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FEATURED ARTICLE

Effects of a combined transcranial magnetic stimulation (TMS) and cognitive training intervention in patients with Alzheimer's disease

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Abstract

Introduction: This clinical trial evaluates the efficacy and safety of a 6-week course of daily neuroAD™ therapy.

Methods: 131 subjects between 60 and 90 years old, unmedicated for Alzheimer's disease (AD), or on stable doses of an acetylcholinesterase inhibitor and/or memantine, with Mini–Mental State Examination scores between 18 and 26, clinical dementia rating scale scores of 1 or 2, enrolled for a prospective, randomized, double-blind, sham-controlled, multicenter clinical trial. Structural brain MRIs were obtained for transcranial magnetic stimulation targeting. Baseline Alzheimer's disease assessment scale—cognitive (ADAS-Cog) and Clinical Global Impression of Change were assessed. 129 participants were randomized to active treatment plus standard of care (SOC) or sham treatments plus SOC.

Results: Subjects with baseline ADAS-Cog ≤ 30 (~85% of study population) showed a statistically significant benefit favoring active over sham. Responder analysis showed 31.7% participants in the active group with ≤ −4 point improvement on ADAS-Cog versus 15.4% in the sham group.

Discussion: neuroAD™ Therapy System provides a low-risk therapeutic benefit for patients with milder AD (baseline ADAS-Cog ≤30) beyond pharmacologic SOC.

KEYWORDS
NeuroAD™, TMS, ADAS-Cog, CGI-C, Alzheimer's disease therapeutics

1 | INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia[1] affecting approximately 5.4 million people in the United States alone. By 2030, an estimated 8.4 million Americans aged 65 years and older will have AD. A growing list of failed phase III studies, exceeding 30 in the past decade, underscores the urgent need for novel therapeutic approaches.

Brain stimulation approaches are relatively new to AD therapeutics but show encouraging preliminary results.[2,3] Repetitive transcranial magnetic stimulation (rTMS) is the most widely studied noninvasive brain stimulation technology.[4,5] TMS is based on the principle of electromagnetic induction. A strong, brief pulse of current passed through a coil generates a time-varying magnetic field pulse that penetrates scalp and skull and induces a secondary current in the brain. The geometry and placement of the coil on the scalp enables targeting specific parts of the brain cortex.[6–9] When applied, repetitively, rTMS can, depending on stimulation parameters, either enhance (e.g., using 5-20 Hz stimulation) or suppress (e.g., using ≤1 Hz stimulation) excitability in the targeted cortical region and modulate activity across specific brain networks.[10,11] Although the exact neurobiological mechanisms of rTMS remain unclear, it has been suggested that modulation of neuroplasticity[12–15] is involved. This suggests that rTMS might serve to "prime" a given targeted cortical region or network to make it more susceptible to a coupled pharmacologic, cognitive, or behavioral intervention. Indeed, several studies have reported positive results on cognitive functions when combining rTMS with specific behavioral or cognitive interventions.[16–18] Nine single-center studies including nearly 150 subjects have reported promising results of the neuroAD™ Therapy System, which delivers neuronavigated, focal rTMS concurrently with cognitive training exercises (Fig. 1) designed to engage the cognitive functions of the brain networks targeted by a preceding rTMS train. No safety concerns were raised in any of these studies, and all found cognitive and functional improvement in the active treatment group.[19–25] Here we report the results of a pivotal (phase III), randomized, sham-controlled, multisite study of neuroAD™ in patients with mild to moderate AD.

2 | METHODS

2.1 | Design

The study, involving nine centers in the United States and one in Israel (list of participating sites in shown in Supplementary Material 2), was designed to assess the efficacy and safety of neuroAD™ (NCT01825330). Main efficacy assessment tools were Alzheimer's disease Assessment Scale—Cognitive (ADAS-Cog) and ADSC Clinical Global Impression of Change (ADSC-CGI-C). Study endpoints were mean change from baseline in ADAS-Cog and ADCS-CGI-C one and six weeks after the intervention (week 7 and week 12).

The study was approved by the local IRB at each of the participating sites. After written informed consent was obtained, participants underwent screening and baseline procedures and were block randomized to active or sham intervention via an interactive voice response system (Fig. 1). The raters who performed the ADAS-Cog and CGI-C testing (two per site) were blinded to the participants' group assignment as well as to each other. Raters were either neuropsychologists or physicians, and all were experienced and certified in delivering the respective cognitive test batteries. All raters completed study-specific program to assure standardization of scales administration. Investigators, subjects, and their caregivers were also blinded. Efficacy of blinding was assessed using a standardized instrument. All participants attended up to 34 visits, including screening, baseline, 30 active or sham treatment sessions (6 weeks, 5 days a week) and two follow-up visits.

