SUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

NEUROLOGICAL DEVICES PANEL

December 10, 2021

Via Microsoft Teams Videoconference

Attendees:

Chairperson

Mary Jensen, M.D.
University of Virginia
Charlottesville, VA

Voting Members

Patrick Lyden, M.D.
University of Southern California
Los Angeles, CA

Julie Pilitsis, M.D., Ph.D.
Albany Medical College
Albany, NY

Temporary Voting Members

Earl Ray Dorsey, M.D., M.B.A.
University of Rochester
Rochester, NY

Magdy H. Selim, M.D.
Harvard University
Boston, MA

Jose' Biller, M.D.
Loyola University Medical Center
Maywood, IL

Gordon H. Baltuch, M.D., Ph.D.
Columbia University Medical Center
New York, NY

Byron G. Thompson, Jr., M.D.
University of Michigan
Ann Arbor, MI

David J. Kennedy, M.D.
Vanderbilt University
Nashville, TN

Rory A. Cooper, Ph.D.
University of Pittsburgh
Pittsburgh, PA

David J. Terris, M.D.
Augusta University
Augusta, GA

Bevan Yueh, M.D., M.P.H.
University of Minnesota
Minneapolis, MN

Randy D. Trumbower, Ph.D.
Harvard University
Cambridge, MA

Richard Chappell, Ph.D.
University of Wisconsin
Madison, WI

Industry Representative

Elijah Wreh, M.S.
Regulatory Affairs Manager
Zimmer Biomet

Consumer Representative

Veverly M. Edwards
Patient Safety Advocate/Affiliate Broker
First National Realty

Patient Representative

Philip Posner, Ph.D.
University of Florida College of Medicine
Gainesville, FL

Food and Drug Administration

Vivek Pinto, Ph.D.
Director, Division of Neuromodulation and
Physical Medicine Devices

Lin Zheng, Ph.D.
Director, Division of Neurosurgical, Neurointerventional
and Neurodiagnostic Devices

John Marler, M.D.
Clinical Deputy Director, Office of Neurological and
Physical Medicine Devices

Christopher Loftus, M.D.
Office Director (Acting), OHT 5 - Neurological and
Physical Medicine Devices

Jarrod Collier, M.S.
Office of Management
Designated Federal Officer

CALL TO ORDER
PANEL INTRODUCTIONS

Panel Chairperson Mary Jensen, M.D., called the meeting to order at 9:00 a.m. She noted the presence of a quorum and affirmed that the Panel members had received training in FDA device law and regulations. She announced that the Panel would be discussing, making recommendations, and voting on information regarding the premarket approval application for the BrainsGate Ischemic Stroke System ISS500.

She then asked the Panel members and the FDA staff to introduce themselves.

CONFLICT OF INTEREST STATEMENT
TEMPORARY VOTING STATUS STATEMENT
GENERAL ANNOUNCEMENTS

Jarrod Collier, M.S., Designated Federal Officer, read the Conflict of Interest statement and reported that no conflict of interest waivers had been issued.

He announced the appointments of Drs. Gordon Baltuch, José Biller, Rory Cooper, Richard Chappell, Earl Ray Dorsey, David Kennedy, Magdy Selim, David Terris, Byron Thompson, Jr., Randy Trumbower, and Bevan Yueh as temporary voting members, and Veverly Edwards as a temporary non-voting member.

He also introduced industry representative Elijah Wreh and press contact James McKinney, and made general announcements regarding speaker identification and transcripts.

SPONSOR PRESENTATION

Introduction

Jeffrey Saver, M.D., FAAN, FAHA, introduced the Ischemic Stroke System as a first-of-a-kind treatment option for patients who experience acute ischemic stroke. He informed the Panel that the clinical development program, which began in 2006, includes four clinical trials, two of which were randomized sham-controlled trials, and that the totality of evidence from these studies indicates a positive benefit-risk profile. He then read the proposed indication for use, outlined the presentation, and introduced the speakers and company consultants.

Ischemic Stroke System

Tom Devlin, M.D., Ph.D., FSVIN, gave a device description and explained the implantation procedure. He noted that improvements made to the current generation of neurostimulator have reduced procedural times and implant complications, that these changes have had no impact on the treatment itself, and that the final system maintains stimulation within a predefined optimal range.

