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April 9, 2019

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Director, Center for Devices and Radiological Health
Food and Drug Administration
U.S. Department of Health and Human Services
WO 66, Room 5442
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Carlos Peña, Ph.D., M.S.
Director, Division of Neurological and Physical Medicine Devices
Center for Devices and Radiological Health
Food and Drug Administration
U.S. Department of Health and Human Services
WO 66, Room 2680
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RE: De novo application for the neuroAD Therapy System submitted by Neuronix, Ltd.

Dear Drs. Shuren and Peña:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, is writing to urge the Food and Drug Administration (FDA) not to approve the de novo premarket application from Neuronix, Ltd. (Neuronix) for the neuroAD Therapy System as an adjunctive treatment for mild-to-moderate dementia of the Alzheimer's type in patients with baseline Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog) scores of 30 or less. The neuroAD Therapy System was the subject of the March 21, 2019, meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee, which took place in response to an appeal filed by Neuronix, Ltd., of the FDA's June 22, 2018, denial of Neuronix's de novo application.

Public Citizen strongly opposes the approval of neuroAD Therapy System because data from the single pivotal clinical study, as well as other studies, failed to provide evidence that this device is effective for its proposed indication. Particularly, the pivotal study comparing subjects with Alzheimer's dementia (AD) who received active treatment with those who received sham treatment did not show any cognitive function benefit with active treatment, nor did a subsequent post-hoc subgroup analysis of the pivotal study data. Based on the data presented, it is irrefutable that this device does not offer any clinically meaningful benefit and that approval of this device would succeed in eviscerating the agency's already weak standards for establishing a reasonable

assurance of effectiveness for approving medical devices under the de novo and premarket approval application pathways.

I. Background and device overview

AD is a progressive neurodegenerative disease that leads to impaired memory, thinking, language, and behavior. Currently, there is an unmet clinical need for treating patients with this disease. The neuroAD Therapy System uses transcranial magnetic stimulation (TMS) in combination with cognitive training exercises presented on a computer screen purportedly to improve cognitive function in patients with AD. This treatment would be given five times a week for several weeks or longer. The sponsor's proposed indication for the neuroAD Therapy System is the following:

> 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.[1]

II. Regulatory history of the neuroAD Therapy System review process and actions taken by FDA

After reviewing the clinical study data included in the de novo application for the neuroAD Therapy System submitted by Neuronix on November 14, 2016, the Office of Device Evaluation (ODE) determined that the initial pivotal clinical study, including a post-hoc subgroup analysis conducted by the sponsor, failed to demonstrate "a clinically or statistically meaningful benefit" for the device.[2] Furthermore, the ODE suggested that the sponsor conduct a new confirmatory clinical study.

After reviewing additional information provided by the sponsor that included clinical data from outside the U.S., which contained data from a Korean pivotal study that enrolled only patients with mild AD — those with baseline ADAS-Cog scores of 30 or less — and consulting with the FDA's Network of Experts, the FDA again concluded that the device had not been shown to be effective and issued a denial of the company's de novo application on June 22, 2018.

III. Pivotal study

a. Study overview

The single pivotal study for the de novo application for the neuroAD Therapy System was prospective, randomized, multi-center, double-blind, and sham-controlled. The study enrolled

[1] Food and Drug Administration. FDA executive summary: Meeting of the Neurological Devices Panel, de novo DEN160053, Neuronix, Ltd., NeuroAD Therapy System. March 21, 2019. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM633726.pdf. Accessed April 3, 2019. PDF page 8.

[2] *Ibid*. PDF page 23.

131 subjects who had been diagnosed with mild or moderate AD and had ADAS-Cog scores above 17, of whom 109 were randomized to either active TMS plus active cognitive training (active group; N=59) or sham TMS plus active cognitive training (sham group; N=50) for five weekly sessions for seven weeks at 10 study sites in the U.S. and Israel.[3] Subjects treated with AD drugs were required to remain on stable doses of the medications for at least 60 days prior to the study and then throughout the course of the study.[4]

The primary efficacy endpoint was the change in ADAS-Cog scores — which measures disturbances of memory, language, attention, and other cognitive abilities — from baseline to week 7.[5] Of note, ADAS-Cog scores range from 0 to 70, with higher scores indicating more severe impairment.