2.2 | Study participants

Patients meeting DSM-IV criteria for mild to moderate AD were eligible for the study. Inclusion criteria included age 60-90 years; Mini–Mental State Examination score 18 to 26; ADAS-Cog >17; a reliable informant caregiver; no deficits in hearing or vision; good English or Hebrew fluency; > 8th grade education; and if medicated for AD, stable doses for >90 days of ChEI or memantine (standard of care [SOC]). Exclusion criteria included clinical dementia rating scale[26] of 0.5 or 3; prominent agitation; use of benzodiazepines or barbiturates up to 2 weeks before screening; pharmacological immunosuppression; participation in a clinical trial with any investigational agent within 6 months before study enrollment; history of seizures or diagnosis of epilepsy; contraindication for MRI or TMS; patients with depression, bipolar disorder or psychotic disorders, or any other neurological or psychiatric condition, which the investigator finds as interfering with the study; alcoholism, drug addiction, or severe sleep deprivation; unstable medical disorder or any neurological/psychiatric disorder other than AD. Sites investigators (all highly experienced) confirmed patients' eligibility to participate in the study.

Overall 131 subjects were enrolled (Fig. 2) over a period of 26 months. The first two subjects recruited at each site were designated "roll-in" and received Active Treatment. These 20 subjects were included only in safety analyses. Two participants were withdrawn

before randomization. The remaining 109 subjects were block randomized to active (n = 59) or sham treatment (n = 50).

2.3 | Intervention

2.3.1 | Active treatment (neuroAD™)

The neuroAD™ Therapy System (Neuronix Ltd., Israel) combines short bursts of rTMS with computerized cognitive training. The intervention targets six different brain regions and networks which map onto cognitive functions prominently afflicted in AD dementia: Broca's area; Wernicke's area; left and right dorsolateral prefrontal cortex; left and right inferior parietal lobule. During each daily session, 3 of these 6 regions are targeted.

Each participant's anatomical brain MRI was used for marking of the personal brain regions, determined by projecting the relevant brain region (as determined by anatomical landmarks) onto the scalp. Using the system's integrated IR/optical neuronavigation unit, continuous monitoring of the precise TMS location relative to the target brain region was performed. Definition and continuous monitoring of precise TMS targeting using the system's integrated IR/optical neuronavigation unit. Neuronavigated TMS was applied by a trained operator with an 8-shaped coil, using the system's integrated IR/optical neuronavigation unit. Daily sessions applied across three targeted regions, with a total of 1300 rTMS pulses at 10 Hz in short bursts of 20 pulses. rTMS intensity was set up to a maximum of 110% of each participant's resting motor threshold, which was determined daily following the recommendations of the International Federation of Clinical Neurophysiology.[27] This stimulation protocol adheres to International Federation of Clinical Neurophysiology safety guidelines.[10,18]

2.4 | Control/sham treatment

The sham procedure was delivered by the same neuroAD™ device, and the sessions were matched in overall participants' experience. Sham rTMS was delivered with a specially designed coil that created identical noise as real rTMS but delivered no electromagnetic energy. Neuronavigation was used as in the real intervention to define the positioning of the coil. Instead of cognitive training, control group participants were engaged in a visual perceptual task, which presented pictures of objects and required to report as like or dislike, and short nature (or other) movies without a demand for any response.

2.5 | Statistical analysis

The primary efficacy (PE) population included all randomized patients who received at least one active or sham treatment. The perprotocol (PP) population is the subset of PE population with no protocol violations and meeting a minimum required number of study sessions. Fig. 2 depicts the subjects' disposition flowchart.

RESEARCH IN CONTEXT

1. Systematic review: The authors did an extensive PubMed search to read and understand the literature that explores the connection between TMS, cognitive stimulations, clinical trials, and treatment of Alzheimer's disease dementia.
2. Interpretation: This prospective, randomized, sham-controlled, blinded, multicenter trial of the neuroAD™ treatment, which integrates neuronavigated rTMS with cognitive training, demonstrated an excellent safety profile, extremely high adherence, and significant efficacy above SOC in patients with milder AD (baseline ADAS-Cog ≤ 30). These data suggest that neuroAD™ is effective as a symptomatic treatment for patients with milder AD.
3. Future directions: The technology is approved in the European Union, Israel, Korea, and Australia for treating AD dementia. Ultimately, it will need to garner FDA approval so that post approval data can be gathered. Furthermore, assessment of longer durations will be needed to gauge prolonged and sustained effects.

We assessed the change in ADAS-Cog from the baseline to follow-up, comparing active and sham treatment groups, using ANCOVA with two-sided alpha = 0.05 for significance. As prior studies have reported an interaction between baseline ADAS-Cog and disease progression[28] baseline ADAS-Cog was prospectively included as a covariate. A subset analysis considered specifically milder afflicted patients (ADAS-Cog ≤ 30, 85% of the participants). ADCS-CGI-C at follow-up was presented with associated 95% confidence interval and comparison between study groups was done using Wilcoxon test, chi-square distribution test, and responders' analysis.