Unmet Need and Pathophysiology

Michael Hill, M.D., M.Sc., FRCPC, provided background information on anatomical processes and insufficiencies associated with ischemic stroke. He noted that approximately 11% of acute stroke patients presenting within 24 hours of onset will not be eligible for the primary treatment options but still meet the criteria for the cortical infarction population for which the ISS500 is intended.

Mechanism of Action of SPG

Dr. Saver presented effectiveness and safety findings from the ImpACT-1, 24A, 24B, and 24M clinical trials. He provided an overall assessment of the benefit-risk, noting that the implantation procedure was found to be safe, that events occurring in patients who received the final device were rare, and that SPG stimulation was not associated with increased risk of mortality, serious adverse events, neurological deterioration, or pneumonia. In addition, there was evidence that the rate of symptomatic intracranial hemorrhage is lower with SPG stimulation as compared to control. He further noted that results from ImpACT-24M demonstrate that the final device and navigation system promote quick and accurate implantation with no major adverse events observed.

Training and Post-Approval Plan

Eyal Shai, EMBA, provided an overview of the intended training and post-approval plan consisting of online instruction, automatic data collection on system performance, and the establishment of a registry to collect information on clinical outcomes, failed implantations, device-related complications, and safety incidents.

Clinical Perspective

Dr. Hill highlighted the need for alternative treatments for patients who cannot receive current guideline recommended reperfusion therapies and made the following points:

- The trials consistently demonstrate that patients with confirmed cortical infarcts are more likely to achieve favorable disability outcomes and improved quality of life compared to sham controls.
- The final device has been engineered to ensure that stimulation is delivered within the most effective dose range and allows for a highly simplified implant procedure.
- The safety profile is favorable with a reduced risk of symptomatic intracerebral hemorrhage.

Q&A

Questions and Comments from the Panel:

Jose' Biller, M.D., asked the following questions:

- Are the aphasic patients intended to be part of an intervention?
- Were they participants or were they excluded?
- Is the device compatible with magnetic resonance imaging?

Magdy H. Selim, M.D., asked what percentage of the ASPECT patients was used as compared to vascular imaging, and how ASPECT was assessed in the trial.

Philip Posner, Ph.D., Patient Representative, asked if the device has the same contraindications as tPA. He also requested information on patients with afib, MS, Parkinson's, and epilepsy.

David J. Terris, M.D., asked for clarification about misplacement of the stimulation device and difficulty with extraction. He also asked if there were any issues with patients who had a large torus palantines.

Bevan Yueh, M.D., M.P.H., asked for further comment on the lower treatment effect in the U.S. population.

Answers and Responses from the Sponsor:

Dr. Saver informed the Panel that patients who received endovascular thrombectomy were excluded from the study. He addressed questions regarding ASPECTS-identified patients, noting that entry-level core lab readings for this group correlated well with Day 5 outcomes. He affirmed that the device has the same contraindications to anticoagulation as tPA; that epilepsy was not an exclusion criteria; and that patients who had Parkinson's, elevated INR, or who were on NOACs were excluded. He noted that difficulties with placement and extraction occurred almost entirely with the original implants and not with the final device. He also provided additional details on the lower treatment effect in the U.S. population.

Mr. Shai verified that the device is MR conditional and was successfully evaluated with a 1.5 and 2.5 tesla. He provided details on placement and extraction difficulties, noting that the first generation implant had a weak extraction thread that sometimes required special equipment to remove it. He specified that abnormalities in the oral cavity that would prevent access to the canal was an immediate exclusion.

Chris Mullin explained that the p-value for the dose effect is from logistic regression with a cubic spline model.

FDA PRESENTATION

Background Information

Xiaorui Tang, Ph.D., outlined the presentation, reviewed the panel discussion topics and the proposed indications for use, and gave a brief description of the device and its regulatory history.

Clinical Data and Testing - Study Summaries

Claudette Brooks, M.D., discussed clinical evidence from the ImpACT 24A, 24B,

and 24M studies and highlighted the following key points:

ImpACT-24A

- The study was intended to be a prospective, randomized, double-blind, sham-controlled, multi-national study.
- The primary objective was to assess the safety and effectiveness of SPG stimulation with the ISS device.
- The planned enrollment of 660 subjects was terminated early due to a high rate of device misplacement.
- Post-hoc analysis evaluated indications of potential benefit in patients with aphasia and cortical infarct.