Additionally, there were three prespecified secondary efficacy endpoints, which included the change from baseline to week 12 in ADAS-Cog scores and the changes from baseline to week 7 and week 12 on the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (CGIC) scores.[6] The CGIC measures the global change in subjects' severity of illness at the time of assessment relative to their baseline assessments.

b. Primary efficacy results

For the primary efficacy endpoint, the results nominally favored the sham group, which had a mean change in the ADAS-Cog score from baseline to week 7 of -1.38 compared with a mean change of +0.07 in the active group, with a net mean difference of +1.45 points between the two groups that was not statistically significant (p=0.09).[7]

For the secondary efficacy endpoint — mean change in the ADAS-Cog scores from baseline to week 12 — there was not a statistically significant difference between the two groups (-0.61 in sham group versus -1.03 in the treatment group; p=0.64).[8] For the secondary efficacy endpoints using the CGIC scores, there were no statistically significant differences in the mean change from baseline to week 7 (4.06 in the sham group versus 4.04; p=0.96)[9] or to week 12 (4.19 in the sham group versus 3.84 in the active group; p=0.12).[10]

c. Post-hoc analysis and associated deficiencies

Confronted with data from the prespecified analysis showing that the neuroAD Therapy System was a complete and utter failure, the sponsor, in a desperate attempt to salvage its device, carried out a post-hoc analysis of a subgroup of selected subjects who had baseline ADAS-Cog scores of

[3] *Ibid.* PDF pages 24-25 and 38-39.
[4] *Ibid*. PDF page 25
[5] *Ibid*. PDF page 31
[6] *Ibid*. PDF page 31
[7] *Ibid*. PDF page 25
[8] *Ibid*. PDF page 58.
[9] *Ibid.* PDF page56.
[10] *Ibid.* PDF page 57.

no more than 30. This subset eliminated eight subjects from both the active group and the sham group.[11]

The post-hoc analysis revealed that the mean change in the ADAS-Cog score from baseline to week 7 was again nominally better in the sham group than the active group (-1.08 versus -0.61 respectively; no p value reported by the FDA because the analysis was post-hoc without pre-specification or multiplicity adjustment).[12] These result were reversed by week 12, nominally favoring the active group (-0.32 in the sham group versus -1.93 in the active group).[13]

Upon review, the FDA concluded that the effects of the neuroAD Therapy System seen in this subgroup could not be confirmed in other studies.[14] Assessments using the CGIC score at weeks 7 and 12 also revealed no clinical differences between the sham and active groups.[15]

The FDA also appropriately highlighted the many dangers of relying on such post-hoc analyses after a study fails to show benefit based on the prespecified efficacy outcome measures:

> [C]hanging the intended population after analyzing the data and finding that the overall test was not significant, amounts to a post-hoc hypothesis test. Therefore, **analyses associated with the subgroup defined by baseline ADAS-Cog <= 30 carry much greater uncertainty. These types of post-hoc analyses are generally considered to be exploratory and hypothesis-generating.**
>
> In contrast to prospective hypothesis tests, a data-driven hypothesis is generated and tested after an examination of the data. After finding the primary endpoint to be non-significant, an investigator might present a nominally significant post-hoc analysis of a subgroup as a substitute for the primary endpoint analysis. However, the usual calculation of type I error may be incorrect, especially when the data themselves suggest the hypothesis test. **The same data should not be used both to generate a new hypothesis and to test it (Piantadosi, 1997).** In this case, the hypothesis is that patients with baseline ADAS-Cog <=30 benefit from the neuroAD device over sham. Since the pivotal study results were used to generate that hypothesis, an independent dataset should generally be used to provide verification.
>
> Post hoc analyses expose the risk of approving medical devices that have no beneficial effect. **An apparent treatment difference discovered after an unplanned post-hoc analysis may be due to coincidence. This phenomenon can manifest itself in post-hoc subgroup analyses, done in the hope of discovering differences that support one treatment over another. Post-hoc analyses are also problematic because they neither apply to the intention to treat population in the study nor conform to the**