3 | RESULTS

There were no differences between the active and sham groups in regard to age, education, gender, disease severity, or number of patients on concomitant AD medications (Table 1). Over 90% of participants completed at least 27 treatment sessions of 30 sessions planned (52 in active and 48 in sham groups).

The blinding to treatment group assignment was maintained across all parties, with most respondents indicating they were not sure of the treatment received: 55%, 57%, 69%, and 70% for subjects, caregivers, ADAS-Cog raters, and CGI-C raters, respectively. No significant differences were found between study groups on any of the blinding questions: *P* values of .597, .431, .391, and .431 for subjects, caregivers, ADAS-Cog raters, and CGI-C raters, respectively, as tested by Fisher's exact test.

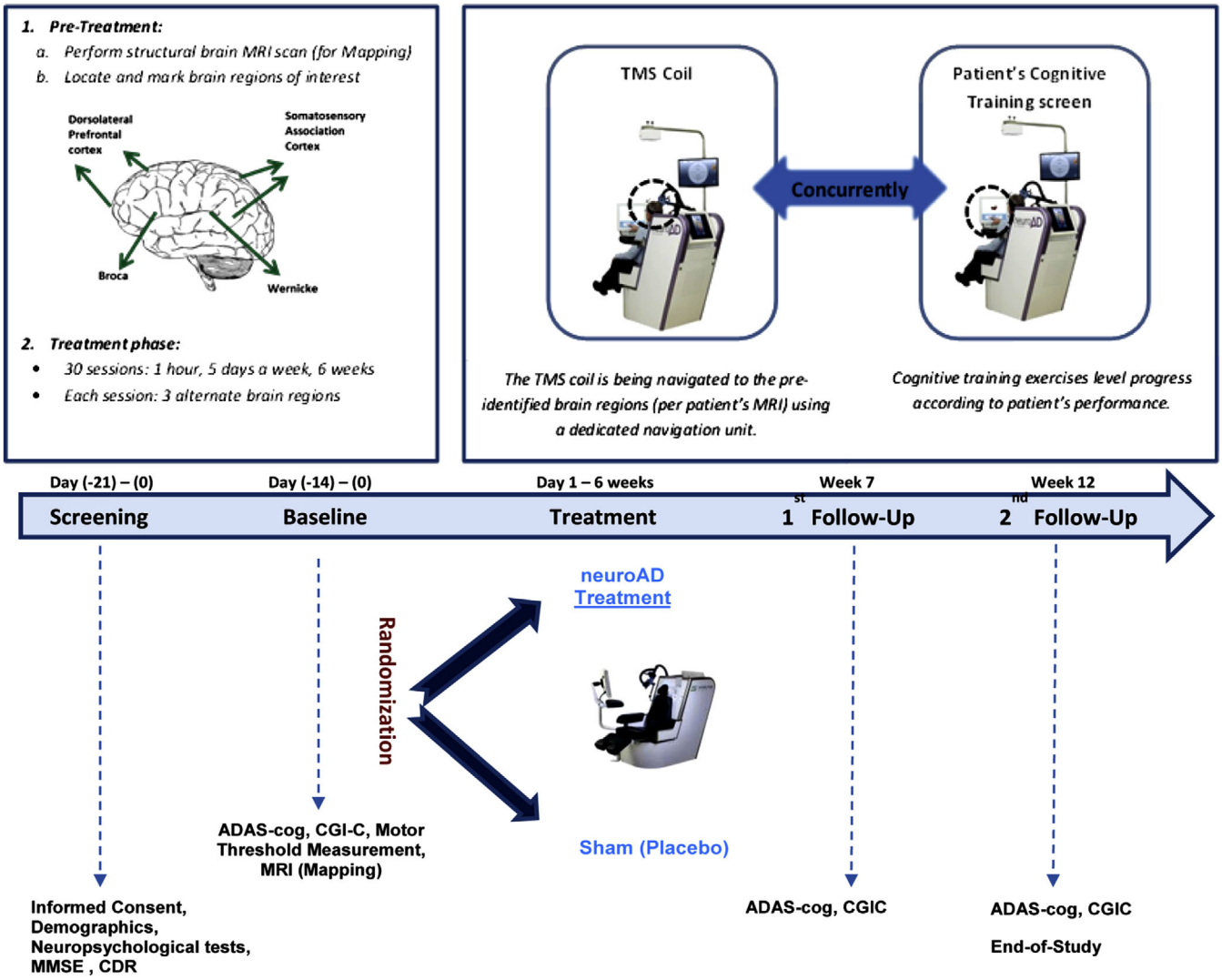

FIGURE 1 Description of the neuroAD system and clinical trial outline. Abbreviations: CDR, clinical dementia rating scale; TMS, transcranial magnetic stimulation.

3.1 | Safety

The safety analysis group included the 109 randomized subjects (active group = 59; sham group = 50) and the 20 roll-in subjects (active treatment). Only 13 participants reported adverse events (AEs) (Table 2): 11 in the active, 2 in the sham group. All AEs were anticipated events commonly associated with rTMS,[6] mainly headache (5.4%), scalp/skin discomfort (3.1%), neck pain/stiffness (1.5%), and fatigue (0.7%). All were mild and most resolved on the day of occurrence with either minor or no action.

