX). Since the endpoints are continuous (i.e. ADAS-Cog change from baseline to 7 and 12 weeks), the means and standard deviations of the two groups (Active and Sham) were used. The effect sizes were calculated using Weighted Mean Difference ("WMD"). Standardized Mean Difference ("SMD") was also calculated. According to the guidelines suggested by Cohen,[109] we consider an SMD of 0.2 as a small effect size, an SMD of 0.5 as a medium effect size, and SMD of 0.8 and higher as a large effect size. Since the SMD is a slightly upwardly biased measurement on small samples, a correction was made using Hedges and Olkin's technique.[110]

Heterogeneity of the studies was explored using Cochrane's Q test of heterogeneity (P<0.1 considered statistically significant). Inconsistency in the studies' results was assessed by I^2 which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. When I^2 ≥50%, we assumed that there was more than moderate inconsistency. Random effects model (DerSimonian and Laird) was chosen if Cochrane's Q test P<0.1 or I^2≥50%. Otherwise, the fixed effects model (inverse variance methods) was chosen.

Table 34: Summary of Difference between Groups for Change in ADAS-Cog at 7 Weeks, Meta-Analysis (Baseline ADAS-Cog ≤30)

Population	Week 7							
	Q test P	Pooled WMD	95%CI	P-value	Q test P	Pooled SMD	95%CI	P-value
Pivotal PE+Korean Studies	0.056	-1.21	-3.53, 1.121	0.31	0.08	-0.32	-0.99, 0.349	0.348

Figure 33: Meta-Analysis of US Pivotal Study (PE Population) and Korean Studies with Baseline ADAS-Cog ≤30 (WMD) at 7 Weeks

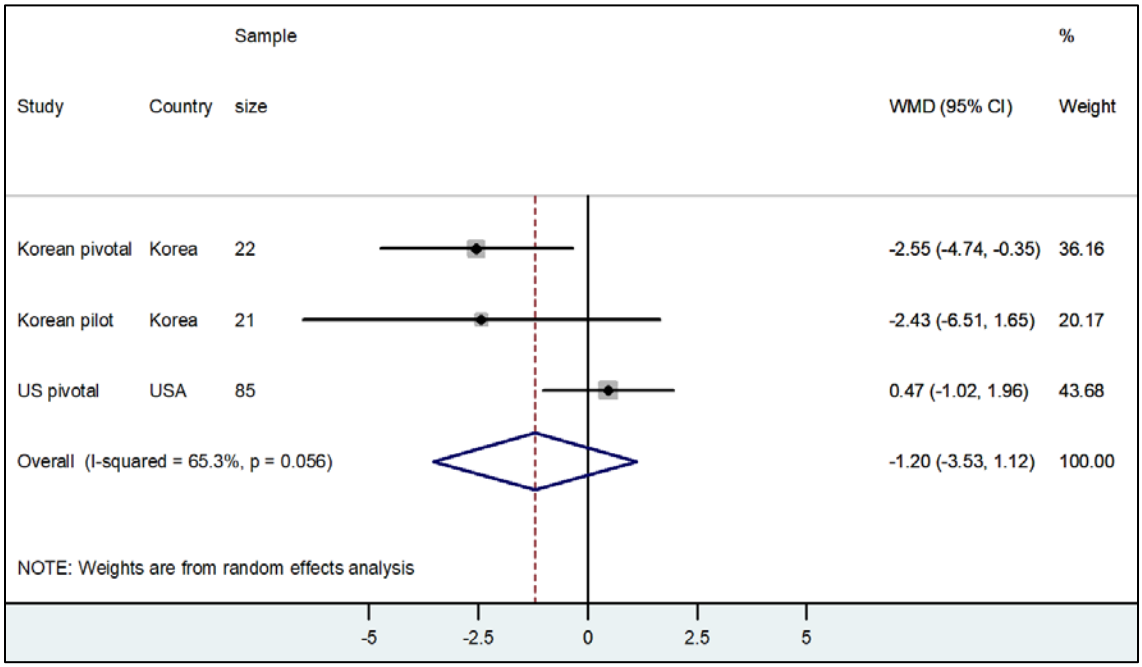


Figure 34: Meta-Analysis of US Pivotal Study(PE Population) and Korean Studies with Baseline ADAS-Cog ≤30 (SMD) at 7 Weeks

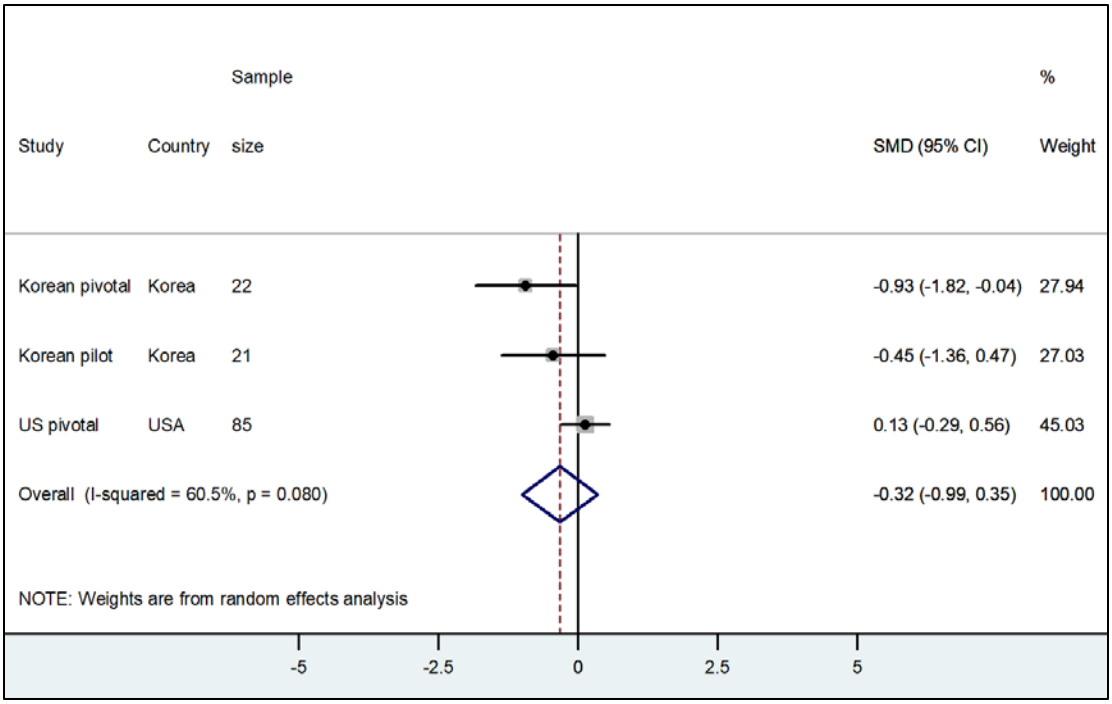


Table 35: Summary of Difference Between Groups for Change in ADAS-Cog at 12 Weeks, Meta-Analysis (Baseline ADAS-Cog ≤30)

Population	Week 12							
	Q test P	Pooled WMD	95%CI	P-value	Q test P	Pooled SMD	95%CI	P-value
Pivotal PE+Korean Studies	0.995	-1.663	-3.03, -0.29	0.017	0.967	-0.399	-0.76, -0.043	0.028

Figure 35: Meta-Analysis of US Pivotal Study (PE Population) and Korean Studies with Baseline ADAS-Cog ≤30 (WMD) at 12 Weeks

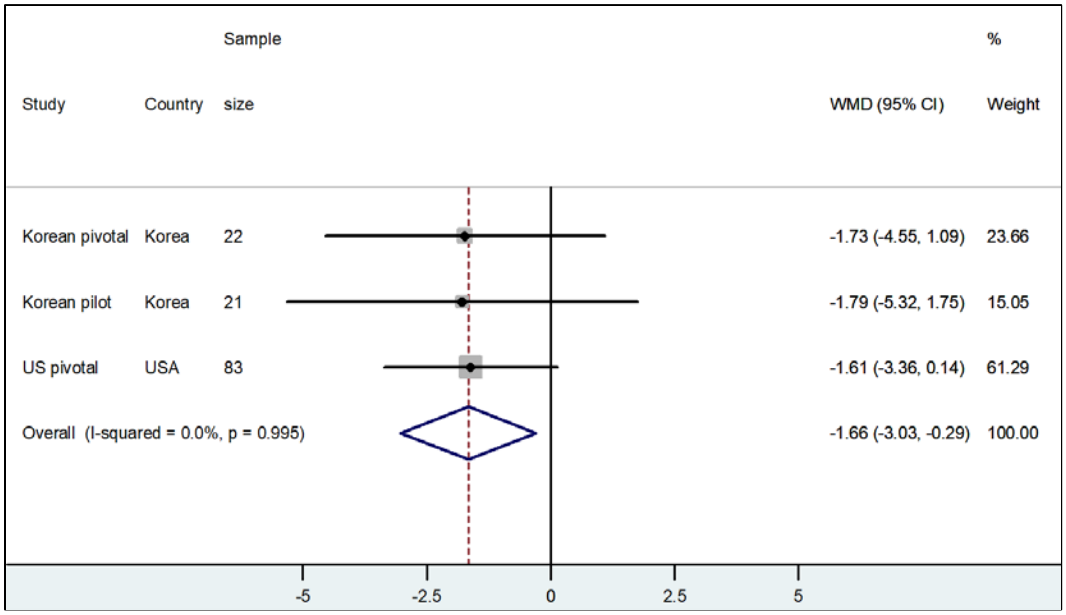
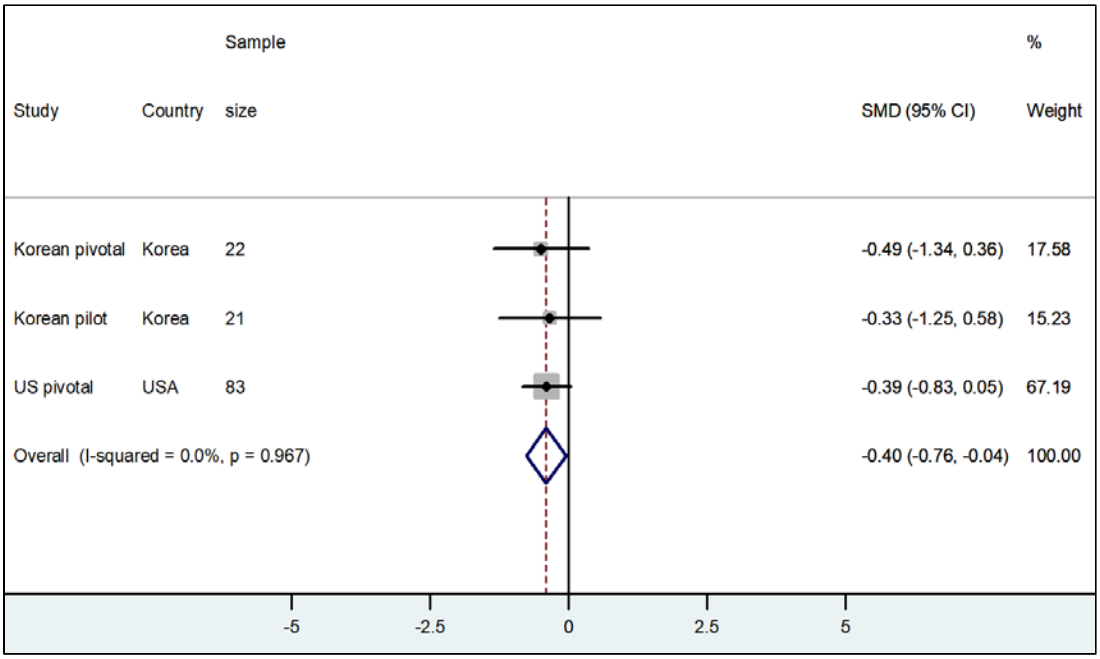


Figure 36: Meta-Analysis of US Pivotal Study (PE Population) and Korean Studies with Baseline ADAS-Cog ≤30 (SMD) at 12 Weeks



The meta-analysis clearly supports the efficacy of the neuroAD Therapy System in the Baseline ADAS-Cog ≤ 30 Subgroup:

1. All meta-analysis outcomes, at both 7 weeks and 12 weeks, show positive outcomes in the Baseline ADAS-Cog ≤ 30 Subgroup.
2. Differences between studies:

    a. While the US Pivotal Study had a different outcome at 7 weeks than the two Korean Studies, the difference is not significant (p-value > 0.05).
    b. More importantly, all 3 studies have practically identical outcomes when considering the Baseline ADAS-Cog ≤ 30 Subgroup at 12 weeks.

3. For the Baseline ADAS-Cog ≤ 30 Subgroup, results are always positive and reach statistical significance at 12 weeks:

    a. At 7 weeks, the pooled WMD is -1.21 (95% CI: -3.53 to 1.12) and the pooled SMD -0.32 (95% CI: -0.99 to 0.349); results are not statistically significant.
    b. At 12 weeks, the pooled WMD is -1.66 (95% CI: -3.03 to -0.29) and the pooled SMD -0.40 (95% CI: -0.76 to -0.043).
    c. Results are statistically significant (p-value = 0.017 and 0.028 for WMD and SMD, respectively), and are also clinically meaningful (-1.66 WMD, -0.40 SMD – moderate effect size).

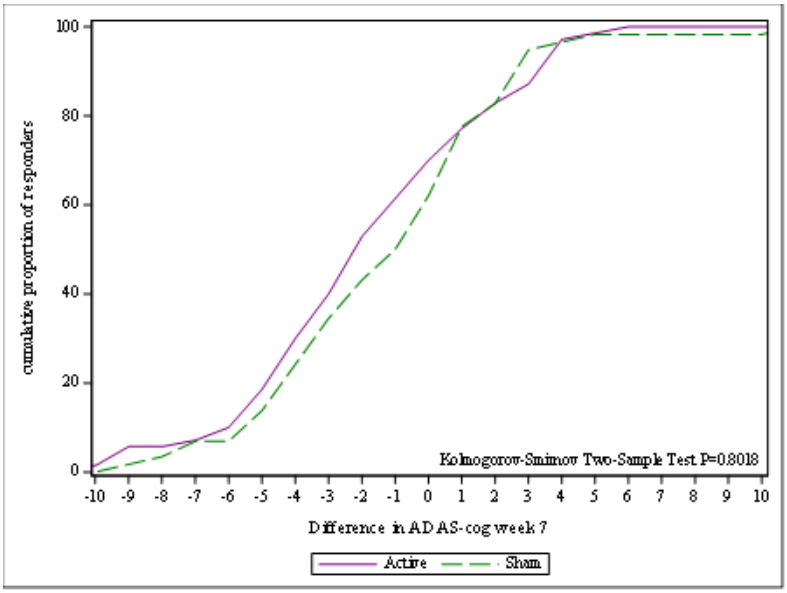
4. Note that when performing the meta-analysis, the results are also positive for the entire PE Population, but do not reach statistical significance.

6.3.4.3 Responder Analysis (S-Curves) for ADAS-Cog

The data was also analyzed using an S-curve plot that tracks along a continuum the percentage of patients achieving at least that degree of change in ADAS-Cog.