[11] *Ibid*. PDF page 63.
[12] *Ibid*. PDF pages 63-64.
[13] *Ibid*. PDF pages 65-66.
[14] *Ibid*. PDF page 71.
[15] *Ibid*. PDF page 67.

> **randomization models of statistical inference** (especially if randomization was not stratified by the subgroup).[16]
>
> [Emphasis added]

In an attempt to validate the post-hoc analysis of its failed pivotal trial, Neuronix presented interim data from a Korean pivotal study. The FDA concluded that the Korean study was insufficient in producing confirmatory data:

> While the sponsor presents interim data from the Korean pivotal study in a very small cohort of patients (22 treated patients, 11 active) with ADAS-Cog<30, this is not sufficient evidence to serve as a confirmatory group.[17]

IV. Assessment of the Neurological Devices Panel

The Neurological Devices Panel agreed that the data from the pivotal study testing the neuroAD Therapy System did not show clinically meaningful benefit as an adjunctive treatment of mild-to-moderate AD and that the device should not be approved, as reflected in the following excerpts from the brief summary of the panel's March 21, 2019, meeting:

> **Questions 2: Does the U.S. pivotal study demonstrate a clinically meaningful benefit for the neuroAD as an adjunctive therapy?**
> The Panel agreed broadly that the data from the US pivotal study did not demonstrate a clinically meaningful benefit, with the potential for results that may inform a future study. Panelists agreed that better, more objective outcome measures were needed to better identify meaningful changes. Other Panelists expressed the need for the development of better outcome measures that were clinically oriented as opposed to research-based. The Panel also suggested that the minimum amount of improvement in the ADAS-Cog alone that could be considered clinically meaningful would be at least 2 points, with several Panelists suggesting 3 to 5 points…
>
> **Question 5: Is the post-hoc identification of the ADAS-Cog≤30 population at a later time point when no treatment is given an adequate analysis of the US pivotal study data, in concert with the supplemental data provided, to demonstrate probable benefit?**
> The Panel agreed that the post-hoc identification of the ADAS-Cog≤30 population did not represent an adequate analysis of the pivotal study data to demonstrate probable benefit…
>
> **Question 6: Do the probable benefits of the neuroAD system outweigh the probable risks?**

[16] *Ibid*. PDF page 68.
[17] *Ibid*. PDF page 71.

> The Panel was in unanimous agreement that the probable benefits to health of the neuroAD™ Therapy System do not outweigh the probable risks to health.[18]
>
> [Emphasis in original]

V. Conclusions

In light of the data from the pivotal study supporting the de novo application submitted by Neuronix, it is clear that neuroAD Therapy System performs no better than sham treatment and therefore does not provide any clinically meaningful benefit. Such a device would not address the unmet clinical needs of AD patients, but instead would offer false hope, exacerbated by financial harm, to vulnerable patients and their loved ones who are desperately seeking effective treatments for AD.

We therefore urge the FDA to definitively reject the de novo premarket application from Neuronix for the neuroAD Therapy System. To approve this device based on the available data would render meaningless the agency's already weak standards for establishing a reasonable assurance of effectiveness for approving medical devices under the de novo and premarket approval application pathways.

Thank you for considering our comments on this important matter.

Sincerely,

Meena M. Aladdin, M.S., Ph.D.
Health Researcher
Public Citizen's Health Research Group

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group

[18] Food and Drug Administration. Brief summary of the Neurological Devices Panel meeting – March 21, 2019 neuroAD Therapy System. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM634424.pdf. Accessed April 4, 2019.