FDA Executive Summary

Ischemic Stroke System (ISS500)

Pxxxxxx

Neurological Devices Advisory Committee Meeting
December 10, 2021

Sponsor: BrainsGate LTD

Synopsis

FDA requests that the Neurological Devices Panel of the Medical Devices Advisory Committee help evaluate the safety and effectiveness of the BrainsGate Ischemic Stroke System (ISS500) 8 to 24 hours after stroke onset for reducing disability at 3 months after acute ischemic stroke in patients with confirmed cortical involvement in the anterior circulation who are ineligible for or have no access to either thrombolysis or endovascular thrombectomy. The ISS500 has three components which provide electrical stimulation to nerves in the region of the sphenopalatine ganglion. The stimulation is applied 4 hours per day for 5 days. The determination of the stimulation level varied between studies.

This synopsis provides an overview for the Panel to consider evidence the sponsor has presented and the safety and effectiveness of the ISS500 device. The results of all analyses in this document have been those performed by the sponsor unless noted otherwise.

The pivotal clinical study is the ImpACT-24B, a 1078-patient, multi-national, sham-controlled, randomized trial. The protocol provided procedures for masking treatment assignment to the patients, the sponsor, and the raters, but not the treating investigators. The sham devices included all components of the device except for the stimulator component of ISS500, which was not implanted. There was no sham stimulator in this trial. Note that the device changed in terms of design during the course of the study. Additionally, the objectives of the study were changed during the course of the study. Significant changes in the primary outcome and statistical analysis were made after two interim analyses and most of the patients in the study had been randomized.

The sponsor chose the modified Rankin Scale (mRS) at 3 months as the primary patient-level clinical outcome measure for the pivotal clinical study. This scale ranks the degree of functional impairment into six categories of disability: none (0), not significant (1), slight (2), moderate (3), moderately severe (4), severe (5) and dead (6). The primary study outcome was the difference between active and sham cohorts in the proportion of patients with an mRS scale score at 90 days after stroke that was 1 point better (lower) than an expected "sliding scale" mRS score determined by a prognostic statistical model using baseline stroke severity (NIH Stroke Scale), age, and affected body side.

The sponsor tested for effectiveness in the 1000-patient modified intent-to-treat population (mITT). Subsequently, a 520-patient "responder" subpopulation of the mITT population was added to the primary study outcome analysis plan late in the study.[1] Reportedly before unblinding, the CCI[2] responder sub population was defined retrospectively using imaging showing signs of stroke in the cortex and an NIH Stroke Scale score greater than 9. In a hierarchical analysis, the boundary for statistical significance in the mITT group was 0.05 and for the responder CCI group was 0.025.

The planned analysis failed to meet statistical significance in the mITT population and responder (CCI) population but were close in the CCI population. See Table 1 below.

[1] The two arms of the study are referred to as "sham" and for the active treatment arm either "ISS," "treatment," or, as the sponsor does, "SPG" referring to the sphenopalatine ganglion.

[2] The sponsor uses the phrase "confirmed cortical involvement" (CCI) to describe the responder subpopulation. "Patients were classified as CCI if they had NIHSS≥10 and their stroke involved at least one of the cortical ASPECT regions (M1-M6 and Insular Cortex). If ASPECTS was not available, patients with NIHSS≥10 and total occlusion of a large anterior circulation vessel on CTA were also considered to have confirmed cortical involvement." Clinical Study Report ImpACT-24B, page 49 of 297.

Primary Effectiveness Outcomes for mITT and CCI Responder Groups Modified Rankin Score Less Serious than Expected at 90 Days after Stroke[3]					
Analysis Group (n)	Response Rate		Absolute Difference	Odds	p-Value
	ISS	Sham			
mITT (1000)	48.6 % (481)	45.5 % (519)	3.2%	1.14 (0.89–1.46)	0.31
CCI Subset of mITT (520)	49.6 % (244)	39.9 % (276)	9.7%	1.48 (1.05–2.10)	0.0258

Table 1 Primary Effectiveness Outcome for ImpACT-24B Trial

Before starting the ImpACT-24B study, the sponsor had identified a number of boundaries for clinical significance, the lowest was a 7% difference favoring the active treatment group.[4] Using this definition of clinically significant, the mITT analysis demonstrated a 3.2% difference (p=0.31) and the subpopulation analysis showed a 9.7% difference (p=0.0258). This table does not differentiate between countries included in the study. FDA has concerns that these analyses underestimate the degree of uncertainty that accompany these results and other explanations for differences observed between groups than ISS500.