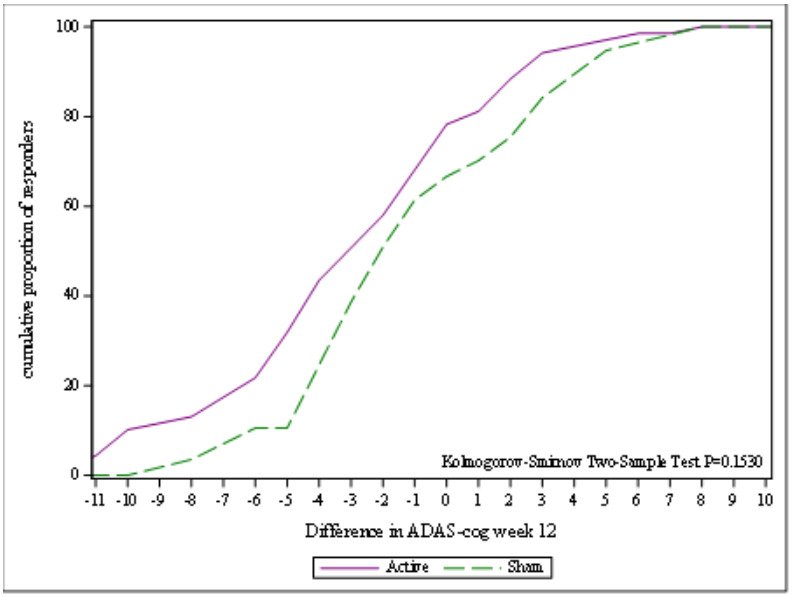
As shown in the figure below, at 7 weeks there is evident separation between the Active and Sham subjects, which favors the Active group, until the point of deterioration is reached (i.e., >0; increasing positive numbers on the x-axis represent deterioration).

Figure 37: Combined Responder Analysis of All Studies with Similar Protocols to US Pivotal Study at Week 7 (Baseline ADAS-Cog ≤30)



At 12 weeks, this separation is even more pronounced, especially in the range showing greater than 1 point of improvement (i.e., -1 or lower on the x-axis).

Figure 38: Combined Responder Analysis of All Studies with Similar Protocols to US Pivotal Study at Week 12 (Baseline ADAS-Cog ≤30)



6.3.4.4 Individual Subject Responses for ADAS-Cog

Overall, among patients in the US Pivotal Study and Korean studies, it is evident that 43.5% of Active patients improve by at least -4 points (compared with 11.8-58% for a typical ChEI),[111] 50.7% improve by at least -3 points, and 78.3% either improve or do not deteriorate (compared with 34.5-87% for a typical ChEI).

To further explore the outcomes for subjects with baseline ADAS-Cog ≤ 30 (i.e., the indicated population) as well as patients with baseline ADAS-Cog > 30, and to review a larger sample size, Neuronix produced waterfall plots analyzing the meta-analysis population, which combines the populations of the US Pivotal Study and Korean studies.

Notably, analysis using the increased sample of Baseline ADAS-Cog >30 subjects (n=22) shows that the Active Baseline ADAS-Cog >30 group is more evenly distributed between improvement and deterioration. In addition, among subjects with Baseline ADAS-Cog >30, a similar proportion in the Active and Sham arms improved at both time points. It is also worth noting that in this larger meta-analysis population, the trend of Active subjects with Baseline ADAS-Cog ≤30 improving at week 12 is even more pronounced.

Figure 39: Waterfall Plot, Meta-Analysis Week 7
(US Pivotal (PE), Korean Pilot, Korean Pivotal)

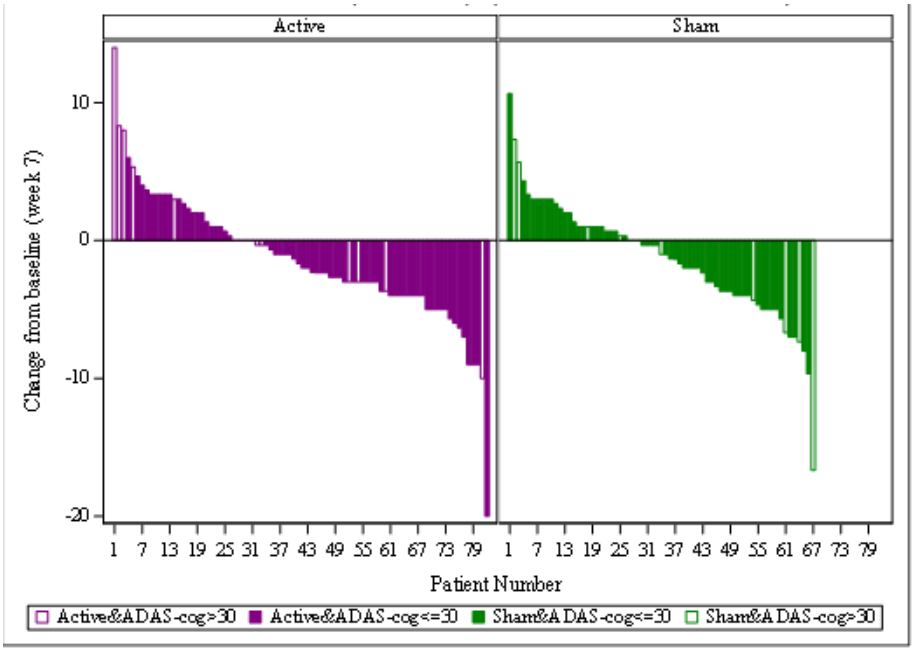
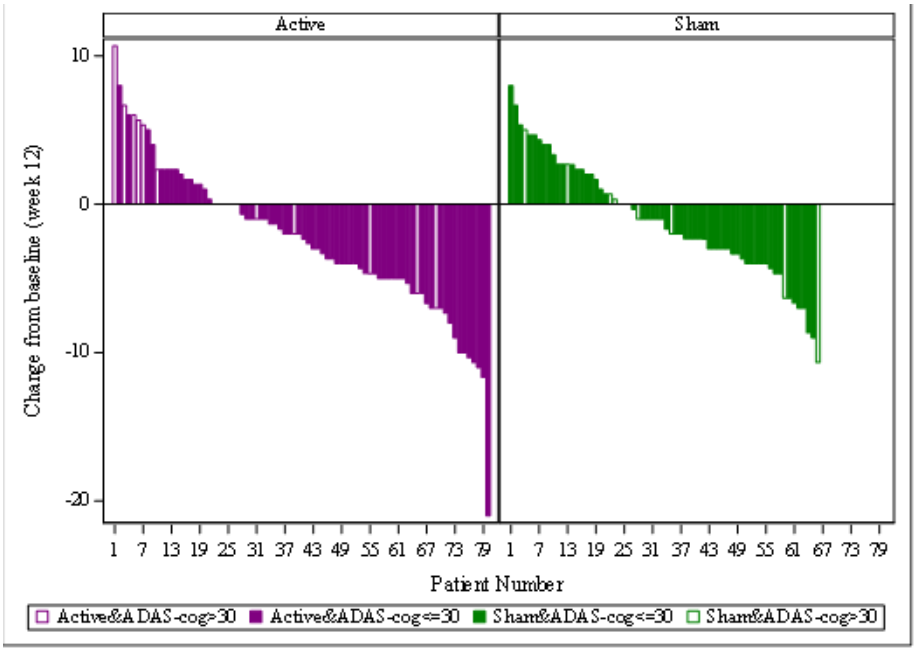


Figure 40: Waterfall Plot, Meta-Analysis Week 12
(US Pivotal (PE), Korean Pilot, Korean Pivotal)



6.3.4.5 Summary

In summary, the US Pivotal Study and two Korean studies were conducted using very similar protocols and subject populations. Patients received the same treatment regimen and were measured using the same assessments. The studies' outcomes are similar enough to justify pooling together. The combined analyses further support the Pivotal Study results and the device's clinical benefits.

Clinically meaningful improvements were observed for all patients with a baseline ADAS-Cog ≤30 for each measure.

Furthermore, the Korean Pivotal Study recruited only mild AD subjects with Baseline ADAS-Cog ≤ 30. Positive outcomes in the Korean Pivotal Study provide further support and independently confirm the conclusion reached that the Baseline ADAS-Cog ≤ 30 Subgroup is most likely to benefit from the treatment.

6.4 Additional Clinical Data Provided in Support of neuroAD

6.4.1 Supplemental Studies that Assessed ADAS-Cog

In addition to the US Pivotal Study and Korean studies discussed above, 10 other studies were performed that also support the risk/benefit profile of the neuroAD, 7 of which used the ADAS-Cog scale for evaluation, and 3 of which used other cognitive measures.

For the 7 studies which reported ADAS-Cog, because the protocols for these studies varied in some respects from the US Pivotal Study protocol (although all studies used the same treatment protocol, 5 days per week over 6 weeks), they are presented separately below. The additional analyses provided below investigate change in ADAS-Cog outcomes and change in ADCS-CGIC outcomes (where applicable). Since different studies employed different follow-up periods, in order to allow consistent presentation of conclusions, the results were grouped into 2 follow-up windows: FU-1 window includes follow-up that was conducted between 6 to 10 weeks after the first treatment day, similar to the first (7 weeks) follow-up in the US Pivotal Study. FU-2 window includes follow-up that was conducted between 10 to 14 weeks after the first treatment day, similar to the second (12-week) follow-up in the US Pivotal Study.

Across all 7 investigations, the Active group reported a reduction in mean ADAS-Cog score at FU-1 window compared to baseline (range: -0.9 to -4.3). Where a second follow-up visit was reported, the improvement in ADAS-Cog was maintained. In addition, 4 pilot studies included a Sham group (Assaf 2, Assaf 3, Harvard, and Italy) and the Active group in all 4 studies outperformed the Sham group at both the FU-1 and FU-2 time points.

A summary of the 7 Supplemental Studies is provided in the table below, which shows results for all subjects regardless of their baseline ADAS-Cog score. Analyses of these additional data, together with the previously presented results, strongly supports the benefit of the device relative to its very low risk, with results replicated across multiple independent investigations at different sites.

Table 36: Summary of Supplemental Investigations of the neuroAD Therapy System that Included the ADAS-Cog Assessment

Study	Study Design	Number of Study Participants	Results
Assaf 1[112]	Open Study 30 neurAD sessions + maintenance	8 participants (8 Active)	- ADAS-Cog (mean) scores improved by 4 points after 6 weeks ($p<0.01$) and 4.5 months ($p<0.05$) of treatment. - ADCS-CGIC scores improved by 1.0 point (6 weeks) and 1.6 points (4.5 months). - MMSE, ADAS-ADL, and Hamilton Depression Scale improved but without statistical significance. NPI did not change. - No related SAEs reported.
Assaf 2[113]	Randomized, double blinded, placebo controlled 30 neurAD sessions + maintenance	15 participants (7 Active, 8 Sham)	- The ADAS-Cog score in the Active group improved by 3.76 points compared to 0.47 points for the Sham group at 6 weeks ($p=0.04$). At 4.5 months, the Active group improved by 3.52 points, compared to the Sham group (0.38 point worsening) ($p=0.05$). - ADCS-CGIC scores improved by 3.57 for the treatment group, compared to 4.25 in the control group at 6 weeks ($p=0.05$). After 4.5 months, the treatment group improved by 3.67 points compared to 4.29 in the placebo group (mild worsening) ($p=0.05$). NPI improved non-significantly. - No related SAEs reported.
Harvard[114]	Randomized, double blinded, multi-arms controlled 3 arm design: 1. Active 2. Sham 3. Cognitive training only (Sham TMS) 30 neuroAD Sessions only	21 participants (10 Active, 6 Sham, 5 cognition training only)	- The ADAS-Cog score in the treatment group improved by 1.79 points at 6 weeks while the control group deteriorated by 0.66 points at 6 weeks (difference -2.45 favoring the treatment, NS). At 10 weeks, the treatment group improved by 4.8 points. No control group subjects continued to 10 weeks. - ADCS-CGIC scores improved 1.5 points for the treatment group compared with control (NS). - No related SAEs reported.
Assaf 3[115]	Randomized, double blinded, placebo controlled 30 neuroAD sessions only	16 participants (10 Active, 6 Sham)	At 7 weeks: - The ADAS-Cog score in the treatment group improved by 1.5 points while the control group deteriorated by 2 points at 6 weeks (p-value = 0.038). - On ADCS-CGIC scale, treatment group improved by -0.9 points while the control group deteriorated by 0.7 points, for a between-group difference of -1.6 points favoring the treatment (NS). - MMSE score in the treatment group improved by 1.2 points compared to the control group which deteriorated by 1.2 points (NS). - No related SAEs reported. At 12 weeks: - The ADAS-Cog score in the treatment group improved by 1.8 points compared to

Study	Study Design	Number of Study Participants	Results
			the control group, which deteriorated by 1.9 points at 6 weeks (NS). - On ADCS-CGIC scale the treatment group improved -0.9 points while the control group deteriorated 1.6 points (difference of -2.5 points favoring treatment). - No related SAEs reported.
NeuroCare Clinic, Israel[116]	Naturalistic follow-up in clinical setting 30 neuroAD sessions only	84 participants (all Active)	- Change (mean) in ADAS-Cog scores at 6-10 weeks was -1.17 points. Change (mean) in ADAS-Cog scores at 10-14 weeks was -0.85 points. - No SAEs were reported to date. Side effects are mild and transient.
Nantes, France[117]	Open label study	10 participants (all Active)	- Average ADAS-Cog improvement on week 7 (day 45) was -2.87 points, and patients returned back to baseline at 6 months follow-up (delta=0). Results were statistically significant (p=0.016, Friedman test). - The only adverse effect resulting from the neuroAD procedure was transient fatigue observed during the third week of treatment in two subjects (did not justify interrupting treatment).
Italy[118]	Double blind, randomized, sham controlled study. 3 arm study: 1. Active 2. Sham 3. Real Cognitive training (as in Active group, but sham TMS) 30 neuroAD sessions only	13 participants (6 Active, 2 Sham, 5 cognition training only)	- ADAS-Cog in the Active group improved by -2.83 points at 7 weeks compared with the Sham group which remained stable (no difference), and the cognitive training only group, which showed an improvement of -1 point. Results were approaching statistical significance when comparing Active arm vs. Sham arm (p=0.15). At week 10, the Active group maintained its improvement at -2.33 points on ADAS-Cog, while the Sham group showed increased improvement of -2.5 points (n=2). The cognitive training only group also continued to improve (-2.6 points). The results of this study should be interpreted with caution due to the small sample size.

The consistency of performance by the Baseline ADAS-Cog ≤ 30 Subgroup is illustrated by the Forest plots provided below, which show the outcome for each of the 7 studies. Forest plots are shown for Active patients only and, for controlled studies, the difference between the Active and Sham results. Assaf 2, Assaf 3, Harvard, and Italy were controlled studies, and Assaf 1, France and NeuroCare were single arm active studies. The charts with only Active patient data present differences from baseline. In addition, please note that only the available data are shown below (the Italy study included 2 Sham patients without data at 6-10 weeks, and Assaf 2 does not have 10-14 week data). Differences are not shown in **Figure 42** as only one study (Assaf 3) has Active and Sham data for patients with baseline ADAS-Cog ≤30 at this time point.

As shown in the plots, the mean change in ADAS-Cog for the Active group consistently shows improvement over Sham (where applicable), with all means to the left of the zero line, indicating improvement.

While the confidence intervals are wide in some of the studies, largely due to small sample sizes, the consistent improvement of the Active group (relative to baseline or relative to Sham) is evident at both time points.