ImpACT-24B

- Primary effectiveness was analyzed on two subgroups of the ITT patient population (mITT and CCI).
- Six percent of patients were U.S. patients (31 CCI patients).
- The observed treatment effect was smaller in U.S. patients.
- The device, study design, and statistical analysis plan were modified throughout the study - the final device was not reviewed.
- The sponsor reported that SPG stimulation did not increase the incidence of serious adverse events, symptomatic intracranial hemorrhage, or mortality compared to sham.
- Interpretation of clinical benefit is unclear.

ImpACT-24M

- The study was a prospective, multicenter, single-arm, seven-day usability study in 50 OUS patients evaluating the final ISS500 device design.
- Participants were mild stroke patients.
- Hand strength assessment showed an increase in the SPG group on the second treatment day.
- Common carotid duplex readings of blood velocity and vessel diameter found increased blood flow in the neck in the SPG group on the second treatment day.
- There was a high rate of successful implantation, shorter time, and fewer adverse events with the improved GuideView navigation system.

Statistical Uncertainties of ImpACT-24B

Anhua Lin, Ph.D., elucidated FDA's concerns regarding low U.S. enrollment in the 24B study and doubts as to whether the results can be applied to U.S. patients. He noted that the sponsor justified the smaller treatment effect by maintaining that the U.S. CCI population was not balanced in certain variables such as sex, diabetes, and obesity. The sponsor concluded that when the imbalance is accounted for, the outcome is on a par with other countries. He emphasized that there are further concerns with the sponsor's poolability

analysis, with ITT evaluation and validity of randomization, and with the use of the sliding dichotomy scale as the primary study endpoint.

Clinical Uncertainties of ImpACT-24B

Dr. Brooks then focused the discussion on ambiguities in the clinical data and reported outcomes. She took note of several significant changes in the device study protocol and SAP throughout the course of the study, such as the addition of the CCI subgroup analysis as a primary outcome, redefinition of the mITT patients, and the use of sliding dichotomous mRS analyses for both populations. In addition, questions surrounding device safety include risks of increasing cerebral blood flow in the target population, the rate of expected hemorrhage in the target population, and safety considerations related to the implantation and explantation procedure.

Benefit-Risk Discussion of ImpACT-24B

Dr. Brooks next identified the following issues related to benefits and risks:

- Observed effectiveness in the treatment population and other clinically relevant outcomes at 90 days did not meet pre-specified thresholds for significance.
- There are certain concerns regarding data, effectiveness results, and applicability to the target population of U.S. patients with acute ischemic stroke due to small sample size, reduced treatment effect, imbalance in risk factors, and reliance on an inaccurate model.
- There is also uncertainty as to whether all significant adverse events can be adequately captured during the treatment period.

Q&A

Questions and Comments from the Panel:

Patrick Lyden, M.D., asked if FDA is aware of any biological differences in the SPG cerebral physiology between U.S. and OUS patients. He also asked if there were any systematic differences in data collection, reporting of adverse events, and monitoring of unfavorable occurrences.

Earl Ray Dorsey, M.D., M.B.A., asked if there are any concerns that un-blinding occurred during the course of the study.

Dr. Selim asked if the study was adequately powered for the CCI population.

Dr. Yueh asked if FDA is cognizant of differences in the rigor of study surveillance and protocol adherence in other countries.

Answers and Responses from FDA:

Clarification on the IDE decision making process was provided by **Vivek Pinto, Ph.D.** He affirmed that the Agency had concerns regarding documentation provided by the sponsor.

Dr. Tang provided additional details on the following topics: the IDE review process,

FDA's recommendation for using a fixed dichotomous analysis, enrollment of U.S. patients, and concerns about un-blinding during the course of the study.

Answers and Responses from the Sponsor:

Dr. Saver presented data showing that 90-94% of the patients received antiplatelet agents or anticoagulants during the first five days when the implant was in place.

Mr. Mullin expounded on the sample size, noting that the volume of the CCI population is approximately the same as the original planned sample size for the variance of 14 percentage points.

OPEN PUBLIC HEARING

Nina Zeldes, Ph.D., spoke on behalf of the National Center for Health Research. She stated that the center agrees with many of the issues highlighted in FDA's review, noting that the most favorable analysis of the CCI group is not relevant to the exact version of the product currently under review and that it would not be appropriate to approve a device based on a pivotal trial that evaluated a different version. She highlighted specific concerns, including interpretation of effectiveness, device revisions and protocol changes, and the small number of U.S. patients in the pivotal trial. She cautioned that serious consequences may have been discounted in the clinical studies, and that the slight benefit seen in U.S. patients is not clinically meaningful.