FDA has carefully reviewed the submission and has identified several concerns for discussion by the Panel. Because there appeared to be a larger effect size in the CCI subpopulation, the sponsor is asking for approval for use only in the CCI subpopulation rather than the mITT population.

While we expect that pivotal studies investigate final, finished devices, the sponsor's pivotal study, ImpACT-24B, included several iterations of the device and different stimulation levels on the recruited patients from June 2011 until March 2018.

The rest of this synopsis provides summaries of some of our concerns for discussion with the Panel. The purpose is to provide a background and not the full detail. More detail is provided in the full document.

Concern #1: Questions regarding the statistical and clinical significance of the results in the indicated population

The ImpACT-24B trial randomized 1078 patients (ITT population). However, patients were excluded because investigators were not able to place the stimulator, or the stimulator was placed but no stimulation was delivered (mITT population). Usually, for a pivotal study, the difference between an ITT and mITT population is a few patients evenly distributed between study cohorts. This was not so in the ImpACT-24B study.[5] There was an imbalance between treatment groups in the number of randomized patients in the ITT population who were excluded from the mITT and CCI populations. See Table 2 below.

[3] Abstracted from Table 3 in Clinical Investigation Report – ImpACT-24B, page 21 of 297.

[4] "If the observed treatment effect is < 7% or the primary endpoint does not reach statistical significance, the Sponsor will consider the study as a failure and will not submit a PMA to the US FDA." June 20, 2018, Protocol for IMPACT-24B Trial, page 63 of 91.

[5] Clinical Investigation Report ImpACT-24B, April 29, 2021, Page 83 of297

CDRH evaluated the effects of this imbalance in the CCI subpopulation.

Responder Group in Study ImpACT-24B CCI Patients Excluded from ITT Population to Form the CCI Population			
	SPG	Sham	Total
Randomized Patients with CCI (n)	278	276	554
CCI Patients not in CCI Population(n)	34	0	34
CCI Patients not in CCI Population(n)	12%	0%	6%
CCI Population(n)	244	276	520

Table 2 Imbalance in CCI Population Excluded from ITT Population

There were 554 randomized patients satisfying the definition of CCI (SPG: 278, sham 276). The final CCI analysis population included all 276 sham patients but excluded 34 (12%) of the CCI patients because they didn't receive SPG stimulation. This difference in the exclusion rates (12% SPG vs. 0% sham) raises the question whether the balance between treatment groups achieved by randomization still holds in the CCI analysis subpopulation. In the ImpACT-24B study, this imbalance between the study cohorts raises serious doubts about the results of the study.

FDA conducted an exploratory ITT analysis on the primary endpoint in the whole CCI subpopulation. The result is that the SPG responder rate is 46.4% and the sham responder rate is 39.9% with p-value: 0.12. This difference is 6.5% which is below the the effectiveness threshold established by the original version of the protocol.[6]

Concern #2: The sliding dichotomy scale outcome measure

The primary effectiveness endpoint of the ImPACT-24B study was the sliding dichotomy mRS at the 90-day visit. Success in the sliding dichotomy primary outcome was defined as mRS better than a prediction of the 90-day mRS score using a statistical model using the NIH stroke scale, patient age, and the side of the stroke from 8 previous trials in the VISTA database.

Because of an unexpected degree of inaccuracy found in the VISTA model prediction, FDA is concerned about the how to interpret the study results from the ImpACT-24B effectiveness analysis. A patient may be labeled as a responder by the model even if the treatment had no or very little effect. To assess the accuracy of the model predeiction, we compared the actual mRS and predicted mRS of the 519 patients in the sham group of the ImpACT 24B study. Because no device was placed in the canal near the SPG, patients in the sham group should not experience any device effects. Therefore, if the model were ideal, there should not be any responders due to device effects in this sham group: any responders would only be due to the non-specific effects of enrollment in the trial. The FDA expectation is that model would accurately predict the 90-day mRS in the sham group. FDA performed a post-hoc analysis that indicates that the VISTA model's accuracy to predict the observed mRS is 22.2%. See Table 3, below.