Four serious AEs were reported: one death, one urinary retention, and one case of asthenia. The 4th serious AE was a cervical fracture, occurring before randomization. All these serious AEs were determined to be unrelated to the study procedure or device by the physician in charge as well as by an independent medical review committee.

3.2 | Efficacy

In the PE population, we found no statistically significant difference on ADAS-Cog between the active and the sham groups at 7 weeks. However, at week 12, ADAS-Cog was back to the baseline for the sham group, whereas the Active group showed a sustained improvement.

A statistically significant interaction between treatment group and baseline ADAS-Cog score ($P = .02$), indicating a nonhomogeneous effect across different baseline values was noted. Thus, modeled after several publications,[24,28,29] an analysis was conducted dividing the study population into those with a baseline ADAS-Cog score > 30 and those with a score of ≤30. Participants with baseline ADAS-Cog ≤ 30 (85% of study population) demonstrated a notably greater effect of the intervention (Fig. 3). Those in the active group (PP population) experienced a mean change in ADAS-Cog score at 12 weeks of −2.11. The equivalent subpopulation in the sham group showed

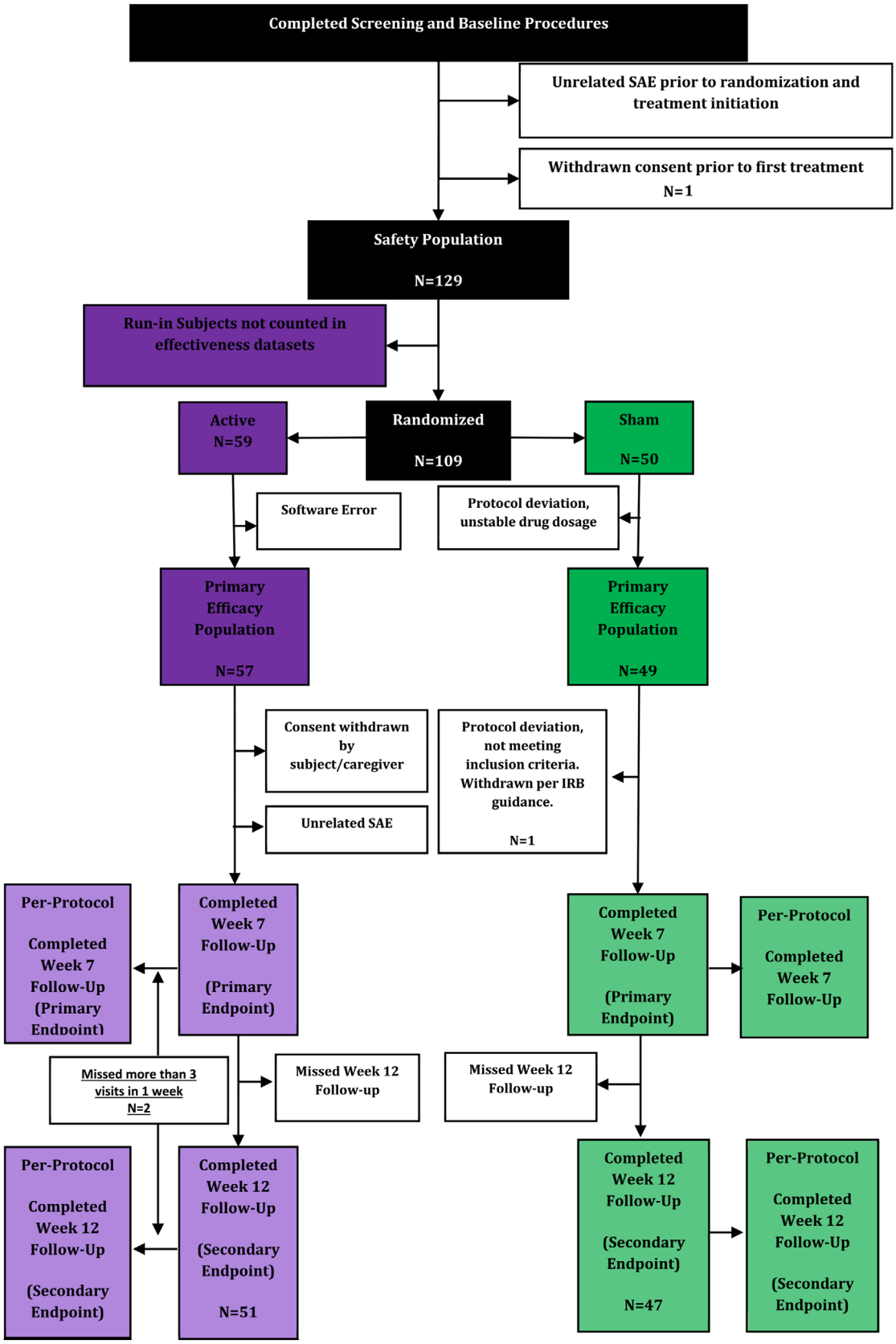

FIGURE 2 Subjects disposition chart.