Figure 41: Mean ADAS Cog Change FU-1 (6-10 Weeks), Supplemental Studies (Baseline ADAS-Cog≤30)

Active Patients Only (Left) and Active-Sham Difference (Right)

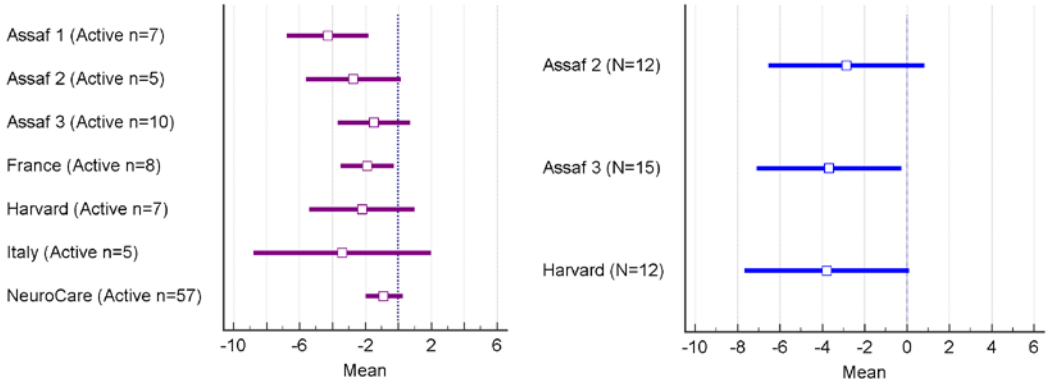
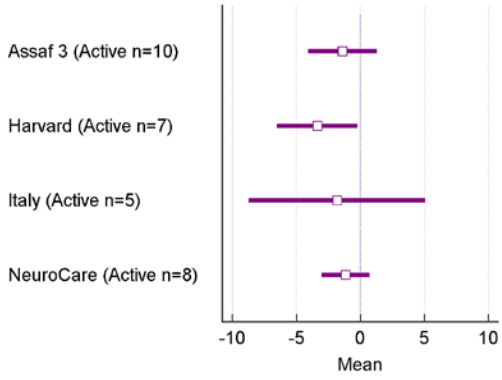


Figure 42: Mean ADAS Cog Change FU-2 (10-14 Weeks) , Supplemental Studies (Baseline ADAS-Cog ≤30)

Active Patients Only



In summary, the totality of the data supports the potential for meaningful benefit of adjunctive use of the neuroAD in patients in the indicated population, defined by a baseline ADAS-Cog score ≤30.

6.4.2 Additional Investigations that Report Other Outcomes

In addition to the 7 Supplemental Studies that assessed ADAS-Cog, results are summarized in **Table 37** below for 29 subjects who underwent the neuroAD Therapy System procedure, but were evaluated using scales other than ADAS-Cog (10 patients from a French commercial clinic, 10 patients from a UK commercial clinic, and 9 patients from Thailand). These data also support the clinical benefit of the neuroAD Therapy System.

Table 37: Additional neuroAD Studies That Do Not Report ADAS-Cog

<table>
<tr><th>Study</th><th>Description</th></tr>
<tr><td>Orsay</td><td>A clinic in Orsay, France (commercial), reported 10 subjects between November 2016 and July 2017. Eight subjects out of the ten were evaluated using the MMSE scale, and improved by 3.75 points on average after 6 weeks of treatment. For the other two subjects, no MMSE data was collected although the clinic reported improvement.</td></tr>
<tr><td>UK</td><td>Two clinics operate in the United Kingdom administering the neuroAD treatment. Both clinics use the Addenbrooke’s Cognitive Examination (ACE-III) scale for the evaluation of cognition.

The ACE-III is considered a ‘brief bedside’ cognitive screening instrument. The assessment focuses on Attention, Memory, Verbal fluency, Language, and Visuospatial abilities. Mistakes are subtracted from a total score of 100, where a cut-off of 82-88 was reported as the cut-off for detecting dementia. Increase in score represents improvement, while decrease in score represents deterioration.

The two clinics in the UK (commercial) administered the neuroAD treatment to 10 subjects since opening (Neuronix clinic in London – 4 subjects, Phoenix Mental Health Services in High Wycombe – 6 subjects). All ten subjects were evaluated using the ACE-III scale, and achieved an average of 4.3 points improvement after 6 weeks of treatment.</td></tr>
<tr><td>Thailand</td><td>A clinic in Thailand conducted a small scale independent clinical study evaluating the neuroAD treatment. The study included 6 Active treatment subjects, and 3 Control subjects who were administered cognitive training only. Assessment was performed at baseline and at 6 months. The study evaluated several scales, including the Thai version of the MMSE, TMSE, MOCA and ACE. The MOCA is a 30-point questionnaire validated for Mild Cognitive Impairment. A score of 26 or above is considered to be normal. Increase in score represents improvement in cognitive function, while decrease in score represents deterioration.

As can be seen in the table below, the Active group showed consistent improvement as evidenced by all cognitive measures: Thai MMSE – improvement by 2 points, MOCA – improvement by 4.5 points; ACE – improvement by 9 points. In comparison, the control group showed equivocal results, probably due to small sample size (3 subjects): Thai MMSE improved (6 points), while MOCA deteriorated (-1) and ACE showed very little change (1 point). Clinical Outcomes for Thai Study

<table>
<tr><th>Group</th><th>Scale</th><th>Baseline</th><th>6-Months</th><th>Delta</th></tr>
<tr><td rowspan="3">Active Treatment (n=6)</td><td>TMSE</td><td>22</td><td>24</td><td>2</td></tr>
<tr><td>MOCA</td><td>12</td><td>16.5</td><td>4.5</td></tr>
<tr><td>ACE</td><td>57</td><td>66</td><td>9</td></tr>
<tr><td rowspan="3">Cognitive Only (n=3)</td><td>TMSE</td><td>15</td><td>21</td><td>6</td></tr>
<tr><td>MOCA</td><td>10</td><td>9</td><td>-1</td></tr>
<tr><td>ACE</td><td>29</td><td>30</td><td>1</td></tr>
</table>
No side effects were reported during the study.</td></tr>
</table>

6.4.3 Safety Information for All Additional Clinical Studies

A summary of the Adverse Event information for the Supplemental Studies and commercial databases including severity and relatedness, where available, is provided in **Table 38** below. This data was provided to Neuronix by the sites.

The data from the Supplemental Studies and commercial clinics supports the safety of the neuroAD, as demonstrated in the Pivotal Study. There were no SAEs associated with the device, and AEs reported were generally mild and transient in nature. No seizures were reported.

Table 38: Summary of Available Adverse Event Information for the Supplemental Studies and Commercial Use

Study	Active/ Sham	# Patients Reporting AE	# AEs	Details/Comments
Assaf 1*	Active (n=8)	1	1	One patient developed sepsis due to a UTI 2 months after beginning treatment; this was unrelated to the trial. Aside from some minor tiredness, no side effects were reported. No other AEs were recorded.
Assaf 2**	Active (n=7)	1	1	1 participant dropped out of the study due to psychiatric symptoms that required medication. This event was unrelated to the device per the PI. No side effects or AEs were reported.
	Sham (n=8)	2	2	2 participants dropped out of the study, one due to a bladder infection and the other due to general weakness. These events were unrelated to the device per the PI. No side effects or AEs were reported.
Assaf 3	Active (n=10)	Unk	Unk	Data requested but not yet provided
	Sham (n=6)	Unk	Unk	Data requested but not yet provided
Harvard^	Active (n=10)	5	21	AEs: - Mild and transient hearing impairment post intervention reported by one Active subject - Blurry vision was reported after looking at computer screen for extended period of time by one Active subject - Mild neck pain/stiffness was reported by 3 Active subjects - Mild scalp pain was reported by 3 Active subjects - Mild soreness at stimulation site was reported by one Active subject

Study	Active/ Sham	# Patients Reporting AE	# AEs	Details/Comments
				- Mild achiness was reported by one Active subject - Mild and transient eye heaviness post intervention was reported by one Active subject - Mild to moderate headache events were reported by 5 Active subjects. Events were assessed as possibly/probably related to the study. - Mild tiredness was reported by 3 Active subjects - Mild dizziness was reported by 1 Active subject - Increase in anxiety was reported by 1 Active subject
	Sham (n=5)	1	1	SAE: One subject from the Sham group experienced a 5cm contusion and subtle rib fracture resulting from a fall at home during the study follow-up phase. Subject was brought to the hospital. Event was assessed as unlikely related to the study.
	Cog Only (n=6)	5	18	AEs: - Mild and transient hearing impairment post intervention reported by one Cog-only subject - Muscle twitching (in bicep and wrist flexor of the right arm at the beginning of a TMS session that lasted for 5 seconds and resolved) by one Cog-only subject. Subject also reported nausea and session was discontinued. - Mild neck pain/stiffness was reported by 2 Cog-only subjects - Mild to moderate headache events were reported by 5 Cog-only subjects. Events were assessed as possibly/probably related to the study. - Mild and transient impaired cognition (reported as tiredness) was reported by one Cog-only subject - Mild and transient trouble concentrating (reported as tiredness) was reported by 4 Cog-only subjects - Mild tiredness was reported by one Cog-only subject

Study	Active/ Sham	# Patients Reporting AE	# AEs	Details/Comments
				- Mild dizziness was reported by one Cog-only subject - Increase in anxiety was reported and one Cog-only subject - Mild daze/depression reported by one Cog-only subject
NeuroCare	Active (n=84)	9	11	No SAEs were reported. 7 headache events, 1 local eye pain (left) event, 1 nausea event, 1 dizziness event, and 1 tiredness event. All events were mild and transient.
France (Nantes)	Active (n=10)	2	2	Both patients reported transient fatigue.
Italy	Active (n=6)	0	0	No adverse events reported.
	Sham (n=2)	0	0	No adverse events reported.
	Cog Only (n=5)	0	0	No adverse events reported.
Thailand[#]	Active (n=6)	N/A	N/A	No side effects reported
	Cog Only (n=3)	N/A	N/A	No side effects reported
Orsay FR	Active (n=10)	N/A	N/A	No side effects reported
UK	Active (n=10)	N/A	N/A	No side effects reported

* Data taken from published article (Bentwich et al 2011)
** Data taken from published article (Rabey et al 2012)
^ Reports reported from the site in aggregate, not by individual subject
[#] Data taken from poster

Safety results from all 13 investigations described in the *de novo* demonstrate a consistently favorable safety profile. **In these supplemental investigations and commercial use, no device or procedure related serious adverse events were ever reported**. The safety profile in the supplemental studies was very similar to the US Pivotal Study. Notably, no patient the company is aware of has discontinued treatment with the neuroAD Therapy System due to related adverse events, and compliance with the treatment protocol is high, demonstrating it is well tolerated.

6.4.4 Conclusions

The fact that there are many studies of the neuroAD Therapy System (in different territories and different settings (clinical trials, commercial programs)) that show consistent benefit demonstrates a repeatable effect. Because it is uncommon to have a total of 13 investigations (including the US Pivotal Study, the Korean Pilot and Pivotal Studies, and all supplemental studies and commercial use) at the time of premarket submission, some additional variability is to be expected compared to a single, uniform study.

Furthermore, the large number of studies reflects the high level of clinical interest in the neuroAD Therapy System, as well as its availability and use outside of the US. Nonetheless, the ability to show benefit across many sites, investigators, and patient groups supports a device effect that is meaningful.

6.5 Long Term Follow-up Data

To date, Neuronix has focused its clinical verification on the short- to medium-term, using studies with immediate follow-up (i.e. between 6 and 10 weeks) as well as follow-up in the range of 12 weeks (10 to 14 weeks, as described above).

Although not collected in specifically-designed, randomized double-blind studies, some evidence has been collected in several dozen patients, mainly coming from commercial clinics, to assess potential duration of efficacy. Acknowledging the limitations of the data shown below, it is presented to provide the most comprehensive understanding of the potential benefits of the neuroAD Therapy beyond the 12-week follow-up.

Table 39: neuroAD Long-Term Follow-Up Data

Study	Design	# of Pts.	Follow-up period	ADAS-Cog score relative to baseline
NeuroCare Study	Retrospective, Naturalistic follow-up in clinical setting	5	9 – 12 months (average 10.2 months)	Improved -0.3 points
Nantes (Clinique Breteche)	Prospective, open label study	10	6 months	0 (back to baseline)
Korean Pilot Study	Naturalistic FU on double blind study	5 Active 3 Sham	24 months	Active: Improved -0.5 points Sham: Deteriorated 6 points

While no claims will be made based on this data, it appears that following the initial (12 week) improvement, patients return to their baseline (pre-treatment) level over a time period of between 6 and 24 months.

6.6 Stakeholder Input

6.6.1 Physician Survey

In response to FDA feedback during the *de novo* review, Neuronix commissioned an independent third-party survey to investigate what US neurologists and psychiatrists believe to be clinically significant improvement on AD cognitive/behavioral scales (full report is attached as **Appendix 4**). In total, 200 US neurologists and psychiatrists completed the survey (100 participants from each specialty). All respondents had substantial professional experience (16.3 years on average), and

personally saw a significant number of AD patients per month (81.5 patients on average). The questionnaire covered the physician's experience in treating patients with mild to moderate AD, how to measure improvement, and what degree of improvement they would consider meaningful in a new treatment. The survey also included questions regarding the physician's perceptions when provided a blinded product profile of the neuroAD device.

When questioned about how improvement in mild to moderate AD patients may be measured, approximately two-thirds of surveyed physicians reported that both cognitive (e.g., ADAS-Cog) and functional/behavioral (e.g., ADCS-CGIC) assessments are equally clinically beneficial when determining treatment effectiveness.

Importantly, 47% of respondents reported that they would consider a -1 point improvement (or less, as long as there is no deterioration) in ADAS-Cog score clinically meaningful. 77% of physicians said they would consider at least a -2 point improvement clinically meaningful.

When coupled with at least a -0.5 point improvement in ADCS-CGIC, 57% of physicians considered a -1 point improvement in ADAS-Cog to be clinically meaningful, and 86% of physicians considered a -2 point improvement in ADAS-Cog clinically meaningful. Notably, all surveyed physicians who personally manage treatment for mild to moderate AD patients reported that improvements are needed for the currently available treatments.