[6] "If the observed treatment effect is < 7% or the primary endpoint does not reach statistical significance, the Sponsor will consider the study as a failure and will not submit a PMA to the US FDA," ImpACT 24B Protocol Version 1A, June 27, 2011, page 64 of 94.

90-day Actual mRS vs. Predicted mRS in mITT Sham Group
ImpACT-24B

Original VISTA Sliding Scale Model

Predicted mRS	0	1	2	3	4	5	6
6					1	1	
5					1	8	8
4	9	10	22	43	32	44	38
3	21	46	54	50	19	15	16
2	14	14	24	17	2	3	4
1	1	1	1				
0							

Actual mRS in Sham Group

The Y-axis of the table is the predicted mRS score using the Original VISTA model, and the X-axis is the actual mRS score. The numbers in orange represent correct predictions where the model prediction matches the actual mRS outcome. The numbers in blue and green are all erroneous predictions. From these data, the model demonstrates 22.2% accuracy (the sum of all orange numbers divided by the number of sham 519 patients, or 115/519).

Table 3 Accuracy of Original Vista Sliding Scale in Sham Group of ImpACT 24-B Trial

FDA considered the imperfect performance of the VISTA model a serious confounder of the sliding dichotomy responder analysis. Discussions with the sponsor did not anticipate 22% accuracy. It is not clear how much of the observed treatment difference between the two arms should be attributed to the imbalance of this factor which cannot be measured. This concern is greater for even smaller cohorts, for example, the United States CCI subgroup with only 19 SPG and 12 sham patients.

Because of the uncertainty associated with the sliding scale analysis, FDA conducted a post-hoc shift analysis using the van Elteren test as described in [Savitz, et al.] to directly compare the distributions of 90-day mRS of the two arms. FDA chose the shift analysis because it also looks at change across the whole spectrum of the mRS and would reasonably be expected to align with the sliding scale if the predicted values were accurate. In early discussions of the patient-level outcome measure, the sponsor had agreed that the shift analysis would be best for a device like the ISS500 that could cause improvement across the entire range of the mRS.[7] Our null hypothesis was that receiving the active or sham treatment was not associated with the 90-day mRS. For the 90-day mRS in the mITT population the p-value was 0.3979 using the van Elteren Test. For the CCI population, the shift analysis p-value was 0.0748, considerably higher than the p-value of 0.0258 using the sliding scale.

We believe the three post-hoc analyses (sponsor's sliding scale with an updated model, and FDA's direct shift comparison) clearly demonstrate the uncertainty inherent in the sliding scale model that the sponsor used to evaluate the effectiveness of the ISS500. This uncertainty is in addition to that caused

[7] G070134/Supplement 040, April 13, 2011, "Rather, the community strongly favors the shift approach, with an acceptable second choice of using the sliding dichotomy … Accordingly, even though the best analysis for this type of effect would be the shift (CMH) analysis, we are willing to compromise on the Sliding Dichotomy responder analysis, as we are striving for a unified US and OUS protocol, with identical end-point analysis and population." Late in the study when the sponsor added the CCI group as a primary outcome using the shift analysis, FDA objected to using different outome measures for the CCI group than the mITT.

by the unbalanced randomization in the CCI population.

Concern #3: The sponsor made significant protocol and SAP changes late in the course of the study

There were several significant changes in the device, study protocol and SAP throughout the 7-year ImpACT-24B study including a change in the pivotal study primary outcome late in the study. Significant changes in the primary outcome analysis and statistical analysis plan were made after two interim analyses and late in the study. Normally, FDA expects the primary statistical analysis to be established before any interim analyses. For that reason, the sponsor submitted a statistical analysis plan before the planned interim analysis described in the protocol. There were procedures to blind patients and raters in the protocol, but none to blind the treating investigators whose expectations and communications with the Steering Committee may have introduced bias during the decisions regarding final protocol changes made after the first and second interim analyses. CDRH generally regards post-hoc protocol changes as increasing the uncertainty of the results. Additonal changes were made after the second interim analysis.