TABLE 1 Selected demographics

Selected demographics	Active group	Sham group
Gender No. (%)		
Male	41 (51.9)	29 (58)
Female	38 (48.1)	21 (42)
Average age (y)	76.9	76.7
BMI (kg/m^2)	25.9	25.7
Education no. (%)		
Completed 8th grade	4 (5.1)	4 (8)
Completed high school	34 (43)	14 (28)
Completed college	40 (50.6)	32 (64)
None of the above	1 (1.3)	0 (0)
Average time from AD diagnosis (y)	1.7	1.8
Medicated for AD (either ChEI or memantine or both) no. (%)	63 (79.7)	41 (82)
Medicated for ChEI alone (%)	34 (64.1)	32 (66.7)
Medicated for memantine alone (%)	19 (35.8)	21 (43.7)
Baseline ADAS-Cog score	23.6	24.4
Baseline MMSE score	21.7	21.3
Baseline TMS motor threshold	75.5	74.2

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's disease assessment scale—cognitive; MMSE, Mini–Mental State Examination; TMS, transcranial magnetic stimulation.
NOTE: None of the differences are statistically significant
NOTE: Of the 129 subjects starting treatment sessions, three dropped out, one was withdrawn for not meeting eligibility criteria, and one passed away unrelated to the study intervention. An additional three subjects did not complete the minimum required number of treatment sessions as defined in the protocol.

TABLE 2 Adverse events by relationship to study device and study group

	Study group		
Relationship to study device	Active group N = 79 No of adverse event (%)	Sham group N = 50 No of adverse event (%)	All N = 129 No of adverse event (%)
Any	63 (41)	31 (32)	94 (37)
Not related	43 (34)	25 (26)	68 (31)
Unlikely	5 (6)	2 (2)	7 (5)
Possible	8 (6)	4 (4)	12 (5)
Probable	5 (5)	0 (0)	5 (3)
Definite	2 (3)	0 (0)	2 (2)

a mean change of −0.32. The between-group difference was statistically significant (−1.79 favoring treatment, 95% CI: −3.57 to −0.01; $P < .05$). For the same analysis in the PE population, the between-group difference approached statistical significance (treatment = −1.92; sham = −0.32;−1.61 favoring treatment, 95% CI: −3.36 to 0.14; $P = .07$).

Note that only 8 subjects in the active and 8 subjects in the sham group (representing 14% and 16% of their different cohorts, respectively) had ADAS-Cog score greater than 30 at baseline (baseline ADAS-Cog >30). Limited conclusions on the efficacy of neuroAD^{TM} for such, more severely afflicted AD patients (baseline ADAS-Cog >30) can be drawn. They showed a very high degree of variability in the effects of the intervention. As can be seen from the Spaghetti plot (Fig. 4), the graph representing the results of patients with baseline ADAS-Cog >30 is about 3 folds wider as the graph of patients with baseline ADAS-Cog ≤30.

The CGI-C scores were similar between study groups at week 7, but at week 12 they were significantly different in favor of active treatment ($P = .037$, chi-square test, PE population; −0.35 favoring treatment, 95% CI: −0.77 to 0.07). Even greater advantages were observed for the active group in the PP population with baseline ADAS-Cog scores ≤30 ($P = .041$, chi-square test) (Fig. 3). This resulted in a difference of 0.45 points between groups at week 12 in favor of the active treatment: 3.69 for the active and 4.14 for the sham treatment ($P = .07$).

Conversely, when examining the week 12 distribution of subjects who experienced worsening per the CGI-C scale, it is notable that only 8 of 50 (16%) subjects worsened in the active group versus 18 of 43 (41.8%) in the sham group. This difference was statistically significant ($P = .01$, two-sided Fisher's exact test). Examining the subgroup of subjects with baseline ADAS-Cog ≤30 in the PE population, only 5 of 42 (11.9%) subjects worsened in the active group versus 14 of 35 (40%) in the sham group ($P < .01$, two-sided Fisher's exact test). Similarly, 30.8% of active subjects show clinically meaningful improvement (scores of 1, 2, or 3).

Finally, a responder-analysis ("S-Curve") shows the percentage of subjects who benefit by at least a certain threshold (Fig. 5), of the baseline ADAS-Cog ≤30 group in the PE population. More than 70% of the active subjects show either improvement or no deterioration (ADAS-Cog change ≤0), compared with 59% of sham subjects. Interestingly, more than double the percentage of active subjects (31.8%) showed an improvement of ≤ −4, than in the sham group (15.4%).

While not surprising that milder patients benefit more from the intervention, it is of an interest to ascertain this when considering the different response of the two groups of patients (those with baseline ADAS-Cog ≤30 compared to those with baseline ADAS-Cog >30), to the neuroAD intervention components.