Figure 43: Summary of Physician Survey Results
Minimal Clinically Meaningful Change in ADAS-Cog – Change in ADAS-Cog Considered Alone

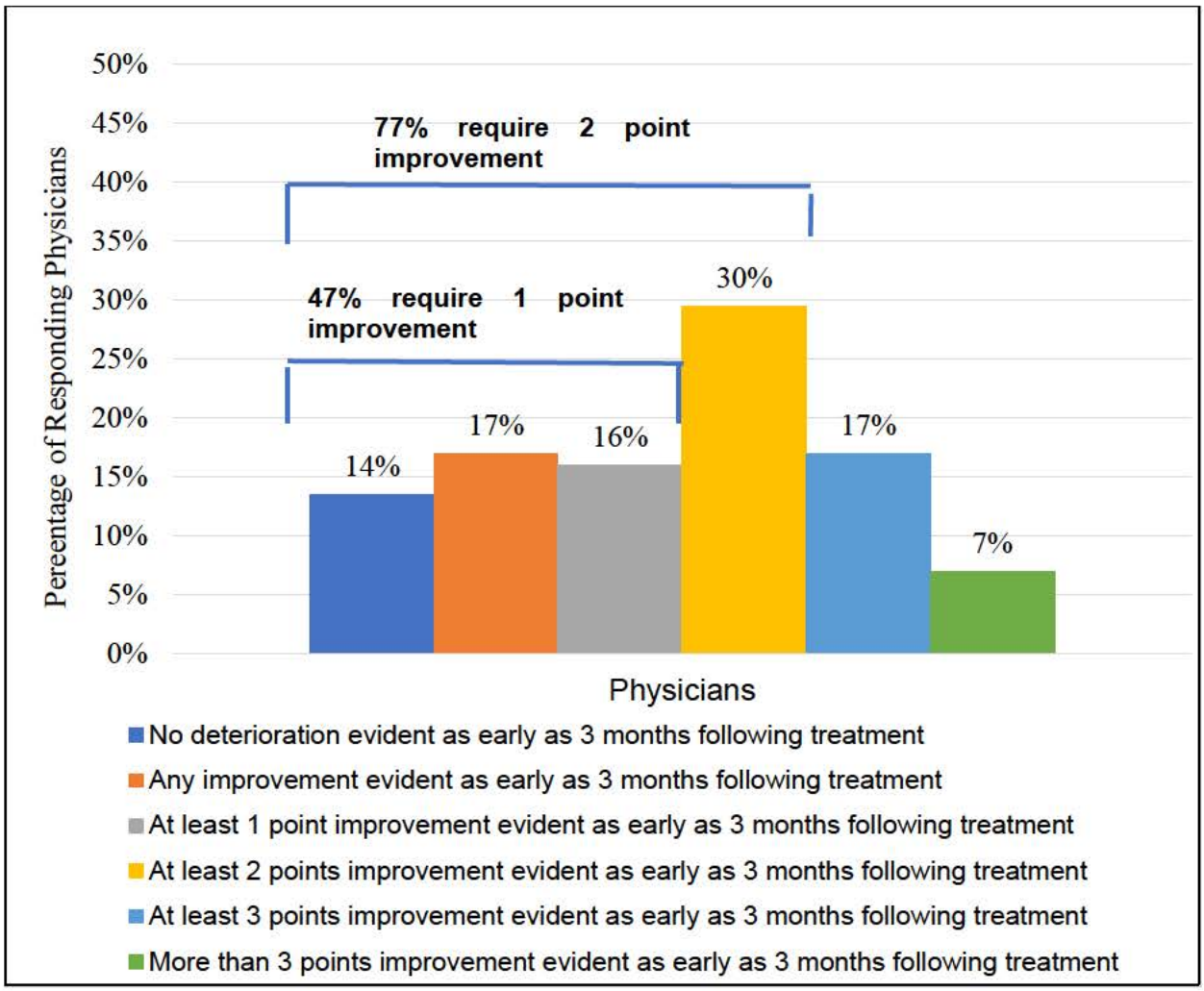
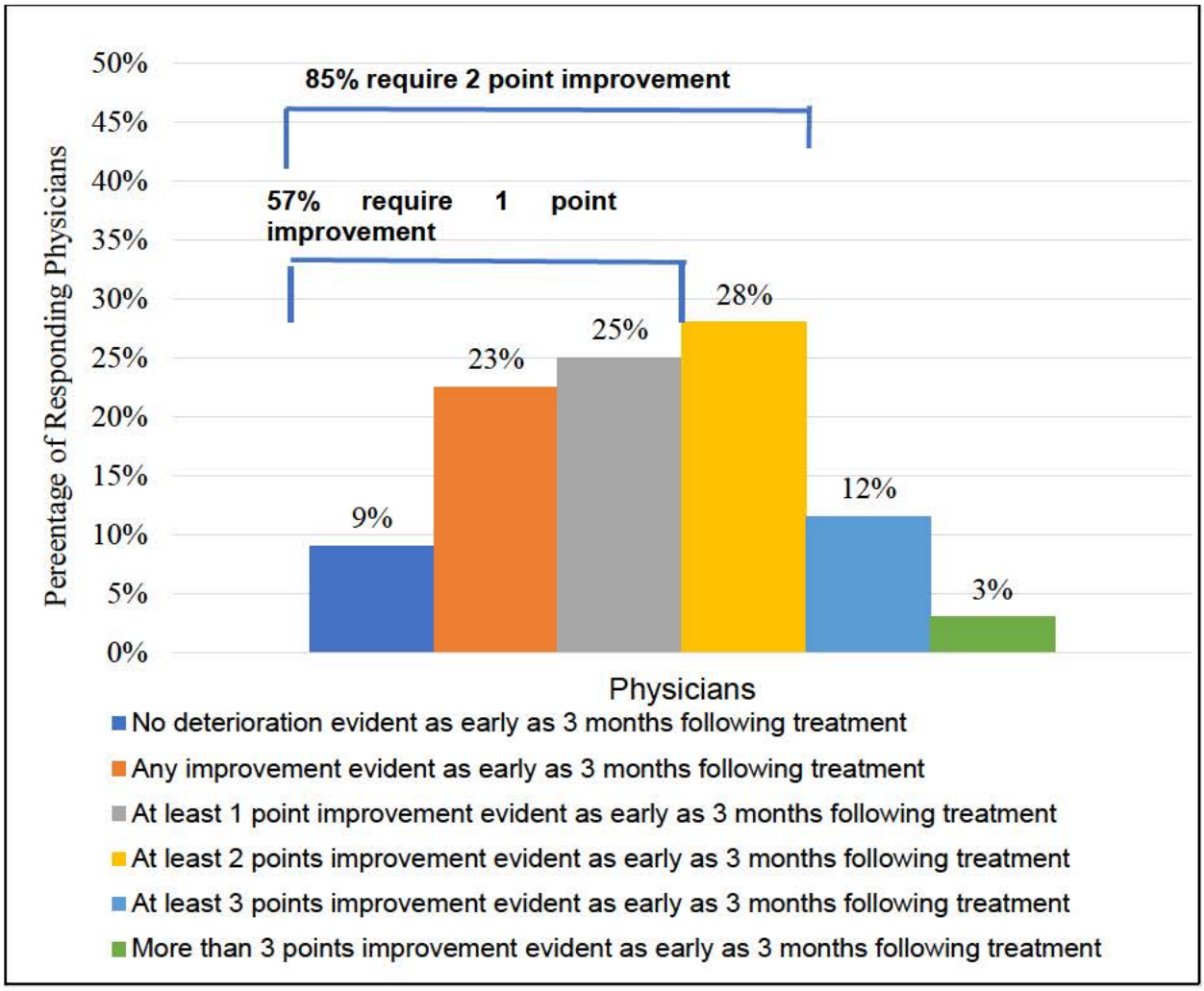


Figure 44: Minimal Clinically Meaningful Change in ADAS-Cog – Change in ADAS-Cog with Corresponding 0.5 Point Average Improvement in ADCS-CGIC



The company believes that this survey provides evidence that the neuroAD's benefits would be considered clinically meaningful by the clinical community for the proposed treatment population, particularly in light of the favorable safety profile of the device.

6.6.2 Patient/Caregiver Survey

The company also conducted a survey (via SurveyMonkey®) regarding US patient caregiver/family member views on new treatments for AD. The survey respondents included 170 people who had a family member diagnosed with AD.

When asked what treatment option their family members received for AD, most of the 150 respondents indicated that their family member received some treatment (73%), with some receiving more than one type of treatment. Specifically, 51% of the respondents indicated that their family member received drug treatment, 27% indicated life style (e.g., exercise, diet, etc.), 13% indicated dietary supplement, and 14% indicated "other" treatment.

When asked whether they are satisfied with currently available treatment options, approximately two-thirds indicated that treatment could be improved or that they were not at all satisfied. Only 3% of the respondents indicated that they were “very satisfied” with current treatment. Moreover, 64% of respondents said that they have seen minimal or no improvement in their family member on their current treatment. In addition, more than one-third of the respondents indicated that their family member experienced side effects from the current treatment. This reflects the high unmet need for additional treatment options.

In the same survey discussed above, 77% of the respondents indicated that they would be very or somewhat likely to want their family member to try a new treatment that required 5 visits per week to a clinic, one hour per day, with minimal to no side effects, and a 70% likelihood of some improvement. Notably, when the survey is limited to principal caregivers of a family member currently living with AD, 81% responded that they were very likely or somewhat likely to want their family member to try the new treatment with 70% likelihood of some improvement. Even if the likelihood of some improvement drops to 50%, a majority of the respondents (66% total, 75% of principal caregivers) would still be very or somewhat likely to want their family member to try this new treatment.

Regarding other benefits, 78% of respondents indicated that helping the family member patient improve vitality and return to one’s original personality was important to them. Low risk of side effects was also important to the majority of the respondents (59%).

These results demonstrate the unmet needs of both patients and their families for additional treatment options. Patients’ family members indicated willingness to accept treatment options even if they would not work for everyone, particularly if safe.

6.6.3 Patient Case Examples

To supplement the above information regarding patient and caregiver preference, two video clips of caregivers and patients treated with the neuroAD Therapy System outside the US that describe the clinically meaningful benefits that were achieved following treatment are provided in **Appendix 5**.

7.0 RISK-BENEFIT ANALYSIS

Based on the totality of evidence from 13 separate clinical studies amounting to data from 374 subjects, including the US Pivotal Study (130 subjects), the probable benefits of the neuroAD Therapy System to treat mild to moderate Alzheimer's disease, in patients with a baseline ADAS-Cog up to 30, clearly outweigh the minimal risks presented by this non-invasive device.

De novo clearance (i.e., downclassification) of the neuroAD Therapy System is consistent with the principles FDA set forth in its August 24, 2016 guidance titled, *Guidance for Industry and Food and Drug Administration Staff. Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications* ("Benefit-Risk Guidance"), including the primary factors FDA considers when making benefit-risk determinations for *de novo* classification decisions. The guidance outlines these factors which include the type of benefit, the magnitude of the benefit, and the probability of a patient experiencing one or more benefits, as well as the severity, types and rates of harmful events associated with device use and the probability and duration of harmful events. Other considerations include the level of uncertainty, the nature of the disease, patient preferences, and the availability of alternative treatments. FDA is to consider all of these factors in making a determination whether the probable benefits of a device outweigh the probable risks.

With regard to *de novo* requests, the guidance provides:

> "***Because devices classified under this pathway (de novo devices) are low to moderate risk devices, they may not need to confer as substantial a benefit to patients in order to have a favorable benefit-risk profile.***" (emphasis added)

In addition, in regard to novel technology addressing unmet medical need specifically, FDA specifically notes ***"[i]t is not unusual for novel devices that address an unmet medical need to have relatively small probable benefits, and FDA may determine the novel device to be reasonably safe and effective even though the applicant demonstrates a relatively small probable benefit.***" (emphasis added)

Neuronix has established the neuroAD Therapy System to have at least a moderate effect size, clearly exceeding the above-mentioned criterion.

FDA has acknowledged the unmet need in AD treatment options by granting expedited access pathway ("EAP") status for the neuroAD Therapy System because the device "*may offer significant, clinically meaningful advantages over existing legally marketed alternatives; and the availability of the device may be in the best interest of patients (e.g. addresses an unmet medical need.)*."

Based on a risk-benefit assessment and as discussed further below, the neuroAD Therapy System is an appropriate candidate for *de novo* clearance. The mild, transient, and low incidence of adverse events associated with the neuroAD Therapy System is substantially outweighed by the demonstrated benefits for patients with mild to moderate AD, who may use the device in conjunction with other pharmacological and non-pharmacological therapies. Furthermore, such risks can be addressed and mitigated with special controls based on the existing clinical data.

7.1 Characterization of the Disease and Available Therapies

As described above, Alzheimer's disease is an acquired cognitive and behavioral impairment of sufficient severity that it markedly interferes with social and occupational functioning and is the most common cause of dementia.[119] No treatment currently available for AD slows or stops the damage to neurons that causes AD symptoms and eventually makes the disease fatal.[120] There are 5.7 million people living with AD, 5.5 million of whom are age 65 years or older.[121] Out of the top 10 leading causes of death in the US, AD is the only disease which cannot be prevented, cured or even slowed down in its progression.

Non-pharmacological strategies for delaying the progression of cognitive deficits and resulting functional impairment in AD (e.g., cognitive training) have produced limited and equivocal results. Furthermore, a recent (2013) Cochrane review of cognitive training alone for treatment of AD concluded that: *"Cognitive training was not associated with positive or negative effects in relation to any reported outcomes. The overall quality of the trials was low to moderate".*[122] When combining into a meta-analysis the 10 available studies, the results show a Standardized Mean Difference (SMD) improvement of 0.10 (non-significant; 95% CI: -0.21 to 0.40).

There are currently no medical devices that have been cleared or approved by FDA for treatment of AD.

Currently available pharmacological treatments for AD have also demonstrated a limited effect. Moreover, patients have shown limited tolerability for these medications, thus further reducing their usefulness.[123]

In a 2006 Cochrane review[124] regarding ChEI for mild to moderate Alzheimer's disease, the authors report regarding ADAS-Cog outcomes that: *"The results of 10 randomized, double blind, placebo controlled trials demonstrate that treatment for 6 months, with donepezil, galantamine or rivastigmine at the recommended dose for people with mild, moderate or severe dementia due to Alzheimer's disease produced improvement in cognitive function, on average -2.37 points (95%CI -2.73 to -2.02, p<0.00001)."* In addition, a more recent Cochrane review in 2015[125] focused on Alzheimer's disease treatment using rivastigmine (one of the FDA-approved ChEI drugs); the authors report that based on 7 trials with 3,450 patients analyzed: *"After 26 weeks of treatment, rivastigmine compared to placebo was associated with better outcomes for cognitive function measured with ADAS-Cog score mean difference -1.79 (95%CI -2.21 to -1.37)."*

TMS is a medical device technology that allows for discrete non-invasive probing and modulation of cortical excitability and functions.[126] Although the exact biological mechanism explaining the effects of rTMS on the brain is still unknown, it has been suggested to involve an increase in synaptic plasticity.[127] TMS treatment is cleared for treatment of refractory depression,[128] migraine headache with aura,[129] and OCD in the US.

The neuroAD Therapy System was developed to provide an additional treatment option for patients with mild to moderate AD, and seeks to improve on prior research by combining TMS with cognitive therapy. As discussed above, TMS is believed to be associated with stimulation induced changes in synaptic plasticity. Consequently, it is believed that TMS may "prime the brain" to be more receptive to cognitive training. TMS treatment paradigms for other illnesses have used a similar approach of combining TMS with environmental stimulus that provoke a response in the targeted area of the brain in order to achieve greater efficacy. Some examples of this approach include TMS treatment of

OCD,[130] alcoholism[131] and other addiction studies,[132] as well as in treatment of PTSD.[133] This recognition of the potential interplay between TMS and cognitive therapy led to the current neuroAD Therapy System.

7.2 Summary of Known and Potential Risks to Health

The potential risks associated with the use of TMS in patients with mild to moderate AD are similar to those associated with use of TMS for treatment of refractory Major Depressive Disorder (MDD), which has been previously cleared by FDA.

The subject neuroAD Therapy System and cleared TMS devices are technologically very similar, though there are key aspects of the treatment by neuroAD System that further lower risk. As previously described, the key energy parameters including the TMS power and number of pulses administered are consistently lower for the neuroAD Therapy System compared to Neuronetics Neurostar TMS Therapy System (K133408) (90% - 110% MT versus 120% MT, and overall 1300 pulses versus overall 3000 pulses per day, respectively). Moreover, the neuroAD Therapy System treatment is spread out over three discrete brain areas per day, unlike other cleared TMS devices, which target a single brain area. Thus, each brain area targeted during treatment with neuroAD Therapy System receives fewer pulses compared to other TMS devices (400 or 500 pulses compared with 3000 pulses).

Lastly, the safety profile of the neuroAD Therapy System has been repeatedly demonstrated in 13 clinical studies across multiple sites.

In the US Pivotal Study, a relatively similar percentage of Active group subjects (41%) and Sham group subjects (32%) experienced adverse events. All adverse events reported that were possibly, probably, or definitely related to the study procedure or study device were mild in severity and resolved within approximately 1 week and often the same day (except for 1 event that lasted 3 weeks). The most commonly reported related adverse events were headache, skin discomfort, and neck pain. In addition, in contrast to approved pharmacotherapies, no subjects the US Pivotal Study discontinued use of neuroAD due to an adverse event.

Furthermore, in the US Pivotal Study all moderate to severe adverse event reports which were reported were determined to be unrelated to the study or to the device.