Michael Abrams, M.P.H., Ph.D., spoke on behalf of Public Citizen. He stated that the organization has strong misgivings about approval of the ISS500 for various reasons, noting that the data failed to provide reasonable assurance of effectiveness, that the post hoc subpopulation analysis is questionable, and that the primary efficacy outcome is suspect in its derivation. He also pointed out that the device used in the pivotal study is not the final product.

Stefan Schwab, Dr.med., Dr.h.c., stated that the ISS500 widens the window of time and opportunity for patients who cannot receive recanalization, and that various aspects of the clinical studies made them unique and scientifically sound.

Megan Trussel shared her experience as a participant in the BrainsGate clinical trial. She testified that she felt no pain during implantation or explantation of the device, that she had no need for aspirin, and that it seemed like nothing had happened.

David Z. Rose, M.D., discussed the unmet needs of stroke patients who do not qualify for medical or device therapies. He encouraged further research and continued usage of the ISS500 if it shows considerable significant improvement in outcomes.

Kathy Palmer recounted her mother-in-law's experience with stroke and as a recipient of the ISS500 in the BrainsGate clinical trial. She stated that the procedure was quick, that it was well-tolerated with no pain or discomfort, and that the rapid improvement in her appearance and mobility was remarkable.

Barbara Barker, a severe stroke patient who received treatment with the ISS500, testified that the procedure went smoothly, that she did not need pain medicine, that she had no loss of memory, and that she can do everything she did before the stroke.

Tracy Vest testified that he chose treatment with the ISS500 for his wife after she suffered a severe stroke. He affirmed that within a few days of the procedure, she had regained consciousness, that she was able to raise her arm, and that she was capable of limited speech and ambulation. He further affirmed that she is now a healthy person and that if they were to find themselves in that situation again, they would choose the same option.

Steven Cramer, M.D., opined that only 5% of ischemic stroke patients have significant improvements in their outcomes as a result of iatrogenic interventions and that treatment options are still limited. He emphasized the need for new, innovative therapies that will improve stroke outcomes and promote neural plasticity.

Jussie Correia Lima, M.D., stated that most of the patients who arrive at his facility are not candidates for any of the current treatments, and that he can only offer to observe them and give them aspirin or clopidogrel. He further stated that he believes the ISS500 could aid in improving their outcomes.

Mauricio Concha, M.D., an investigator in the ImpACT-24B trial, made the following observations:

- There is a need for this type of treatment.
- The subgroup of patients who can be offered the possibility of mechanical thrombectomy is limited.
- The system stimulates collateral circulation around the stroke area, improving blood flow near the blocked artery.

He averred that the procedures he performed were uncomplicated and well tolerated, that none of his patients had issues with aspiration, that there were no infections or hemorrhages, and that removal was simple with no anesthesia required.

FOLLOW-UP QUESTIONS TO MORNING SESSION

Questions and Comments from the Panel:

Rory A. Cooper, Ph.D., asked if there were any device failures or unexpected responses.

Byron G. Thompson, Jr., M.D., asked for additional info on device placement confirmation.

Answers and Responses from the Sponsor:

Dr. Saver specified that the bias treatment was consistent throughout 24A and 24B,

that there was variation in the implantation process, and that the treatment regimen was the same. He indicated that placement was confirmed in all of the active patients and that the learning curve was successfully traversed to the final device.

Mr. Shai confirmed that all electrical parameters were identical in both implant types and provided details on biocompatibility, electro-magnetical, and functional testing. He presented a slide showing placement of the electrodes near the SPG and confirmed that there were no cases of major bleeding. He also noted that the distal electrode is smooth and rounded and would not penetrate an artery.

SPONSOR AND FDA RESPONSE

Dr. Saver presented the following data in response to questions posed by the Panel:

- absolute change in end-diastolic cranial flow;
- key components factoring into the adjustment of imbalance between the U.S. cohort and CCI population;
- quantitative numbers showing that blinding was not penetrated in the study;
- Day 5 CT-scan findings of radiologic hemorrhages; and
- analysis of high-income countries.