3.3 | Magnetic stimulation component

The motor threshold was found to be significantly correlated ($P < .001$) to the baseline ADAS-Cog score of the patients, with correlation coefficient −0.4. This is not surprising, as the baseline motor threshold is known to correlate with the progression of the disease,[30–33] as indicative to disease severity. Furthermore, subjects with baseline ADAS-Cog ≤30 has significantly higher motor threshold values, as compared with subjects with baseline ADAS-Cog >30 ($P = .0028$). Interestingly, there was also a difference found in the percentage of patients medicated with *N*-methyl-D-aspartate receptor (35.3% of the subjects

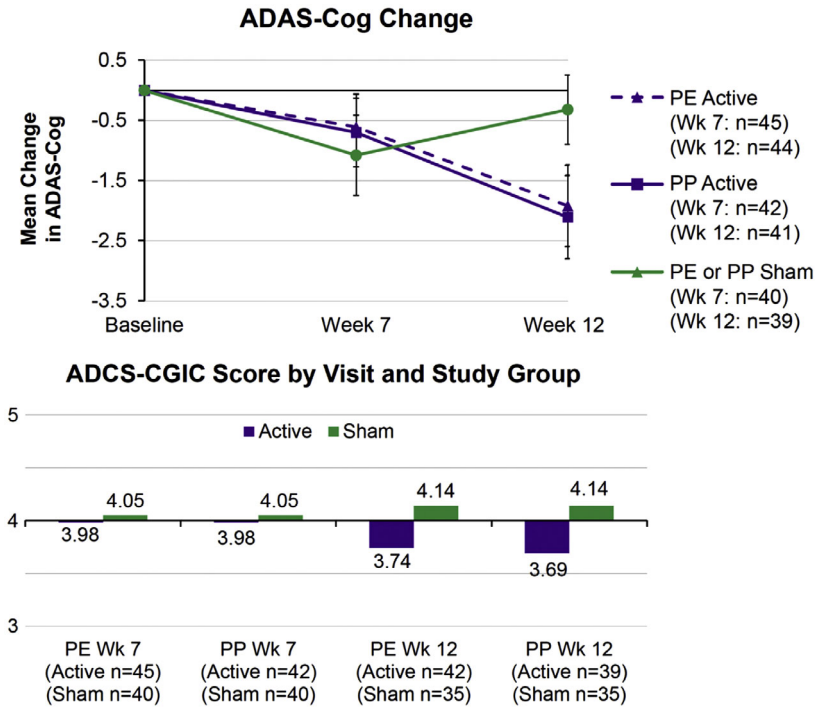

FIGURE 3 Efficacy outcomes, ADAS-Cog, and ADCS-CGI-C, PE population, for subjects with baseline ADAS-Cog ≤30. Abbreviations: ADAS-Cog, Alzheimer's disease assessment scale—cognitive; PE, primary efficacy; PP, perprotocol.

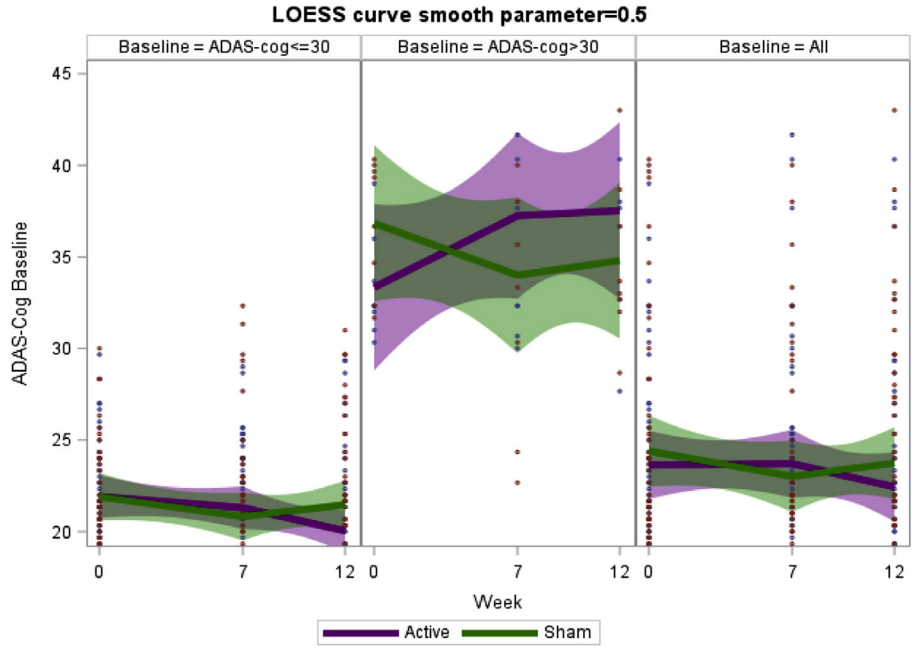

FIGURE 4 LOESS spaghetti line plots, PE population, subjects with baseline ADAS-Cog ≤30 compared with subjects with baseline ADAS-Cog >30. Abbreviations: ADAS-Cog, Alzheimer's disease assessment scale—cognitive; PE, primary efficacy.

with baseline ADAS-Cog ≤30, compared with 62.5% of the subjects with baseline ADAS-Cog >30), which may also influence the lower recorded motor threshold.[34] There was no difference between the two groups in uptake of ChEI drugs (64.7% of the subjects with baseline ADAS-Cog ≤30, and 68.7% of the subjects with baseline ADAS-Cog >30).