In the supplemental investigations and commercial use, no device or procedure related SAEs were ever reported. The safety profile was very similar to the US Pivotal Study. Notably, no patient the company is aware of has discontinued treatment with the neuroAD Therapy System due to related adverse events, and compliance with the treatment protocol is high, demonstrating it is well tolerated.

Thus, therapy with the neuroAD Therapy System is associated with a very similar safety profile compared to the sham treatment and the device did not cause any serious adverse events. Events considered related to the study device or procedure were always mild and transient.

It is noted that the neuroAD Therapy System is intended to treat an older patient population than TMS devices for refractory MDD. However, even prior to the Pivotal Study of the neuroAD Therapy System, active TMS had already been demonstrated to be safe for use in an elderly population similar in age to the neuroAD Therapy System target population in multiple published studies (Milev

et al. (2009),[134] Moser et al., (2002).[135] Moreover, a recent meta-analysis reviewed TMS treatment for geriatric depression (Sabesan et al., 2015)[136] and assessed the evidence regarding safety in the geriatric population of these studies. The authors reported that *"a consistent observation supporting a high degree of tolerability and safety among the elderly patients emerged across the Randomized Controlled Trials and the uncontrolled trials."* Thus, there is no increased risk associated with use in an older population, as would be expected with AD.

In conclusion, the device has demonstrated a highly favorable and benign safety profile.

7.3 Summary of Benefits

As noted above, there are no FDA-cleared or approved devices indicated for the treatment of AD. In addition, alternative treatment methods for AD offer limited benefits to patients. The neuroAD Therapy System treatment represents a novel approach to AD treatment. The available clinical data from the US Pivotal Study and supplemental studies support the effectiveness of the device in treating AD.

7.3.1 Pivotal Study Efficacy Data

As detailed above in **Section 6.2.2.6** and **6.2.2.7**, although the original primary endpoint assessing mean change in ADAS-Cog at 7 weeks was not achieved in the overall study population, a prospectively-defined analysis of the interaction between baseline ADAS-Cog and ADAS-Cog outcome revealed a strong correlation between baseline ADAS-Cog and clinical outcome. The indicated population was therefore defined as subjects with baseline ADAS-Cog ≤ 30, representing 85% of the study cohort, which were identified to benefit more consistently from the treatment. For discussion purposes, this group is referred to as the Baseline ADAS-Cog ≤ 30 Subgroup.

For the Baseline ADAS-Cog ≤ 30 Subgroup, at 7 weeks the difference between the neuroAD Therapy System treatment and the Sham with respect to the ADAS-Cog or ADCS-CGIC was not significant.

However, by 12 weeks, the Active group outperformed the Sham group in both scales, both independently as well as jointly:

- With respect to ADAS-Cog score, Active was favored by -1.61 for the PE Population and -1.79 for PP Population (p-value = 0.077 and 0.049, respectively).
    - Furthermore, 31% of Active patients improve by at least -4 points (compared with 11.8-58% for typical ChEI), 40% improve by at least -3 points, and 70% either improve or do not deteriorate (compared with 34.5-87% for typical ChEI).
- With respect to ADCS-CGIC, Active was favored over Sham by -0.40 for the PE Population and -0.45 for PP (Wilcoxon test = 0.10 and 0.074, respectively; Chi-square test = 0.041 and 0.035, respectively).
    - Furthermore, only 5 out of 42 (11.9%) subjects worsened in the treatment group versus 14 out of 35 (40.0%) that worsened subjects in the Sham group. This difference was statistically significant (p<0.01, two-sided Fisher's exact test).
- When considering a post-hoc dual end point analysis (combining subjects' performance on both ADAS-Cog and ADCS-CGIC), the Active arm of the Baseline ADAS-Cog ≤ 30 Subgroup

outperforms the Sham arm, and this difference is statistically significant (Fisher's Exact test p-value = 0.0463). 64.3% of the Active group either improved or did not change both on ADAS-Cog and ADCS-CGIC compared to 42.9% of the Sham group. In addition, only 7.1% of the Active reported worsening on both measures compared to 22.9% of the Sham group.

Figure 45: Mean Change in ADAS-Cog from Baseline to Weeks 7 and 12, US Pivotal Study (Baseline ADAS-Cog ≤30 Subgroup)

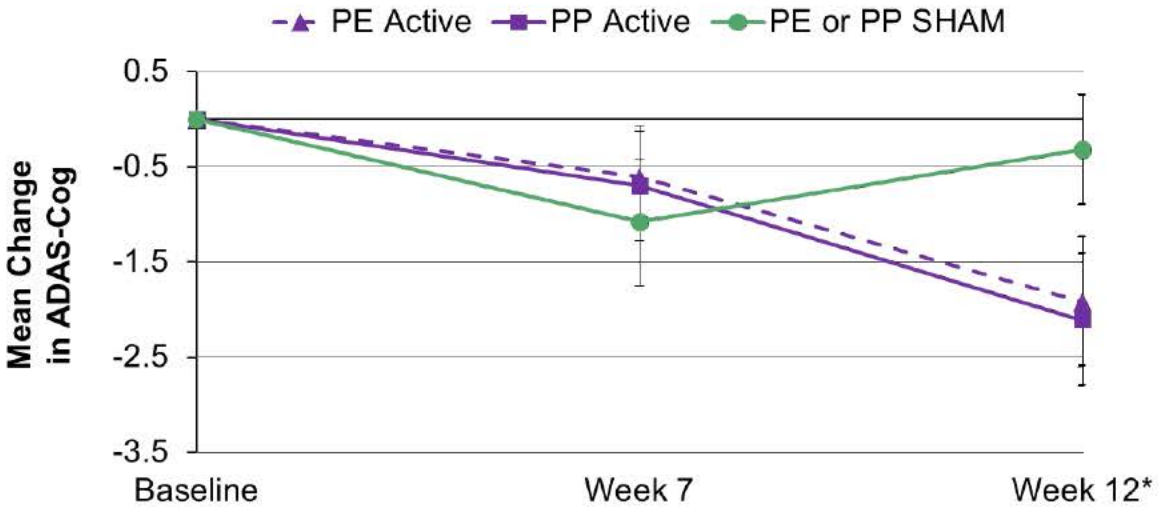
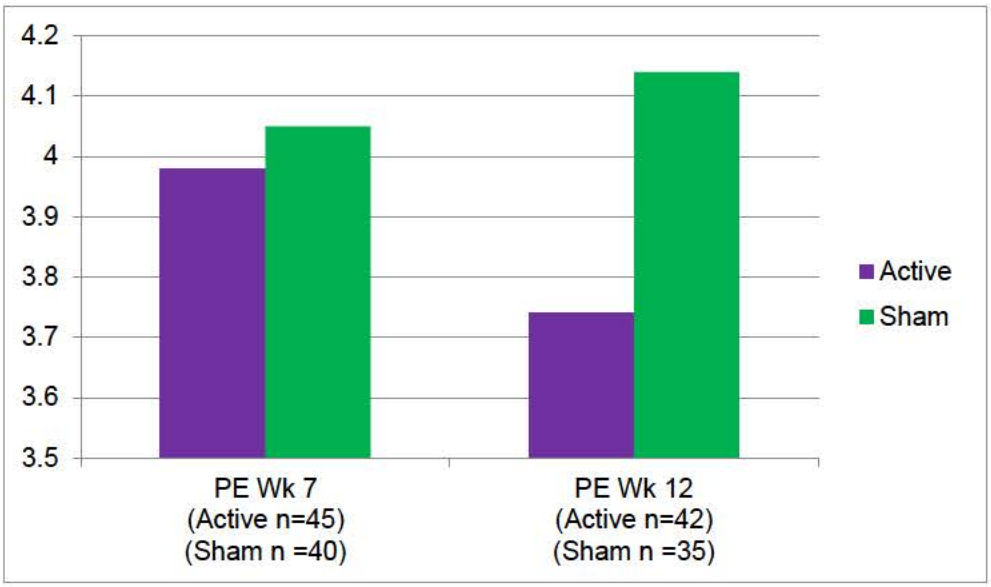


Figure 46: ADCS-CGIC Score by Visit and Study Group, US Pivotal Study (Baseline ADAS-Cog ≤30 Subgroup)



The above-listed positive outcomes, both in cognitive (ADAS-Cog) as well as functional (ADCS-CGIC) scales, provide clear evidence for the efficacy of the neuroAD Therapy System. As explained further below, these effects are on par with those of FDA-approved drugs for treatment of mild to

moderate AD, while neuroAD therapy brings additive value, by being adjunctive to those FDA-approved treatments.

7.3.2 Supporting Studies and Meta-Analysis

The results in the US Pivotal Study for the Baseline ADAS-Cog ≤ 30 Subgroup are primarily supported by the Korean Pilot and Pivotal Studies. Those studies were conducted independently of Neuronix, and employed a highly similar protocol to the US Pivotal. As noted in **Section 6.3** the Korean Pilot Study enrolled patients with baseline ADAS-Cog above and below 30. The independent investigators in these studies also concluded that the milder subset of patients with lower baseline severity were more likely to benefit based on the results of their Pilot Study, as reported in the study publication.[137] Subsequently, the investigators restricted their Pivotal Study population to patients with baseline ADAS-Cog of 17-30, which matches the proposed indicated subgroup population from the US Pivotal Study. Thus, this study can serve as an independent confirmatory study to validate the Baseline ADAS-Cog ≤ 30 Subgroup. The determinations that milder patients are more likely to benefit from treatment and that the cut-off to confirm this theory should be baseline ADAS-Cog ≤30 were made independent of Neuronix and prior to the US Pivotal Study results being available.

Results of both studies (Korean Pilot and Korean Pivotal) showed positive outcomes (Active group outperformed Sham group) at both time points: both at 7 weeks (differences of -2.43 and -2.54, favoring Active, for Korean Pilot and Korean Pivotal, respectively) and at 12 weeks (differences of -1.70 and -1.73, favoring Active, for Korean Pilot and Korean Pivotal, respectively).

These results further reinforce the conclusion that the Baseline ADAS-Cog ≤ 30 Subgroup is a clinically justified subgroup that benefits from device treatment.

Furthermore, a meta-analysis of the US Pivotal Study coupled with the two Korean studies was performed. For the Baseline ADAS-Cog ≤ 30 Subgroup, the Active group outperformed the Sham group at both time points: at 7 weeks, the Active group outperformed the Sham group by -1.21 (95% CI: -3.53 to 1.12, p-value = 0.31); and at 12 weeks, the Active group significantly outperformed the Sham group by -1.66 (95% CI: -3.03 to -0.29, p-value = 0.017). Conversely, when considering SMD (Standardized Mean Difference), the Active group outperformed the Sham group by -0.40 (95% -0.76 to -0.04, p-value = 0.028).

7.3.3 Discussion of Benefits

7.3.3.1 Improvement in ADAS-Cog is Clinically Meaningful

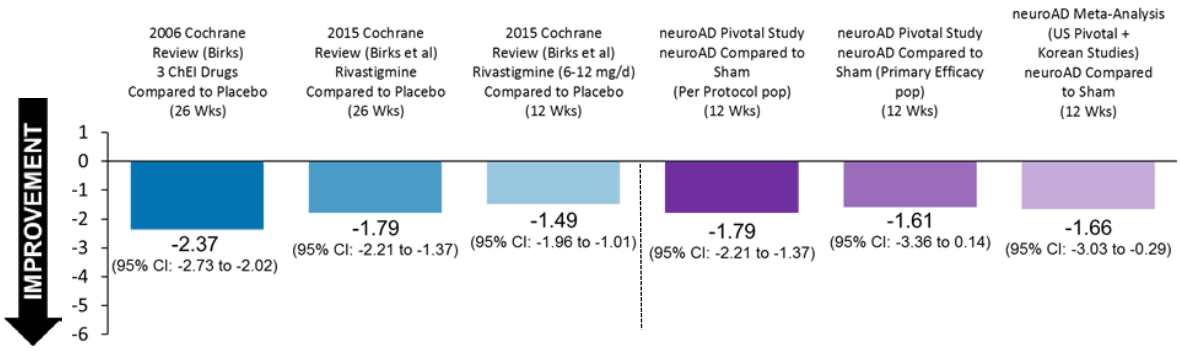
A definitive minimal clinically important difference (i.e., MCID) for change in ADAS-Cog has not been established in the academic literature. Nevertheless, some literature, such as the publication by Schrag et al., discusses a 3-point difference as being meaningful when considering AD deterioration.[138] The company does not believe that the Schrag conclusion is applicable to the discussion of the benefit of the neuroAD Therapy System due to limitations described by the authors in the article. First, Schrag measured clinical change over a 6-month period, not 12 weeks; a similar analysis over a shorter period of 12 weeks would be expected to result in a smaller effect size and thus a lower threshold. Second, Schrag measures natural deterioration and the authors indicate that the conclusions may not be appropriate for improvement in AD. This important point has been further validated by a more recent publication of a larger sample size, by Rockwood et al. (2017).[139] In that publication, the authors investigated the clinical meaningfulness of change in ADAS-Cog at 6

months, and concluded that they *"found no cut-off point on the ADAS-Cog that optimally classified patients in respect of their clinical response."* Moreover, a letter authored by Oremus[140] published in *Alzheimer's and Dementia* concluded that no threshold for clinically meaningful change in ADAS-Cog could be cited as a possible, validated threshold for clinically meaningful change.

In the absence of a consensus in the published literature of an accepted MCID for ADAS-Cog, the strongest evidence of what is considered a clinically meaningful change comes from FDA-approved pharmacologic therapies to treat mild to moderate Alzheimer's disease, which are widely used. Multiple approved drug treatments and dosages for AD have demonstrated a similar (approximately 2 point) change in ADAS-Cog to neuroAD.

Figure 47 below shows the change in ADAS-Cog reported for approved drugs (cholinesterase inhibitors) from two recent Cochrane reviews.[141] The first Cochrane review (2006) concluded that ChEI drugs produced an improvement on average of -2.37 points on the ADAS-Cog scale (95% CI: -2.73 to -2.02). A more recent Cochrane review (2015) concluded that Rivastigmine (one of the approved ChEI drugs) produced an improvement on average of -1.49 (95% CI: -1.96 to -1.01) at a 12 week time point and -1.79 (95%CI: -2.21 to -1.37) at a 26 week time point. These results are similar to the results of the neuroAD in the Baseline ADAS-Cog ≤ 30 Subgroup at 12 weeks in the US Pivotal and Korean studies (-1.79 to -1.61). Due to a number of factors, including the systemic effect of drugs vs. the local/physical effect of medical devices, the complexity of designing and recruiting for device trials (e.g., randomization, control group, blinding, etc.), and different regulatory standards for approval, it is well-recognized [142] that clinical studies to support approval of pharmaceuticals are typically far larger than device studies, especially for low risk *de novo* devices. An analysis of the 25 most recent *de novo* clearances for intervention medical devices which included a clinical study and where a Decision Summary was available showed an average study size of approximately 150 patients (active and control). Regardless of this difference, the magnitude of the effect seen in ADAS-Cog for neuroAD was similar to drugs and the sample size of the neuroAD US Pivotal Study was sufficient to detect this 2-point difference.