He affirmed that there were no events of facial numbness, weakness, or vision loss; that there were fewer hemorrhages in the SPG group; and that aphasia patients were included in the pivotal trial. He also noted that there was very high compliance with the monitoring plan and that 100% of charts and critical data were observed.

Dr. Pinto provided additional information on changes to the protocol with respect to un-blinding, and commented on the precision of study observation in other countries.

Dr. Lin expounded on inaccuracies of the VISTA model, and disparity between the ITT and mITT analyses.

Dr. Saver explained how adequate blinding was achieved in the sham group and asserted that the sponsor, investigators, and the steering committee were not aware of the data from 24B when the CCI population was added. He spoke to the performance of the VISTA model, noting that other ways of looking at the data all show the same thing as the sliding dichotomy. He affirmed that there was a biologic constraint on the approach to dosing and that the tolerance level did not seem to be related to stroke severity. He presented data showing similarities in age, stroke severity, and stroke scales in excluded patients and subjects in the CCI population, noting that misplacements were part of the developmental process and were not due to patient characteristics.

PANEL DELIBERATIONS

There was general discussion about aerosolization during device deployment and whether or not the CCI population is a recognized subgroup. Panel members overarchingly

agreed that an alternative therapy is needed and that the post hoc analysis is a cause for concern.

Elijah Wreh, M.S., Industry Representative, pointed out that all stroke patients have unmet needs and can benefit from the device, and that the A+P/A+B poolability is supported by a draft guidance issued by FDA.

Dr. Posner commented that as a stroke patient himself, he would have been glad to have an option that was contingent on what the potential adverse effects might be. He also expressed concern about how much voltage is being delivered to the ganglion and what effect the procedure may have on the trigeminal nerve.

Veverly M. Edwards, Consumer Representative, stated that she would have opted for a new and less invasive treatment for her daughter if it had been available. She pointed out that there are questions that need to be answered and more research that needs to be done.

FDA QUESTIONS

Dr. Pinto read Question 1: The ImpACT-24B pivotal study was conducted from 2011-2018. The sponsor selected the 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 SPG stimulation group after randomization, compared to 0 from the sham group.

Please discuss the effect on the external validity of the trial results.

A discussion took place regarding the decision to modify the intent to treat population. **Richard Chappell, Ph.D.,** pointed out that there was very little change in the subgroup analysis, while **Dr. Selim** expressed misgivings about the post hoc nature of the addition of the CCI population and whether the sample size is sufficient to have a definite answer for this subgroup.

Dr. Yueh pointed out that there was enough dropout to substantially change the precision of the randomization, and questioned whether the CCI is actually accepted by physicians as a subgroup in the clinical realm.

Panel members then shared their perspectives on the efficacy of the treatment. It was noted by **Dr. Lyden** that if there was a robust effect, the outcomes would be more consistent. **Dr. Pinto** confirmed that the procedure could be limited to certain professionals as a risk mitigation strategy, along with labeling, product redesign, and restricting the indications for use to specific populations. **Dr. Cooper** also recommended additional data collection on the U.S. patients.

Chairperson Jensen noted that the Panel does not seem to think that there is no validity to the trial results, but that it is difficult to determine how strong that validity is. She further noted that another issue is determining whether or not the CCI is actually a group that should be studied independently regarding the treatment effect.

John Marler, M.D., then asked the Panel members for input on the importance of having blinded treating investigators. The general consensus was that if patients do not

know what they are getting and are subsequently followed up by evaluators who do not know what they got, it would not matter if the implanter knows or not.

Dr. Pinto read Question 2: U.S. patients comprised 6% of the patients in the 24B trial and the patients treated at U.S. sites demonstrated a smaller clinical effect (2.6% effect in the CCI subgroup) compared to those treated OUS (9.9% effect in the 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?

Several of the panelists answered no. **Dr. Lyden** disagreed that OUS results cannot be generalized to the U.S. population. He then made the following points:

- FDA did not present any biological rationale as to why patients would be different in one country versus another with respect to anatomy and physiology relevant to the device.
- There is no statistical evidence of an interaction effect.
- All of the treatment effects appear to be concordant and identical.
- The sponsor asserted that monitoring was done in the same way across countries.

Dr. Selim questioned why the biology would be different. He added that his main concern is the small number of U.S. patients.

Chairperson Jensen noted that the Panel members have concerns, but there is no real consensus.