Some examples of changes include:

1. Adding patients with CCI as an additional primary endpoint.
2. A second interim analysis not mentioned in the initial protocol and performed before significant changes were made in the protocol and statistical analysis plan. Although the sponsor was blinded to the results, the DSMB was aware that the results indicated an unexpectedly small 2.47% difference between responder rates in the mITT population.[8]
3. Revising the SAP to define the mITT population as only the patients in which the implant was placed within 5mm from the SPG (instead of 15 mm).
4. Adding additional analyses on:
    a. Dichotomy mRS 0-2;
    b. Dichotomy mRS 0-3;
    c. Subgroup analyses by age, history of diabetes, history of atrial fibrillation; and
    d. Covariates that were not stratified when performing the adjusted analysis (age, baseline NIHSS, imaging showing cortical involvement).

Many of these changes were implemented in the last year of the study after more than 1000 patients were randomized, athough before locking the dataset. FDA is concerned about how the timing of these significant changes to the study protocol affects interpretation of the effectiveness study result, or the extent to which they were informed by information from interim analyses or unblinded treating investigators.

A change in design and clinical use during a study may affect effectiveness and safety. FDA generally considers that the device used in a pivotal clinical study should be the final device, and the device should be used consistently throughout the trial unless it is found to raise safety concerns or present a danger to patients (in which case, changes to the device or study protocol would be appropriate and necessary). As the ImpACT-24B proceeded the device changed and the sponsor changed the implantation procedure, stimulation levels, and implant placement parameters.

The new analysis plans were retrofitted to patients that were treated in different stimulation levels and with different models of the device. This was done rather than performing a second study with the final device in an appropriately powered sample of patients from the intended use population, which may have reduced the uncertainty present in the ImpACT-24B safety and effectiveness results.

[8] DSMB Confidential Closed Minutes, May 15, 2016.

Concern #4: Applicability of study results to US patients

In the 1000-patient ImpACT-24B mITT population, there were 60 US subjects (6%) from 6 sites who enrolled in the trial between 2012 and 2015. Within the 520-patient confirmed cortical involvement (CCI) subpopulation, there were 31 US subjects (6%). In the US CCI population, the success rates were 52.6% and 50.0% for treated versus sham patients (10 of 19 and 6 of 12, respectively). This 2.6% difference between groups is smaller than the 9.9% rate in patients from sites outside the US but similar to the difference seen in the mITT group. See Table 4, below.

	US Subjects			OUS Subjects			Interaction P-value
	SPG stim (N=19)	Sham stim (N=12)	Odds ratio (95% CI)	SPG stim (N=225)	Sham stim (N=264)	Odds ratio (95% CI)	
Sliding Dichotomy	52.6% (10/19)	50.0% (6/12)	1.11 (0.26-4.72)	49.3% (111/225)	39.4% (104/264)	1.50 (1.05-2.15)	0.69

Table 4 Comparison of US and Outside US Primary Effectiveness Results in CCI Subgroup[9]

FDA expressed concern to the sponsor about the lack of effectiveness in the US population during the course of review. In response, the sponsor noted that the lower CCI success rate in the US CCI population was likely due to imbalanced baseline characteristics between the two study arms.

Concern #5: Safety of the device – treatment timeframe

FDA is concerned about the risk associated with direct and indirect consequences of implantation of the device and subsequent use that may have been under-represented in the clinical studies. These consequences may be uncommon but serious. Implantation of the device involves a puncture in the mucosa of the upper palate and insertion of the implantable neurostimulator (INS). Acute stroke patients may have different or changing levels of alertness depending on underlying health conditions and changing significance of blood flow changes hour by hour as the acute brain injury evolves.

Although not reported in the clinical studies, FDA is concerned that technical insertion difficulties for stroke patients who are already being treated with non-steroidal anti-inflammatory drugs (NSAIDs) may result in palate laceration, bleeding and swelling, and this may result in airway endangerment, laryngospasm, microaspiration, chronic neuropathic pain, acute pain, and the associated serious subsequent consequences. Most acute ischemic stroke patients, if not on these drugs prior to the stroke, are usually placed on antiplatelet or antithrombotic drugs with 24-48 hours of stroke onset as part of secondary stroke prevention treatment. This includes those patients that are ineligible for intravenous thrombolysis with TPA or endovascular thrombectomy (EVT).