Because the absolute magnetic stimulation power is set relative to the motor threshold, this implies that subjects with baseline ADAS-Cog ≤30 underwent significantly greater power magnetic stimulation, thus suggesting greater efficacy.

3.4 | Cognitive training component

When analyzing the progression of the subjects on the cognitive training exercises, it is evident that subjects with baseline ADAS-Cog

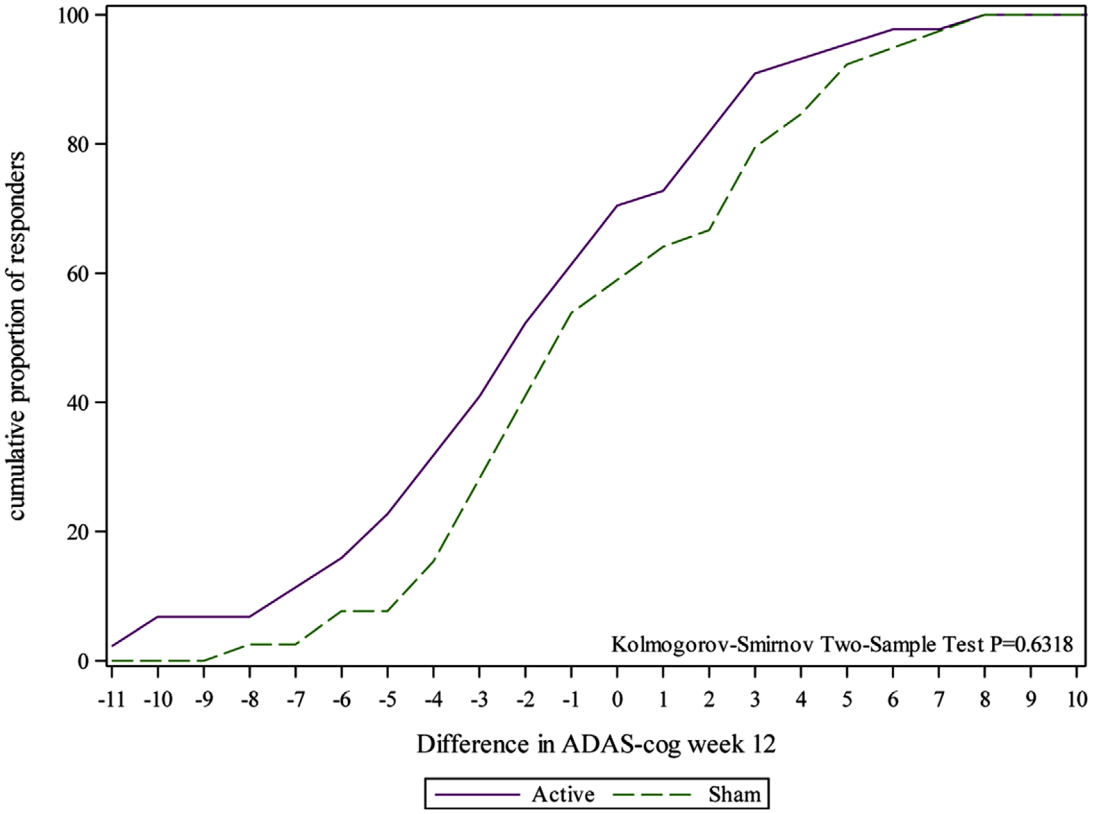

FIGURE 5 ADAS-Cog S-curve analysis at week 12, PE population, subjects with baseline ADAS-Cog ≤30. Abbreviations: ADAS-Cog, Alzheimer's disease assessment scale—cognitive; PE, primary efficacy.

≤30 advanced significantly more on their cognitive training exercises ($P < .001$). This implies that subjects with baseline ADAS-Cog ≤30 benefited more from the cognitive training exercises, probably due to their less diminished cognitive reservoir.

4 | DISCUSSION

This prospective, randomized, sham-controlled, blinded, multicenter trial of the neuroAD™ treatment, which integrates neuronavigated rTMS with cognitive training, demonstrated an excellent safety profile, extremely high adherence, and significant efficacy above SOC in patients with milder AD (baseline ADAS-Cog ≤ 30). While the study did not meet its prespecified primary endpoint, we believe that the positive results shown on the later follow-up period (prespecified as secondary endpoint) suggest that neuroAD™ is effective as a symptomatic treatment for patients with milder AD.