A discussion then took place as to why stroke is the fifth leading cause of death in the United States but the second leading cause in the rest of the world. Some members theorized that there is greater access to different therapies in the United States, and that cause of death may be defined differently in other countries. Other members opined that it might have something to do with genetic differences and prevalence of tobacco use.

Dr. Pinto read Question 3: The sliding dichotomous scale used a prognostic model (VISTA) to predict 3-month disease natural history outcome of all subjects in the ImpACT24B 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?

Dr. Selim pointed out that no information was provided regarding the clinical characteristics of the VISTA population compared to the study population and that he disagrees with using the sliding dichotomy as a primary outcome.

Dr. Lyden specified that what he observed is natural variation in a prediction model, that he did not see evidence of inaccuracy, and that he has not seen anything to indicate that the model is erroneous or invalid.

Dr. Yueh agreed that there is some variation. He added that the shift analysis convinces him that if there is an effect, it's for the SPG group.

Chairperson Jensen summarized the Panel's response:

- The VISTA model is not inaccurate.
- The sliding dichotomy had the same magnitude of treatment effect in other outcomes; therefore, the evidence that was shown is correct.

Dr. Pinto read 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 U.S.

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?

Randy D. Trumbower, Ph.D., made the following observations:

- The modifications would, in some way, compromise the rigor.
- Making these kinds of adjustments during the course of a pivotal trial would not be expected and a follow-up study may be required.

Dr. Terris agreed that it would be atypical to make changes like these in the middle of a trial. He added that they seem to have been attempts to improve the device and make it easier to use.

Dr. Chappell asserted that changing the analysis after seeing the data will degrade the quality of a study.

Chairperson Jensen summarized the Panel's response:

- The device changes are not troubling, it is something that should be anticipated over a 10-year period; subsequent iterations should be expected to make a device safer or easier to use.
- There is more concern about the study design changes; this could be the result of knowledge gained at an earlier phase of the trial and may necessitate a follow-up study.

Dr. Pinto read Question 5a: 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?

The Panel also discussed Question 5b: The rate of hemorrhage was quite a bit lower

than expected in this population. Was the imaging data sufficient to assess this adverse event?

Dr. Selim pointed out that the data did not suggest an increased risk of hemorrhagic transformation.

Dr. Lyden observed that the rates of symptomatic ICH in the trial were appropriate for stroke patients who are getting some form of treatment.

It was also noted that the data is concordant with what would be expected from other studies and publications.

A discussion then took place regarding magnetic resonance imaging versus computed tomography as a more appropriate vehicle for detecting potential complications.

Julie Pilitsis, M.D., Ph.D., stated that the adverse events were on par with what would be expected and that she is not unduly concerned about whether the imaging could have been better.

Chairperson Jensen summarized the Panel's response:

- The information collected was sufficient to look for potential risks to health (primarily hemorrhage).
- There is uncertainty as to whether or not another imaging study is needed.
- MR imaging may be useful at some point in time and should perhaps be considered.

Dr. Pinto read Question 5c: 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?

Dr. Posner mentioned the possibility of hyperactive gag reflex. There was agreement that coughing and aspiration are always potential issues, and **Dr. Selim** pointed out that there was no specific mention of dysphasia.

A discussion then ensued about potential risks in the palate and issues with sphenopalatine ganglion stimulation.

Dr. Terris stated that the technique is good, that it is reasonably safe, and that he would not expect major issues.

Chairperson Jensen noted that the Panel believes the device is reasonably safe and that there are no concerns about long-term serious effects.

Dr. Pinto read 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)?
b. What expertise would be needed to implant the device, and is the training program proposed by the sponsor sufficient?

There was discussion regarding the appropriate number of training sessions. **Dr. Thompson** was of the opinion that it would take more than five while **Dr. Pilitsis** noted that that amount is in accordance with current ACGME pain therapy guidelines.

Other members indicated that it seems to be a safe procedure and could probably be picked up fairly easily. **Dr. Yueh** pointed out that some neurologists may not be comfortable doing it and that it could take a while to get to five cases in centers that don't have much volume.

Gordon H. Baltuch, M.D., Ph.D., asked where these procedures will take place and pointed out that there had been no discussion about problems with the navigation system.