Figure 47: ADAS-Cog Performance for Approved AD Drugs Compared to ADAS-Cog Performance for the neuroAD Baseline ADAS-Cog ≤ 30 Subgroup



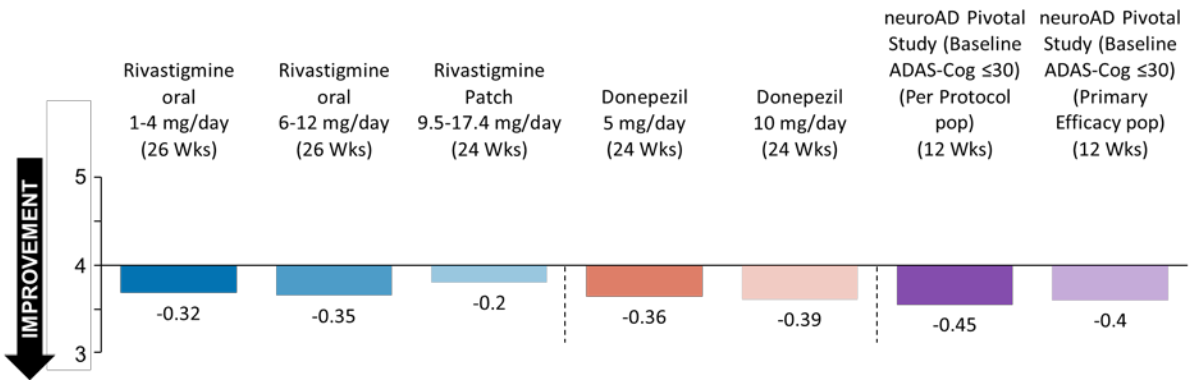
Thus, FDA has recognized that even for a primary treatment modality, such as drug treatments, an approximately 2-point change (or even less) on ADAS-Cog may be clinically useful. For a low risk adjunctive treatment such as the neuroAD, one would expect an even lower threshold to be acceptable; however, the neuroAD has shown results which are similar to monotherapies. Confirming the relevance of this level of improvement, in a survey of 200 US neurologists and psychiatrists, nearly 50% of respondents reported that they would consider a -1 point improvement

(or less, as long as there is no deterioration) in ADAS-Cog score clinically meaningful. Approximately 77% of physicians said they would consider at least a -2 point improvement clinically meaningful. See **Appendix 4** for the report of the survey.

In addition, in terms of responders, 31% of Active neuroAD patients improve by at least -4 points on ADAS-Cog (compared with 11.8-58% for typical ChEI), 40% improve by at least -3 points, and 70% either improve or do not deteriorate (compared with 34.5-87% for typical ChEI).

Furthermore, when considering what a clinically meaningful change is in AD, it is important to consider clinical outcomes measured on a functional scale such as CGIC. **Figure 48** below shows the change in CGIC reported for approved ChEI drugs from their respective Package Inserts.[143] All of the approved drugs show benefits ranging from -0.20 to -0.35 in CGIC. The ADCS-CGIC results associated with the neuroAD (US Pivotal results of -0.40) were either on par with or better than the approved drugs.

Figure 48: CGIC Performance for Approved AD Drugs Compared to CGIC Performance for neuroAD Baseline ADAS-Cog ≤ 30 Subgroup



As the CGIC is applied along with the demonstration of cognitive benefit, any positive effect on the CGIC is clinically meaningful by definition and an indicator of meaningful cognitive effect as well. In the context of Alzheimer's disease clinical trials, in the presence of a statistically significant cognitive effect on an approved and protocol-designated multi-item cognitive test, e.g., the ADAS-Cog, any statistically significant, positive effect on the ADCS-CGIC would be considered an indicator of clinical meaning.

Recognizing the difficulty of developing therapies to treat AD, in an open letter published recently by ResearchersAgainstAlzheimer's, leading AD researchers have advocated that FDA not establish a threshold so high that it would interfere with the availability of new treatments.[144] Researchers have also proposed alternative regulatory approaches to Alzheimer's disease treatment development, such as conditional approval, as a result of the challenges that have faced the over 400 failed drug compounds to date.[145] This is consistent with FDA's recently issued guidance on drug development for Alzheimer's disease, which supports a flexible approach to establishing benefit, particularly in earlier stages of disease.[146]

All of the above points indicate that an approximately 2-point improvement in ADAS-Cog for neuroAD therapy, when coupled with -0.40 improvement on ADCS-CGIC scale, is clinically meaningful, and even more so when achieved on top of the current SOC.

7.3.3.2 Clinical Meaningfulness of AD Patients with Baseline ADAS-Cog ≤30

FDA has commented that the specific baseline ADAS-Cog ≤30 threshold was identified through post-hoc analysis of the US Pivotal Study. While this is correct, there are several important reasons why this subgroup is scientifically justified, and why patients with baseline ADAS-Cog ≤ 30 represent a clinically defined group.

The Statistical Analysis Plan (SAP) prospectively included baseline ADAS-Cog as a covariate to assess interaction with efficacy outcome. This analysis revealed a statistically significant interaction between treatment group outcome at 7 weeks and baseline ADAS-Cog score (p-value = 0.029). This interaction was even more pronounced at 12 weeks (p-value = 0.0072).

This strong interaction indicates a non-homogeneous effect across different baseline values. Although a specific cut-off for baseline ADAS-Cog was not pre-specified, a cut-off of 30 was selected based on published literature. For example, Rutherford et al.[147] conducted a TMS intervention study on AD patients, and concluded that patients with baseline ADAS-Cog ≤ 30 responded better to the intervention than patients with baseline ADAS-Cog > 30. Ito et al.[148] performed a meta-analysis on 52 AD studies (including approximately 20,000 AD patients) and found that baseline ADAS-Cog is a significant covariate affecting the rate of disease progression, and that more demented patients (i.e., patients with baseline ADAS-Cog > 30) deteriorate faster than less affected patients (i.e., patients with baseline ADAS-Cog ≤ 30).

As such, Neuronix performed a subgroup analysis for subjects with baseline ADAS-Cog ≤ 30, representing 85% of the study cohort.

Analyzing the data among subjects with baseline ADAS-Cog scores ≤30 at 7 weeks showed that both Active and Sham groups improved, with a small and non-significant difference (Active = -0.61 and -0.70 for PE and PP, respectively; Sham = -1.08 for PE and PP). At 12 weeks in the Baseline ADAS-Cog ≤ 30 Subgroup, the Active group continued to improve while the Sham group deteriorated towards baseline (Active = -1.92 and -2.11 for PE and PP, respectively; Sham = -0.32 for PE and PP). In terms of between-group difference for mean change in ADAS-Cog at 12 weeks, the Active group significantly outperformed the Sham group in the PP Population (difference -1.79, p-value = 0.049) and neared statistical significance in the PE Population (difference -1.61, p-value =0.07).

In addition, a cut-off of 30 is supported by review of the data related to cognitive training performance, and baseline Motor Threshold which guides the TMS power setting. The maximum level of performance of patients on the neuroAD Cognitive Paradigms was significantly different (p-value < 0.01) between subjects with baseline ADAS-Cog ≤ 30 and subjects with baseline ADAS-Cog > 30, indicating that more demented patients could not engage with and progress through the cognitive training paradigm as well as less severe patients. In addition, analyses showed that patients with lower ADAS-Cog values at baseline had higher baseline Motor Thresholds and therefore, higher TMS power settings. When comparing Motor Threshold values between groups, subjects with baseline ADAS-Cog ≤ 30 have significantly higher Motor Threshold values than subjects with baseline ADAS-Cog > 30 (p-value = 0.0028). Thus, more seriously affected patients are potentially less likely to benefit from both the cognitive training component and TMS component of neuroAD treatment.

Moreover, as discussed above, the Active group with baseline ADAS-Cog ≤30 demonstrated more reliable improvement than the Active group with baseline ADAS-Cog >30. The LOESS line plots demonstrated that the outcomes for the Baseline ADAS-Cog >30 group, in both study arms, were more variable than the outcomes for Baseline ADAS-Cog ≤30 group and the all subjects group. The area for subjects with Baseline ADAS-Cog >30 is approximately three times wider than the corresponding area for Baseline ADAS-Cog ≤30.

Therefore, based on the available clinical data, the company elected to limit the indicated population to those most likely to benefit, and with less variability in the outcomes.

The subgroup determination has since been confirmed in an independent study performed in Korea using the neuroAD Therapy System. The Korean Pilot enrolled both mild and moderate AD patients. Following the results of that study, the Korean PIs, independently of Neuronix and prior to the US Pivotal Study results being available, concluded that milder patients respond better to the intervention. Consequently, they designed the Korean Pivotal Study to recruit only mild patients with baseline ADAS-Cog ≤30. The Korean Pivotal Study therefore can serve as an independent data set, which was obtained after the completion of the US Pivotal Study, which verifies the positive results of the US Pivotal Study in the Baseline ADAS-Cog ≤ 30 Subgroup.

7.4 Risk-Benefit Conclusions

Per FDA regulations, a *de novo* request should be granted when the probable benefits outweigh the probable risks, provided that special controls can be established. Especially for low risk *de novo* systems and EAP-designated technologies, FDA recognizes that due to technology novelty, initial studies may show relatively small benefit, and that greater uncertainty regarding benefits and risks may be acceptable to patients for such novel devices.

For neuroAD, both direct probable risks (e.g., side effects) as well as indirect probable risks (e.g., foregoing other treatments) are minimal, as the device has been demonstrated to be safe and can be used in conjunction with other therapies. Probable benefits clearly exist, as shown by improvements in both ADAS-Cog and ADCS-CGIC.

It is important to note that the benefit shown in the neuroAD clinical studies is on top of the SOC. The neuroAD Therapy System is particularly beneficial because it can be added to drug therapy and allows use of other treatments in conjunction. In the Pivotal Study PE Population, Active group subjects experienced benefit whether or not they were taking medication.

Given the extremely low risks of the device, even a modest benefit outweighing these risks would be sufficient to meet the statutory standard for clearance of the *de novo* request. However, the totality of the evidence demonstrates that the benefit provided by the device is on par with currently-approved, first line AD drugs, and therefore significantly outweighs its minimal risks.

The availability of this novel, low risk adjunctive device treatment for mild to moderate AD is of critical importance to patients and their families given the lack of new treatment options. Development of a complementary treatment modality that can be added to existing alternatives also supports current efforts to develop multidimensional treatment approaches. The neuroAD offers a treatment method, combining TMS with cognitive therapy that works in an entirely different manner than existing drug therapies and can be added to those therapies without significant adverse effects.

In an open letter published in 2018 by ResearchersAgainstAlzheimer's, leading AD researchers advocated that FDA not establish a threshold so high that it would interfere with the availability of new treatments,[149] recognizing that development in this area requires recognition of incremental improvement as clinically meaningful. This philosophy has led to movement away from the dual endpoint criteria for evaluation of AD treatments. Recent studies have been designed to detect relatively small differences in only one endpoint rather than two. This approach is consistent with FDA standards for approval of *de novo* submissions, which require probable benefit that outweighs probable risk, rather than the more stringent standard that applies to higher risk devices. FDA's guidance on the Expedited Access Pathway (EAP) also supports approval of safe devices that offer modest benefits, recognizing that patient access to safe, innovative therapies in areas of unmet need is critical. Patient and caregiver interviews demonstrating the need for additional treatments and the potential benefit of the neuroAD are included in **Appendix 5**.

Given the potential for a large proportion of the indicated population to experience at least some degree of clinically meaningful benefit with very low potential risk, the data provides strong support that the neuroAD meets the applicable standard for FDA clearance.

8.0 OVERALL CONCLUSIONS

The totality of the evidence submitted in support of the *de novo* for the neuroAD allows the following conclusions:

neuroAD Therapy System is an Extremely Safe Modality

- neuroAD complies with all relevant TMS safety guidelines. With the extensive literature available, TMS is regarded as a safe modality, and has been FDA cleared and in frequent use for over 10 years in what is estimated to be millions of treatments.
- A low rate of device and procedure-related AEs was reported in the US Pivotal Study, all of which were mild in nature and resolved spontaneously.
- No device-related SAEs have been reported with the neuroAD Therapy System, in any of its clinical settings (clinical trials or commercial settings).

neuroAD Therapy System Performance on ADAS-Cog

- The available neuroAD clinical data supports a moderate improvement in the Baseline ADAS-Cog ≤ 30 Subgroup as measured on the ADAS-Cog scale. In the US Pivotal Study, both the PE and PP Active groups reached nearly 2 points improvement at 12 weeks relative to Sham (-1.61 and -1.79, respectively), with near significance in the PE Population (p-value=0.077) and significance in the PP Population (p-value=0.049). Similar results were achieved in two independent studies in Korea that were conducted under protocols that were very similar to the US Pivotal Study protocol. A meta-analysis of the US PE Pivotal Study with the Korean studies provides further evidence that the Active group outperformed the Sham group by -1.66 (95% CI: -3.03 to -0.29, p-value = 0.017).
- In 10 other supplemental studies, the Active group always outperformed the Sham group (or improved relative to baseline in non-controlled studies).

neuroAD Therapy System Performance on ADCS-CGIC

- The US Pivotal Study showed efficacy on the ADCS-CGIC endpoint in the Baseline ADAS-Cog ≤ 30 Subgroup, with difference between Active and Sham groups of -0.45 in the PP Population (p=0.074, Wilcoxon test; p=0.035, Chi-square test) and -0.40 in the PE Population (p=0.10, Wilcoxon test; p=0.041, Chi-square test).
- When considering deterioration, only 11.9% of subjects worsened in the Active group compared with 40% that worsened in the Sham group (statistically significant, p-value<0.01, two-sided Fisher's exact test).

Clinical Meaningfulness on ADAS-Cog and ADCS-CGIC

- A definitive minimal clinically important difference (i.e., MCID) for change in ADAS-Cog has not been established in the academic literature. However, there is evidence supporting that either a 2 point improvement or no deterioration is clinically meaningful.
- In regard to improvement on ADCS-CGIC, by definition, any change on this scale measures clinically meaningful change, per the scientific literature.
- When comparing ADAS-Cog scores, neuroAD Therapy System outcomes are consistent with currently-approved ChEI drugs. When considering also CGIC scores, neuroAD is either consistent with or superior to currently-approved ChEI drugs.

Clinical Validity of the Baseline ADAS-Cog ≤ 30 Subgroup

- Although a specific cut-off for baseline ADAS-Cog was not pre-specified, a cut-off of 30 was selected based on published literature (e.g., Rutherford et al. 2015[150] and Ito et al. 2010[151]). An analysis of interaction between baseline ADAS-Cog and study outcomes was prospectively defined and revealed a statistically significant interaction between treatment

group outcome at 7 weeks and baseline ADAS-Cog score (p-value = 0.029). This interaction was even more pronounced at 12 weeks (p-value = 0.0072).

- Patients with baseline ADAS-Cog ≤30 progressed significantly more with the cognitive training levels, as compared with the more severe patients with baseline ADAS-Cog >30 (p-value < 0.01).
- The data demonstrates that patients with a more severe baseline ADAS-Cog >30 improve with less consistency compared to patients with a baseline score ≤30. Thus, the proposed intended use population is limited to patients with an ADAS-Cog score of up to 30.
- This subgroup was independently confirmed in the Korean Pivotal Study.

Benefit-Risk Determination

- Risks associated with the device are extremely low as evidenced by the US Pivotal Study and all other global clinical experience with the device.
- The assessment of whether the benefits outweigh the risks is a proportional assessment (i.e., very low risk requires only modest benefit to favor clearance).
- Because the device is an adjunctive treatment and addresses an unmet need, a lower threshold for improvement should be expected than for primary therapies.
- Nevertheless, the magnitude of the benefit in ADAS-Cog and CGIC was similar or superior to FDA-approved drugs for treatment of mild to moderate AD.
- The benefits observed are clinically meaningful, and clearly outweigh the minimal risks associated with the device.