The success rate of treatment for dementia due to AD is extremely low. Of hundreds of clinical studies and compounds, no new treatment has been approved or introduced to the market in the past 15 years.[35] In this study, we found significant effects on dual-outcome assessment scales evaluating cognitive (ADAS-Cog) and functional change (ADCS-CGI-C). This supports the clinical meaningfulness of the treatment. While the average improvement on ADAS-Cog scale measured for the active patients was −2.11 (or −1.79 compared with sham), note also that responder analysis further shows that over 31% of active patients derived a substantial clinical as evidenced by either ADAS-Cog scale (benefit of ≤ −4 points) or the CGI-C scale (scores of 1, 2, or 3).

In a review of pharmaceutical treatments outcomes for mild to moderate AD, the difference in mean reduction in ADAS-Cog at 12 weeks compared to baseline (treatment vs. placebo, mostly in untreated naïve participants) ranges from −0.31 to −2.99.[36,37] Hence, the effect size of the neuroAD™ treatment is within the range of ChEIs. Yet it should be emphasized that ChEIs were tested against true placebo, whereas in this study, the sham treatment still received pharmacologic SOC. Furthermore, the effects demonstrated in the present study are superimposed on concurrent use of ChEI and memantine suggesting that neuroAD™ offers an additive effect to pharmacological therapies.

The contribution of the rTMS to the success of the treatment and if similar results may have been achieved with cognitive training alone bear questioning. Although not evaluated in this study, previous reports found that patients treated with the same cognitive training combined with sham rTMS showed less benefits than those receiving the combination of cognitive training with real TMS.[21,22] The mechanism of action of rTMS is unclear, but a prevalent theory involves the induction of long-term potentiation—such as plasticity. Enhanced plasticity may make the brain more receptive to cognitive training. In more advanced patients, this benefit of rTMS might be diminished, hence accounting for reduced efficacy. In addition, in more severely affected patients, greater brain atrophy and altered cortical excitability can

alter the cortical impact of rTMS and thus reduce its efficacy. Considering the decrease in motor threshold in more severely impaired patients, as also evidenced by this study, may suggest that a higher rTMS intensity relative to the motor threshold may be required in those patients to increase efficacy. Further studies are needed to explore such issues. Another relevant observation found in this study is that the therapeutic effect of such neuromodulatory intervention may take time to fully develop and translate in clinical benefits (as evidenced by comparing outcomes on 12 weeks and 7 weeks). Such phenomena have been observed in other TMS studies.[38–40] In addition, the finding that active group participants continued to improve from one to six weeks after the intervention suggests that the duration of effect may be longer lasting. Several small studies have reported beneficial effects lasting 9 months[41] to two years.[42] Consequently, further research is warranted to explore the time course of the therapeutic efficacy as well as the longevity of effect; this can be achieved by following up the patients for longer periods, with up to 12 months after the intervention course. Other aspects of research could be to capture some of the clinical benefits using other standardized measures (e.g., Apathy scale[23]) or goal attainment scale, to treat patients with higher stimulation power as well as more challenging cognitive training suite. Finally, the technology may have the potential for disease-modifying effects but further research may be necessary to gain more understanding.

To the best of our knowledge, this is the first study of its size and design to test therapeutic potential of a noninvasive medical device technology. As mentioned, 400 attempts in the past 15 years to develop new pharmaceutical therapies for AD, including disease-modifying agents, have repeatedly failed.[43] Hence, there is a greater-than-ever need to bring an armament of therapies, which can be combined together, each providing its own benefit for the patient. This approach has also been highlighted in a recent public letter by a group of leading AD researchers, who have argued that "the future of Alzheimer's disease treatment lies in combination therapy…".[44] The neuroAD system represents such new approach of combining noninvasive and safe medical device modality, together with currently approved ChEI drugs.

The results of the study further demonstrate that the therapeutic effects not only last beyond the acute intervention phase (6 weeks), but actually increase with the time lapse after the completion of the intervention. While long-term effects were evidenced in small scale studies, further research to quantify these effects is of clear value. We believe that further research on the population of those who benefited from this treatment throughout a period of up to one year will allow a better understanding of the nature of the effect, and will provide physicians with the required tools to set long-term treatment scheme, potentially using repeated treatment courses. Further research on the more severe patients may also be of value, yet will require identifying different treatment parameters.

Finally, as previously mentioned, the exact neurobiological mechanisms of rTMS remain unclear. Looking to evaluate the clinical effect of this symptomatic therapy on the neurobiological characteristics and mechanisms of actions was not researched and may warrant further research. In summary, this pivotal study provides evidence that the neuroAD™ Therapy System is a valuable therapeutic option with low risks and meaningful clinical benefit in patients with mild AD, even those already on SOC pharmacologic treatment.

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Lead authors Marwan Sabbagh and Alvaro Pascual-Leone took responsibility over analysis and interpretation of the data. All other co-authors had full access to the data, participated in the interpretation of the findings, reviewed and approved the final manuscript before submission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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