Chairperson Jensen summarized the Panel's response:

- There are always potential risks, but the device seems to be relatively safe, accurate, and reliable in terms of implantation.
- There is some concern that five procedures may not be enough for an individual to be considered sufficiently trained.
- Sites are encouraged to make use of all subspecialty physicians in utilizing the device.
- More information is needed on the actual training and what the sponsor can provide in terms of backup support.

A discussion then took place regarding what measures could be added to a post-approval study to address these concerns. **David J. Kennedy, M.D.,** suggested definition of the learning curve based on the newest version of the device and **Dr. Pilitsis** requested post-op saggital images.

SUMMATIONS

Dr. Pinto thanked the Panel, the FDA staff, the sponsor, and all of the patients who participated in the clinical trials.

Dr. Saver stated that he believes the data has shown that safety was demonstrated in a large randomized trial population, that an increased effect was seen in the confirmed cortical infarct cohort, and that there was consistency across all of the endpoint analyses. He further stated that the sponsor is of the opinion that there is a positive benefit-risk profile, and that the evidence provides a strong assurance of safety and reasonable assurance of effectiveness.

FINAL COMMENTS

Ms. Edwards stated that there is a need for more information and additional trials.

Dr. Posner remarked that the device will not only be of benefit to him, but to all stroke patients who cannot get to the ER in time.

PANEL VOTE

Mr. Collier read the safety and effectiveness definitions. He explained the voting procedure and read the voting questions.

Question 1: 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 unanimously 13 yes.

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

The Panel voted 3 yes, 7 no, with 3 abstentions.

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

The Panel voted 3 yes, 7 no, with 3 abstentions.

Chairperson Jensen asked the Panel members to discuss their votes.

Dr. Baltuch indicated that he voted yes, no, and no. He stated that he would be more convinced with a study that had been done mainly in the United States with more robust evidence for effectiveness.

Dr. Selim indicated that he voted yes, no, and no. He stated that his concern is with the post hoc analysis and that he would be in favor of a new prospective study that would address this issue with an explicit image-based definition of cortical infarct.

Dr. Yueh indicated that he voted yes on Question 1, no on Question 2, and abstained on Question 3. He stated that more data on the CCI population would be helpful.

Dr. Cooper indicated that he abstained on Question 2 and voted no on Question 3. He stated that more U.S. evidence is needed, including MRI imaging.

Dr. Thompson indicated that he voted yes, no, and no. He stated that his no votes were based on the ad hoc changes and the way that they compromised the study results.

Dr. Kennedy indicated that he voted yes, no, and no. He stated that his no votes were based on concerns about the ad hoc and statistical changes in the studies.

Dr. Biller indicated that he voted yes on Question 1 and abstained on Questions 2 and 3. He stated that he hopes more data will become available.

Dr. Pilitsis indicated that she voted yes on all three questions. She stated that her votes were influenced by the poolability and size of the data, and that the risk profile is

minimal.

Dr. Lyden indicated that he voted yes, no, and no. He stated that the trial failed on its primary and modified intention-to-treat endpoints, that he has no concerns about the poolability across countries, and that the rest of the methodology was effective and worthwhile.

Dr. Chappell indicated that he voted yes on all three questions. He stated that he would like to see a confirmatory trial using the subgroups that were specified from the beginning, as well as the outcomes recommended by the Panel.

Dr. Dorsey indicated that he voted yes on all three questions. He stated that there was a reasonable assurance of efficacy based on the data and that the study was well conducted.

Dr. Trumbower indicated that he voted yes, no, and no. He stated that the effectiveness for the primary endpoint was not convincing and that he would like to see a replicated prospective study that is focused on the new, more convincing endpoint.

ADJOURNMENT

Chairperson Jensen thanked the Panel, FDA, the sponsor, and the open public hearing speakers for their contributions to the meeting.

Dr. Pinto expressed his appreciation for the Panel's attention and feedback.

Christopher Loftus, M.D., thanked the Panel members for sharing their expertise.

Chairperson Jensen then adjourned the meeting at 6:25 p.m.

I certify that I attended this meeting on December 10, 2021 and that these minutes accurately reflect what transpired.

Jarrod W. Collier -S

Digitally signed by Jarrod W. Collier -S
Date: 2022.09.19 14:46:41 -04'00'

Jarrod Collier, M.S.
Designated Federal Officer

I approve the minutes of this meeting as recorded in this summary.

Mary Jensen, M.D.
Chairperson

Summary Prepared by

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