Consistent with FDA's goal of incorporating the voice of the patient in its decision-making, Neuronix has included in **Appendix 5** video clips of patients who received neuroAD treatment outside the US. In these and other testimonials, patients explain, for example, that treatment gave them hope, improved their confidence, allowed them to resume their hobbies, and helped them to become more "*like themselves*" again. Patients have stated that they "*would absolutely recommend this treatment without hesitation*" and "*it's made me want to live*." Caregivers and family members have commented that the treatment helped patients to interact with their family and join in conversations. The perspective of the caregiver was also collected and explains that "*there has definitely been an improvement . . . she's back to the way she was before and she had the initiative to go back to painting again*" and that they were "*able to see improvements and he (the patient) is now taking piano lessons. The teacher gives him new pieces that begins to play and remembers. It's very encouraging.*" Until treatments become available that can modify the course of AD, tools like neuroAD that can help to delay progression and improve quality of life for patients and caregivers are urgently needed.

9.0 APPENDICES

The following documents are attached:

Appendix 1	Pivotal Study Protocol
Appendix 2	ADAS-Cog Administration and Scoring Manual
Appendix 3	ADCS-CGIC Scale (Report Forms)
Appendix 4	Physician Survey Report
Appendix 5	Patient Case Example Videos
Appendix 6	Key Publications

10.0 REFERENCES

[1] James BD, Leurgans SE, Hebert LE, Scherr PA, Yaffe K, Bennett DA, Contribution of Alzheimer disease to mortality in the United States. *Neurology*. 2014; 82(12):1045-50.

[2] Dr. Scott Gottlieb, FDA Commissioner, "The FDA recognizes the urgent need for new medical treatments for many serious conditions including neurological disorders such as . . . Alzheimer's disease . . . ." Press Release (Feb 15, 2018).

[3] Lisanby SH, Luber B, Perera T, Sackeim HA, Transcranial magnetic stimulation: applications in basic neuroscience and neuropsychopharmacology. Int J Neuropsychopharmacol. (2000); 3(3):259-273.

[4] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol (2009); 120(12):2008–2039.

[5] Siebner HR, Rothwell J, Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res (2003); 148(1):1–16; and Thickbroom GW, Transcranial magnetic stimulation and synaptic plasticity: experimental framework and human models. Exp Brain Res (2007) 180(4):583–593.

[6] See, e.g., K143531, available at http://www.accessdata.fda.gov/cdrh_docs/pdf14/K143531.pdf.

[7] See K130556 available at http://www.accessdata.fda.gov/cdrh_docs/reviews/K130556.pdf.

[8] See DEN170078 available at https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170078.pdf.

[9] Cotelli M, Calabria M, Manetti R, et al. Improved language performance in Alzheimer disease following brain stimulation. J Neurol Neurosurg Psychiatry 2011 Jul;82(7):794-7; Ahmed M, Darwish E, Khedr E, El serogy Y, Ali A. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. J Neurol (2012) 259:83-92.

[10] http://ir.neuronetics.com/phoenix.zhtml?c=254709&p=irol-newsArticle&ID=2371292.

[11] Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, (2009); 120(12), 2008-2039.

[12] Schutter DJ, van Honk J, A standardized motor threshold estimation procedure for transcranial magnetic stimulation research. J ECT. 2006 22(3):176-8.

[13] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, and the Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009 Dec; 120(12):2008-2039.

Wassermann EM, Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr Clin Neurophysiol. 1998 Jan; 108(1):1-16.

[14] Ito, K et al. Disease progression meta-analysis model in Alzheimer's disease. Alzheimer & Dementia 2010; 6, 39-53.

[15] Schneider LN, et al., Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study, Alzheimer Dis Assoc Disord. 1997; 11 Suppl 2:S22-32.

[16] Simone Rossi, Mark Hallett, Paolo M. Rossini, Alvaro Pascual-Leone, and The Safety of TMS Consensus Group, *Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and Research*; Clin Neurophysiol. 2009 December; 120(12): 2008–2039; doi:10.1016/j.clinph.2009.08.016.

[17] Eric M. Wassermann, *Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996.* Electroencephalography and clinical Neurophysiology 108 (1998) 1–16.

[18] Guidance for Industry and Food and Drug Administration Staff: *Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems*. Document issued on: July 26, 2011.

[19] Rutherford et al., Short and Long-term Effects of rTMS Treatment on Alzheimer's Disease at Different Stages: A Pilot Study, J. Experimental Neuroscience, 2015; 9 43-51.

[20] Ito, K et al. Disease progression meta-analysis model in Alzheimer's disease. Alzheimer & Dementia 2010; 6, 39-53.

[21] Lee et al. Treatment of Alzheimer's Disease with Repetitive Transcranial Magnetic Stimulation Combined with Cognitive Training: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study. J Clin Neurol 2015.

[22] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, and the Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009 Dec; 120(12):2008-2039.

Wassermann EM, Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr Clin Neurophysiol. 1998 Jan; 108(1):1-16.

[23] Lee J et al. Treatment of Alzheimer's Disease with Repetitive Transcranial Magnetic Stimulation Combined with Cognitive Training: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study. J Clin Neurol. 2016 Jan; 12(1):57-64.

[24] Birks J, Cholinesterase inhibitors in Alzheimer's Disease, Cochrane Database of Systemic Reviews 2006; (1): CD005593.

[25] Birks J, Chong LY, and Grimley EJ, Rivastigmine for Alzheimer's disease (Review), Cochrane Database of Systemic Reviews 2015; (9).

[26] https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/21025lbl.pdf. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022083lbl.pdf. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020690s035,021720s008,022568s005lbl.pdf

[27] Vradenburg G, Fillit H, Morgan D, Sabbagh M, Aisen P, & Mohs R, for Researchers Against Alzheimer's. Single Endpoint for New Drug Approvals for Alzheimer's Disease, (May 11, 2017) *available at* https://www.usagainstalzheimers.org/sites/default/files/Researchers-Against-Alzheimer%27s-Endpoints-Analysis-FINAL-5-10-17.pdf**.**

[28] CDRH, CBER, Guidance for Industry and Food and Drug Administration Staff 1 Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications. August 24, 2016. Available at: https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm517504.pdf.

[29] WorldPharmaNews, Alzheimer's experts call for changes in FDA drug approval standards, *available at* http://www.worldpharmanews.com/development/3931-alzheimer-s-experts-call-for-changes-in-fda-drug-approval-standards**.**

[30] Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, Steffens DX, Willis RJ, Wallace RB, Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology (2007); 29(1–2):125–132.

[31] Alzheimer's Association, 2018 Alzheimer's Disease Facts and Figures, available at https://www.alz.org/media/HomeOffice/Facts%20and%20Figures/facts-and-figures.pdf**.**

[32] Alzheimer's Association, 2018 Alzheimer's Disease Facts and Figures, available at https://www.alz.org/media/HomeOffice/Facts%20and%20Figures/facts-and-figures.pdf.
[33] Alzheimer's Association, 2018 Alzheimer's Disease Facts and Figures, available at https://www.alz.org/media/HomeOffice/Facts%20and%20Figures/facts-and-figures.pdf.
[34] CDC, National Vital Statistics Reports, Vol. 66:No. 6 (Nov. 27, 2017) available at https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_06.pdf.
[35] Ito, K et al. Disease progression meta-analysis model in Alzheimer's disease. Alzheimer & Dementia 2010; 6, 39-53.
[36] Schneider LN, et al., Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study, Alzheimer Dis Assoc Disord. 1997; 11 Suppl 2:S22-32.
[37] Leber P, Criteria used by Drug Regulatory Authorities. In: Qizilbash N, Schneider L, Chui H, et al., eds. Evidence-based Dementia Practice. Oxford: Blackwell Science Ltd; 2002; 376-87.
[38] Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. *Alzheimer Disease & Associated Disorders* 1997; 11: 33-9.
[39] Vradenburg G, Fillit H, Morgan D, Sabbagh M, Aisen P, & Mohs R, for Researchers Against Alzheimer's. Single Endpoint for New Drug Approvals for Alzheimer's Disease, (May 11, 2017) *available at* https://www.usagainstalzheimers.org/sites/default/files/Researchers-Against-Alzheimer%27s-Endpoints-Analysis-FINAL-5-10-17.pdf.
[40] Food and Drug Administration, Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry (Feb. 2018) *available at* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596728.pdf.
[41] Alzheimer's Association, 2018 Alzheimer's Disease Facts and Figures, available at https://www.alz.org/media/HomeOffice/Facts%20and%20Figures/facts-and-figures.pdf.
[42] Casey D, Antimisiaris D, and O'Brien J., Drugs for Alzheimer's Disease: Are They Effective? P&T 2010 Apr; 35(4): 208–211.
[43] Birks J., Cholinesterase inhibitors in Alzheimer's Disease, Cochrane Database of Systematic Reviews 2006; (1); CD005593.
[44] Birks J. Chong LT and Grimley EJ, Rivastigmine for Alzheimer's disease (review), Cochrane Database of Systematic Reviews 2105; (9).
[45] https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/21025lbl.pdf.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022083lbl.pdf.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020690s035,021720s008,022568s005lbl.pdf
[46] Spector A, Thorgrimsen L, Woods B, Royan L, Davies S, Butterworth M, Orrell M; Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. Br J Psychiatry (2003); 183:248–254; Onder G, Zanetti O, Giacobini E, Frisoni GB, Bartorelli L, Carbone G, Lambertucci P, Silveri MC, Bernabei R, Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: randomised controlled trial. Br J Psychiatry (2005); 187:450–455; and Foerster S, Buschert VC, Buchholz HG, Teipel SJ, Zach C, Hampel H, Bartenstein P, Buerger K, Positive effects of a 6-month stage-specific cognitive intervention program on brain metabolism in subjects with amnestic mild cognitive impairment (aMCI) and mild Alzheimer's Disease (AD). Alzheimers Dementia (2009); 5(4 Suppl 1):38.
[47] Tárraga L, Boada M, Modinos G, Espinosa A, Diego S, Morera A, Guitart M, Balcells J, Lopez OL, Becker JT, A randomised pilot study to assess the efficacy of an interactive, multimedia tool of cognitive stimulation in Alzheimer's disease. J Neurol Neurosurg Psychiatry (2006); 77(10):1116–1121.
[48] Sitzer DI, Twamley EW, Jeste DV, Cognitive training in Alzheimer's disease: a metaanalysis of the literature. Acta Psychiatr Scand (2006); 114(2):75–90.
[49] Birks J, Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 1:CD005593 (2006).
[50] Reichman W E; Fiocco A J; Rose N S, Exercising the Brain to Avoid Cognitive Decline Examining the Evidence. Aging health. (2010); 6(5):565-584.

[51] Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD003260.
[52] Cummings, J, Morstorg, T & Zhong, K, Alzheimer's disease drug-development pipeline: few candidates, frequent failures, Alzheimer's Research & Therapy, 2014, 6:37 (*available at* https://alzres.biomedcentral.com/track/pdf/10.1186/alzrt269); Janssen Halts Clinical Studies of Alzheimer's Candidate (May 18, 2018), Genetic Engineering & Biotechnology News, *available at* https://www.genengnews.com/news/janssen-halts-clinical-studies-of-alzheimers-candidate/.
[53] Fernandez, C, Clinical Trials in Alzheimer's Disease Are Failing: What Can Be Done? LABIOTECH, *available at* https://labiotech.eu/features/alzheimers-disease-clinical-trials/**;** Garde, D, Series of setbacks raises doubt on the drug industry's next big idea to treat Alzheimer's, STAT, *available at https://www.statnews.com/2018/05/23/alzheimers-bace-trials/***.**
[54] https://www.wsj.com/articles/cures-welcome-at-fda-1520803007.
[55] WorldPharmaNews, Alzheimer's experts call for changes in FDA drug approval standards, *available at* http://www.worldpharmanews.com/development/3931-alzheimer-s-experts-call-for-changes-in-fda-drug-approval-standards**.**
[56] Dr. Scott Gottlieb, FDA Commissioner, "The FDA recognizes the urgent need for new medical treatments for many serious conditions including neurological disorders such as . . . Alzheimer's disease . . . ." Press Release (Feb 15, 2018).
[57] Alzheimer's Association, 2018 Alzheimer's Disease Facts and Figures, available at https://www.alz.org/media/HomeOffice/Facts%20and%20Figures/facts-and-figures.pdf**.**
[58] Lisanby SH, Luber B, Perera T, Sackeim HA, Transcranial magnetic stimulation: applications in basic neuroscience and neuropsychopharmacology. Int J Neuropsychopharmacol. (2000); 3(3):259-273.
[59] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol (2009); 120(12):2008–2039.
[60] Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, (2009); *120*(12), 2008-2039.
[61] Groppa, S., et al. A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, (2012); *123*(5), 858-82.
[62] Mantovani A, Lisanby SH, Applications of transcranial magnetic stimulation to therapy in psychiatry. Psychiatric Times 21(9); and George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, Anderson B, Nahas Z, Bulow P, Zarkowski P, Holtzheimer PE 3rd, Schwartz T, Sackeim HA (2010) Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry (2004); 67(5):507–516.
[63] Siebner HR, Rothwell J, Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res (2003); 148(1):1–16; and Thickbroom GW, Transcranial magnetic stimulation and synaptic plasticity: experimental framework and human models. Exp Brain Res (2007); 180(4):583–593.
[64] See, e.g., K143531, available at http://www.accessdata.fda.gov/cdrh_docs/pdf14/K143531.pdf**.**
[65] See K130556 available at http://www.accessdata.fda.gov/cdrh_docs/reviews/K130556.pdf**.**
[66] See DEN170078 available at https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170078.pdf**.**
[67] http://ir.neuronetics.com/phoenix.zhtml?c=254709&p=irol-newsArticle&ID=2371292**.**
[68] Cooke SF, Bliss TV, Plasticity in the human central nervous system. Brain (2006); 239(Pt 7):1659–1673.
[69] Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann EM, Repella JD, Danielson AL, Willis MW, Benson BE, Speer AM, Osuch E, George MS, Post RM, Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. Biol Psychiatry (1999); 46(12):1603–1613.
[70] Guse B, Falkai P, Wobrock T, Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. J Neural Transm (2010); 117(1):105–122.

