FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

Brief Summary of the Neurological Devices Panel Meeting December 10, 2021

BrainsGate Ischemic Stroke System (ISS500)

Introduction:

The Neurological Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met On December 10, 2021, to discuss, make recommendations, and vote on information regarding the premarket approval application (PMA) P200008 for the BrainsGate Ischemic Stroke System (ISS500) by BrainsGate Ltd.

The sponsor has proposed the following Indications for Use:

The ISS500 is indicated to increase cerebral blood flow and reduce disability in adult patients with acute ischemic stroke with confirmed cortical involvement in the anterior circulation who are ineligible or have no access to IV-tPA and endovascular thrombectomy. Treatment is to be initiated between 8 and 24 hours from stroke onset (last known well).

Panel Deliberations/FDA Questions:

Question 1: The ImpACT-24B pivotal study was conducted from 2011-2018. The sponsor selected the confirmed cortical involvement (CCI) subgroup as an analysis cohort in 2018 after a large proportion of the patients had been randomized and completed the study, and the selection may have altered the comparability of the treatment groups. Further influencing the comparability of the CCI treatment groups, 34 patients (12%) were removed from the sphenopalatine ganglion (SPG) stimulation group after randomization, compared to 0 from the sham group. Please discuss the effect on the external validity of the trial results.

Overall, the Neurological Devices Panel ("the Panel") felt this was a difficult question to answer and did not identify a consensus answer. One panelist expressed concern regarding why the modified intention to treat (mITT) group was used for analysis instead of the intention to treat (ITT) group, and the panelist also expressed concern that the trial results were not robust. The Panel did not believe that there was no external validity, but they were not able to determine the extent of the validity.

Another issue brought up was that whether the CCI is truly a group that needs to be extracted and studied on its own for the treatment effect.

Question 2: US patients comprised 6% of the patients in the 24B trial and the patients treated at US sites demonstrated a smaller clinical effect (2.6% effect in CCI subgroup) compared to those treated OUS (9.9% effect in CCI subgroup). Additionally, there were many low enrollment countries with a large variability in responder rates across countries. Can the overall results of the trial be generalized to the U.S. indicated population?

The Panel did not reach consensus on this question, but most were on the fence or slightly felt that the results could not be generalized to the US indicated population. Some panelists clearly stated that the results were not generalizable, while one stated clearly that the results could be generalizable to the US population based upon the presentation that was given by the company and some of the questions that were answered. Others suggested that the US sample could possibly be represented either by the high-income countries or in the countries with larger enrollees. Several panelists expressed a concern that there was a very small number of US patients that were enrolled in the trial, especially given the prevalence of stroke in the US.

Question 3: The sliding dichotomous scale used a prognostic model (VISTA) to predict 3-month disease natural history outcome of all subjects in the ImpACT-24B study. Considering the accuracy of the VISTA model, to what extent does the evidence show that treatment with the ISS500 causes the difference from sham observed in the clinical study?

Overall, the Panel did not believe the VISTA model is inaccurate, although many of them identified that they do not prefer use of the sliding dichotomy analysis. The Panel generally felt that the sliding dichotomy analysis provides the same magnitude of the treatment effect as in other outcomes, and therefore they felt that the evidence shown was accurate and usable.

Question 4: A change in device design and how it was studied may have an impact on the effectiveness observed in clinical trials. The device studied in the ImpACT-24B trial is not the final device the sponsor intends to market in the US. Given the uncertainties raised from the device changes, study design changes, and statistical analysis plan changes implemented during the conduct of the ImpACT-24B trial, do you believe the evidence from the clinical studies is sufficient to accurately predict the effectiveness of the current version of the ISS500 in the proposed indications for use population?

Many Panel members felt that the changes to the device itself over time were not troublesome and were probably expected over the 10 years of trial time, and they hoped that the modifications were made over time to make the device safer and easier to use. However, some panelists noted that the changes weren't precisely known because they were considered proprietary by the company. The Panel was more troubled about changing parameters in the trial design itself, and potentially changing those based on the data already accumulated earlier in the trial to try to chase a certain outcome or effect. The Panel stated that doing so may mean that a follow up study is necessary.

Question 5: The clinical trials included information on the adverse events experienced by the subjects.

a. Based on the design of the study and amount of data collected, was the information collected sufficient to adequately assess the probable risks to health? For example, are the risks of increasing cerebral blood flow in the target population adequately addressed with the existing data?

Please refer to the response to question 5b.

b. The rate of hemorrhage was quite a bit lower than expected in this population. Was the imaging data sufficient to assess this adverse event?

At least for 5a and 5b, the Panel feels that the information collected was sufficient to look for potential risks to health – the primary one being hemorrhage. The Panel is uncertain what imaging study and what time period would be useful to help answer the question regarding risks related to of cerebral blood flow (CBF) (*reperfusion injury*). MR imaging may be helpful and can be considered.

c. Although there were no reports in the trials, based on the intended use of the device, how serious are the risks of bleeding and swelling at the implantation site, airway endangerment, laryngospasm, microaspiration, chronic neuropathic pain, acute pain, among other risks to health with use of the device?

The Panel feels this is a reasonably safe device and is not concerned with long term effects.

Question 6: The injectable neurostimulator (INS) is implanted through an image guided procedure using the Guide View optical navigation system. There are multiple steps to

use this system, including the pre-procedural CT, optical targeting, and obtaining dental impressions of the gums and teeth.

a. What concerns are there regarding safety, accuracy, and reliability of using the system to implant the INS in a location near the sphenopalatine ganglion (SPG)?

The Panel felt that there are always potential risks whenever you put a device into a particular location. Based on the information that the sponsor gave, it seems that this particular system was relatively safe, accurate and reliable, and allows you to place the device at the sphenopalatine ganglion location.

d. What expertise would be needed to implant the device, and is the training program proposed by the sponsor sufficient?

In terms of expertise, there is concern whether five implantations is enough to consider that individual or operator as sufficiently trained. The Panel encouraged sites to look at using all their available subspecialty physicians in utilizing this device.

There needs to be more information on what the actual training is. What can the sponsor provide to trainees for education via video or hands-on and for back-up support?

Vote:

1. **Question: Is there reasonable assurance that the BrainsGate Ischemic Stroke System (ISS500) is safe for use in patients who meet the criteria specified in the proposed indication?**

   The Panel voted:
   - Yes – 13
   - No – 0:
   - Abstain – 0

2. **Question 2: Is there reasonable assurance that the BrainsGate Ischemic Stroke System (ISS500) is effective for use in the patients who meet the criteria specified in the proposed indication?**

   The Panel voted:
   - Yes – 3
   - No – 7
   - Abstain – 3

3. **Question 3: Do the benefits of the BrainsGate Ischemic Stroke System (ISS500) outweigh the risk for use in the patients who meet the criteria specified in the proposed indication?**

   The Panel voted:
   - Yes – 3
   - No – 7
   - Abstain – 3

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