[71] Moser DJ, Jorge RE, Manes F, Paradiso S, Benjamin ML, Robinson RG, Improved executive functioning following repetitive transcranial magnetic stimulation. Neurology. (2002); 58(8):1288-1290.
[72] O'Connor MG, Jerskey BA, Robertson EM, Brenninkmeyer C, Ozdemir E, Leone AP, The effects of repetitive transcranial magnetic stimulation (rTMS) on procedural memory and dysphoric mood in patients with major depressive disorder. Cogn Behav Neurol. (2005); Dec; 18(4):223-7.
[73] Ahmed MA, Darwish ES, Khedr EM, El Serogy YM, Ali AM. (2012) Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. J Neurol. 259(1):83-92.
[74] Freitas C, Mondragon-Llorca H, Pascual-Leone A, Noninvasive brain stimulation in Alzheimer's disease: Systematic review and perspectives for the future. Exp Gerontol. (2011); 46: 611–627.
[75] Cotelli M, Manenti R, Cappa SF, Geroldi C, Zanetti O, Rossini PM, Miniussi C, Effect of transcranial magnetic stimulation on action naming in patients with Alzheimer disease. Arch Neurol (2006); 63(11):1602–1604.
[76] Cotelli M, Manenti R, Cappa SF, Geroldi C, Zanetti O, Rossini PM, Miniussi C, Effect of transcranial magnetic stimulation on action naming in patients with Alzheimer disease. Arch Neurol (2006); 63(11):1602–1604.
[77] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, and the Safety of TMS Consensus Group, Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009 Dec; 120(12):2008-2039.
Wassermann EM, Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr Clin Neurophysiol. 1998 Jan; 108(1):1-16.
[78] NeuroStarTM System for Major Depressive Disorder; 510(k) K061053, Neurological Devices FDA Advisory Panel Meeting Package, Sponsor Executive Summary. Available at http://web.archive.org/web/20100323091111/http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4273b1_02-SponsorExecutiveSummary.pdf.
[79] Ahdab R, Ayache SS, Brugières P, Goujon C, Lefaucheur JP, Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression. Neurophysiol Clin. 2010 Mar; 40(1):27-36.
[80] Siebner HR, Rothwell J, Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res (2003); 148(1):1–16; and Thickbroom GW, Transcranial magnetic stimulation and synaptic plasticity: experimental framework and human models. Exp Brain Res (2007); 180(4):583–593.
[81] See Brainways' Brainsway DTMS System for adjunctive treatment OCD (DEN170078), which combines TMS with individualized provocation.
[82] Tendler, A., Roth, Y., Barnea-Ygael, N., Zangen, A. How to Use the H1 Deep Transcranial Magnetic Stimulation Coil for Conditions Other than Depression. J. Vis. Exp. (2017); (119), e55100, doi: 10.3791/55100.
[83] Dinur-Klein L et al., Smoking Cessation Induced by Deep Repetitive Transcranial Magnetic Stimulation of the Prefrontal and Insular Cortices: A Prospective, Randomized Controlled Trial, Biological Psychiatry, (Nov. 2014); Vol 76; Issue 9.
[84] Isserle M et al., Effectiveness of Deep Transcranial Magnetic Stimulation Combined with a Brief Exposure Procedure in Post-Traumatic Stress Disorder – A Pilot Study, Brain Stimulation, (May 2013); Vol 6; Issue 3.
[85] Schutter DJ, van Honk J, A standardized motor threshold estimation procedure for transcranial magnetic stimulation research. J ECT. 2006 22(3):176-8.
[86] Guidance for Industry and Food and Drug Administration Staff: *Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems*. Document issued on: July 26, 2011.
[87] Lee et al. Treatment of Alzheimer's Disease with Repetitive Transcranial Magnetic Stimulation Combined with Cognitive Training: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study. J Clin Neurol 2015.
[88] Ito, K et al. Disease progression meta-analysis model in Alzheimer's disease. Alzheimer & Dementia 2010; 6, 39-53.

[89] Keel JC, Smith MJ, Wassermann EM, A safety screening questionnaire for transcranial magnetic stimulation. Clin Neurophysiol. 2001 Apr; 112(4):720.
[90] Schutter DJ, van Honk J, A standardized motor threshold estimation procedure for transcranial magnetic stimulation research. J ECT. 2006; 22(3):176-8.
[91] John P. O'Reardon, H. Brent Solvason, Philip G. Janicak, Shirlene Sampson, Keith E. Isenberg, Ziad Nahas, William M. McDonald, David Avery, Paul B. Fitzgerald, Colleen Loo, Mark A. Demitrack, Mark S. George, and Harold A. Sackeim, *Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial*, BIOL PSYCHIATRY 2007; 62:1208–1216; doi:10.1016/j.biopsych.2007.01.018.
[92] Yechiel Levkovitz, Moshe Isserles, Frank Padberg, Sarah H. Lisanby, Alexander Bystritsky, Guohua Xia, Aron Tendler, Zafiris J. Daskalakis, Jaron L. Winston, Pinhas Dannon, Hisham M. Hafez, Irving M. Reti, Oscar G. Morales, Thomas E. Schlaepfer, Eric Hollander, Joshua A. Berman, Mustafa M. Husain, Uzi Sofer, Ahava Stein, Shmulik Adler, Lisa Deutsch, Frederic Deutsch, Yiftach Roth, Mark S. George and Abraham Zangen, *Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial*, World Psychiatry, February 2015; Volume 14, Issue 1, pages 64–73; DOI: 10.1002/wps.20199.
[93] Simone Rossi, Mark Hallett, Paolo M. Rossini, Alvaro Pascual-Leone, and The Safety of TMS Consensus Group, *Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and Research*, Clin Neurophysiol. 2009 December; 120(12): 2008–2039; doi:10.1016/j.clinph.2009.08.016.
[94] Eric M. Wassermann, *Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996*, Electroencephalography and clinical Neurophysiology (1998); 108 1–16.
[95] Guidance for Industry and Food and Drug Administration Staff: *Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems*. Document issued on: July 26, 2011.
[96] Pascual-Leone A1, Valls-Solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain. 1994 Aug; 117 (Pt 4):847-58; Hallett M. Transcranial magnetic stimulation: a primer. Neuron. 2007 Jul 19; 55(2):187-99; Huang YZ et al. Plasticity induced by non-invasive transcranial brain stimulation: A position paper. Clin Neurophysiol. 2017 Nov; 128(11):2318-2329; & Tang AD et al. Low intensity repetitive transcranial magnetic stimulation modulates skilled motor learning in adult mice. Sci Rep. 2018 Mar 5; 8(1):4016.
[97] Cotelli M, Calabria M, Manetti R, et al. Improved language performance in Alzheimer disease following brain stimulation. J Neurol Neurosurg Psychiatry 2011 Jul;82(7):794-7; Ahmed M, Darwish E, Khedr E, El serogy Y, Ali A. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. J Neurol (2012) 259:83-92.
[98] Serge Gauthier, *Clinical Diagnosis and Management of Alzheimer's Disease*, 2007; Third Edition.
[99] Ito, K et al. Disease progression meta-analysis model in Alzheimer's disease. Alzheimer & Dementia 2010; 6, 39-53; Rutherford et al., Short and Long-term Effects of rTMS Treatment on Alzheimer's Disease at Different Stages: A Pilot Study, J. Experimental Neuroscience, 2015, 9 43-51.
[100] Rutherford et al., Short and Long-term Effects of rTMS Treatment on Alzheimer's Disease at Different Stages: A Pilot Study, J. Experimental Neuroscience, 2015, 9 43-51.
[101] Ito, K et al. Disease progression meta-analysis model in Alzheimer's disease. Alzheimer & Dementia 2010, 6, 39-53.
[102] Aricept label – https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020690s039,021720s012,022568s008lbl.pdf Exelon label - https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/21025lbl.pdf
[103] Giovanna Alagona, Rita Bella, Raffaele Ferri, Anna Carnemolla, Alessandra Pappalardo, Erminio Costanzo, Giovanni Pennisi, *Transcranial magnetic stimulation in Alzheimer disease: motor cortex excitability and cognitive severity*, Neuroscience Letters (2001); 314 57–60.
[104] Giovanna Alagona, Raffaele Ferri, Salvatore Greco, Domenico Santonocito, Alessandra Pappalardo, Rita Bella, Giovanni Pennisi, *Motor cortex excitability in Alzheimer disease: one year follow-up study*, Neuroscience Letters 329 (2002); 293–296.

[105] V Di Lazzaro, A Oliviero, F Pilato, E Saturno, M Dileone, C Marra, A Daniele, S Ghirlanda, G Gainotti, P A Tonali, *Motor cortex hyperexcitability to transcranial magnetic stimulation in Alzheimer's disease,* J Neurol Neurosurg Psychiatry 2004; 75:555–559.
[106] Florinda Ferreri, MD, Flavia Pauri, MD, PhD, Patrizio Pasqualetti, PhD, Rita Fini, Tech, Gloria Dal Forno, MD, and Paolo Maria Rossini, MD, PhD, *Motor cortex excitability in Alzheimer's disease: A transcranial magnetic stimulation study*, Annals of Neurology, January 2003; 53(1):102-8.
[107] Lee et al. Treatment of Alzheimer's Disease with Repetitive Transcranial Magnetic Stimulation Combined with Cognitive Training: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study. J Clin Neurol 2015.
[108] Lee J, Choi BH, Oh E, Sohn EH, Lee AY, Treatment of Alzheimer's Disease with Repetitive Transcranial Magnetic Stimulation Combined with Cognitive Training: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study, J Clin Neurol. 2016 Jan; 12(1):57-64. doi: 10.3988/jcn.2016.12.1.57. Epub 2015 Sep 11.
[109] J. Cohen, Statistical Power Analysis for the Behavioral Sciences, (Routledge 1988), 2nd edn.
[110] L.V. Hedges, I. Olkin, Statistical Methods for Meta-Analysis (1985; Academic Press, New York).
[111] Aricept label – https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020690s039,021720s012,022568s008lbl.pdf Exelon label - https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/21025lbl.pdf
[112] Bentwich et al., *Beneficial effect of repetitive magnetic stimulation combined with cognitive training for treatment of Alzheimer's Disease: a proof of concept study*. J. Neural Trans (2011); 118: 462-471.
[113] Rabey et al., *Repetitive transcranial stimulation combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's Disease: a randomized, double-blind study*. J. Neural Trans (2013); 120(5): 813-9.
[114] Pascual-Leone et al., *Combined cognitive training and repetitive transcranial magnetic stimulation (rTMS) in Alzheimer's disease: a proof-of-principle, randomized, sham-controlled clinical trial* [Pending full publication].
[115] *Effects of a Combined TMS Stimulation and Cognitive Training in Alzheimer Patients: a single-center, randomized, double-blind, placebo-controlled study*. [Not published].
[116] *Repetitive transcranial magnetic stimulation (rTMS) combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: Clinical Experience* [Not published].
[117] Jean-Paul Nguyen et al., *Repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease*; Clinical Neurophysiology (2017); 47, 47-53.
[118] Paolo Rossini et al. *Cognitive Rehabilitation Combined with Transcranial Magnetic Stimulation (using NeuroAD System) in Patients with Mild to Moderate Alzheimer's Dementia: a single-center, randomized, double-blind, sham-controlled.*
[119] Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, Steffens DX, Willis RJ, Wallace RB (2007) Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 29(1–2):125–132.
[120] Alzheimer's Association, 2018 Alzheimer's Disease Facts and Figures, available at https://www.alz.org/media/HomeOffice/Facts%20and%20Figures/facts-and-figures.pdf**.**
[121] Alzheimer's Association, 2018 Alzheimer's Disease Facts and Figures, available at https://www.alz.org/media/HomeOffice/Facts%20and%20Figures/facts-and-figures.pdf**.**
[122] Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD003260.
[123] Casey D, Antimisiaris D, and O'Brien J., Drugs for Alzheimer's Disease: Are They Effective? P&T 2010 Apr; 35(4): 208–211.
[124] Birks J. Cholinesterase inhibitors in Alzheimer's Disease, Cochrane Database of Systematic Reviews 2006; (1); CD005593.
[125] Birks J. Chong LT and Grimley EJ, Rivastigmine for Alzheimer's disease (review), Cochrane Database of Systematic Reviews 2015; (9).
[126] Lisanby SH, Luber B, Perera T, Sackeim HA, Transcranial magnetic stimulation: applications in basic neuroscience and neuropsychopharmacology. Int J Neuropsychopharmacol. (2000); 3(3):259-273.

[127] Siebner HR, Rothwell J, Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res (2003); 148(1):1–16; and Thickbroom GW, Transcranial magnetic stimulation and synaptic plasticity: experimental framework and human models. Exp Brain Res (2007); 180(4):583–593.
[128] See, e.g., K143531, available at https://www.accessdata.fda.gov/cdrh_docs/pdf14/K143531.pdf.
[129] See K130556 available at https://www.accessdata.fda.gov/cdrh_docs/reviews/K130556.pdf.
[130] See Brainways' Brainsway DTMS System for adjunctive treatment OCD (DEN170078), which combines TMS with individualized provocation.
[131] Tendler, A., Roth, Y., Barnea-Ygael, N., Zangen, A. How to Use the H1 Deep Transcranial Magnetic Stimulation Coil for Conditions Other than Depression. J. Vis. Exp. (2017); (119), e55100, doi: 10.3791/55100.
[132] Dinur-Klein L et al., Smoking Cessation Induced by Deep Repetitive Transcranial Magnetic Stimulation of the Prefrontal and Insular Cortices: A Prospective, Randomized Controlled Trial, Biological Psychiatry, (Nov. 2014); Vol 76; Issue 9.
[133] Isserle M et al., Effectiveness of Deep Transcranial Magnetic Stimulation Combined with a Brief Exposure Procedure in Post-Traumatic Stress Disorder – A Pilot Study, Brain Stimulation, (May 2013); Vol 6; Issue 3.
[134] Milev R, Abraham G, Hasey G, Cabaj JL, Repetitive Transcranial Magnetic Stimulation for Treatment of Medication-Resistant Depression in Older Adults. Journal of ECT (2009); 25(1):44-9.
[135] Moser DJ, Jorge RE, Manes F, Paradiso S, Benjamin ML, Robinson RG, Improved executive functioning following repetitive transcranial magnetic stimulation. Neurology. (2002); 58(8):1288-1290.
[136] Sabesan et al. Transcranial magnetic stimulation for geriatric depression: Promises and pitfalls. World J Psychiatr, 2015 June 22; 5(2): 170-181.
[137] Lee et al. Treatment of Alzheimer's Disease with Repetitive Transcranial Magnetic Stimulation Combined with Cognitive Training: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study. J Clin Neurol 2015.
[138] Schrag et. al., What is the Clinically Relevant Change on the ADAS-Cog?, J Neurol Neurosurg Psychiatry 2012; 83:171-173.
[139] Rockwood et al., Clinical meaningfulness of Alzheimer's Disease Assessment Scale-Cognitive subscale change in relation to goal attainment in patients on cholinesterase inhibitors, Alzheimer's Dement. 2017 Oct; 13(10):1098-1106.
[140] Oremus, M., Does the Evidence Say a 4-point Change in ADAS-Cog Score is Clinically Significant? Alzheimer's & Dementia 10 (2014); 416-417.
[141] Birks J. Cholinesterase inhibitors in Alzheimer's Disease, Cochrane Database of Systematic Reviews 2006; (1); CD005593.
Birks J. Chong LT and Grimley EJ, Rivastigmine for Alzheimer's disease (review), Cochrane Database of Systematic Reviews 2015; (9).
[142] Gelijns AC, editor, FDA Training Presentation: Clinical trials for medical devices: FDA and the IDE process https://www.fda.gov/downloads/training/clinicalinvestigatortrainingcourse/ucm378265.pdf.
Appendix A - Comparing the Development of Drugs, Devices, and Clinical Procedures. Modern Methods of Clinical Investigation: Medical Innovation at the Crossroads: Volume I. Institute of Medicine (US) Committee on Technological Innovation in Medicine; Washington (DC): National Academies Press (US); 1990.
[143] https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/21025lbl.pdf.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022083lbl.pdf.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020690s035,021720s008,022568s005lbl.pdf
[144] WorldPharmaNews, Alzheimer's experts call for changes in FDA drug approval standards, *available at* http://www.worldpharmanews.com/development/3931-alzheimer-s-experts-call-for-changes-in-fda-drug-approval-standards.
[145] Becker and Grieg, A new regulatory roadmap for Alzheimer's Disease drug development. Curr Alz Res (2014); 215-220.
[146]

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596728.pdf.

[147] Rutherford et al., Short and Long-term Effects of rTMS Treatment on Alzheimer's Disease at Different Stages: A Pilot Study, J. Experimental Neuroscience, 2015; 9 43-51.
[148] Ito, K et al. Disease progression mea-analysis model in Alzheimer's disease. Alzheimer & Dementia 2010; 6, 39-53.
[149] WorldPharmaNews, Alzheimer's experts call for changes in FDA drug approval standards, *available at* http://www.worldpharmanews.com/development/3931-alzheimer-s-experts-call-for-changes-in-fda-drug-approval-standards.
[150] Rutherford et al., Short and Long-term Effects of rTMS Treatment on Alzheimer's Disease at Different Stages: A Pilot Study, J. Experimental Neuroscience, 2015; 9 43-51.
[151] Ito, K et al. Disease progression meta-analysis model in Alzheimer's disease. Alzheimer & Dementia 2010; 6, 39-53.