Although not reported in the clinical studies, other safety concerns include potential risk to patients with sleep apnea or other chronic pulmonary conditions (upper or lower airway), the use or initiation of antiplatelet or antithrombotic drugs before, during or post implantation and explantation of the INS, bleeding, hematoma formation or infection within the implantation site or extension to involve the SPG, the effects of pain on an acute stroke patient that may include tachycardia and increased blood pressure.

There is concern regarding the unclear dose response in increased cerebral flow and other hemodynamic parameters that may result during this first neurostimulation treatment. The ischemic stroke patient is prone to cerebrovascular dysautoregulation. There is clinical concern regarding the next 5 days of treatment that occurs during a period when, in AIS, the cerebral tissue – the ischemic core and the penumbra – would be considered in a fragile state. Hemorrhagic transformation usually

[9] Abstracted from Table 95 in Clinical Investigation Report – ImpACT-24B, page 211 of 297.

occurs during this timeframe and cerebral edema that occurs usually peaks at day 3-5 post ictus. The proposed mechanism of action (MoA) for neurostimulation of the SPG is to increase cerebral blood flow (CBF) via collateral circulation to preserve as much cerebral tissue as possible. The device safety and effectiveness are not clear from the current results, particularly on the US CCI population and the totality of the data. It is not clear regarding the rationale for and safety of the use of the device on 4 successive days in AIS patients particularly those that have not undergone attempted or confirmed revascularization during a period when cerebral tissues are vulnerable in general and may be at risk for reperfusion injury as well as those previously mentioned. It is unclear if there is any or minimal benefit, and if it outweighs the risk of the full procedures of device use over 5 days (implantation and neurostimulation).

Concern #6 Can practicing physicians accurately select the same CCI subpopulation as that defined late in the ImpACT-24B study?

The ImpACT-24B study protocol did not appear to prospectively define the CCI subpopulation and did not appear to obtain consistent information necessary to determine whether a patient was in the CCI subpopulation. Decisions made in the acute care situation may not duplicate the characteristics of the CCI subgroup in the ImpACT-24B. This means the proposed indication for use may result in a group of patients with important differences from the CCI subgroup in ImpACT-24B and a failure of the trial results to translate to the clinical practice situation. If the ISS500 is effective in the CCI group, then the practicing clinician must be able to accurately determine whether a specific patient fits in the CCI group and is likely to benefit from treatment.

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1 Introduction

This document is FDA's Executive Summary of premarket approval (PMA) application Pxxxxxx from BrainsGate, Ltd, for the Ischemic Stroke System (ISS500) intended to treat acute ischemic stroke patients with confirmed cortical involvement in the anterior circulation between 8-24 hours from stroke onset.

This summary contains a brief device description, proposed indications for use of the subject device and a summary of the three clinical studies, ImpACT-24A, ImpACT-24B and ImpACT-24M, that are presented in support of a marketing application for the ISS500. Table 5 (below) summarizes the three clinical studies.

Study	N	Stage	Design	Dates	Main Objective
ImpACT-24A	253	Feasibility	Randomized Controlled Trial (RCT)	2009-2011	Safety and Signal of Efficacy
ImpACT-24B (pivotal)	1000	Pivotal	RCT	22011-2018	Safety and Effectiveness
ImpACT-24M	50	Usability	Single-Arm	2017-2018	Validate Implantation Procedure and Stimulation Level
Total	1303				

Table 5 Summary of the Clinical Studies Used to Support the Marketing of ISS500

ImpACT-24A was a prospective, randomized, double-blind, sham-controlled, multicenter study. The primary objective of the study was to assess the safety and effectiveness of Sphenopalatine Ganglion (SPG) stimulation with the ISS device. The first patient was enrolled in January 2009, and the last follow-up visit was in January 2011. The planned enrollment was 660 subjects. The study was terminated early due to a high rate of device misplacements before recruiting the planned sample size and was therefore underpowered to confirm or reject any hypotheses about safety and effectiveness.

ImpACT-24B was the primary (pivotal) study submitted to support the US marketing of the ISS500. ImpACT-24B was a prospective, randomized, double-blind, sham-controlled, multicenter study. The primary objective of the study was to assess the safety and effectiveness of SPG stimulation with the ISS500 in patients with confirmed cortical involvement (CCI) within 24 hours from stroke onset. Patients were recruited and randomized beginning June, 2011, and the last follow-up visit was in June, 2018. The multiplicity-adjusted

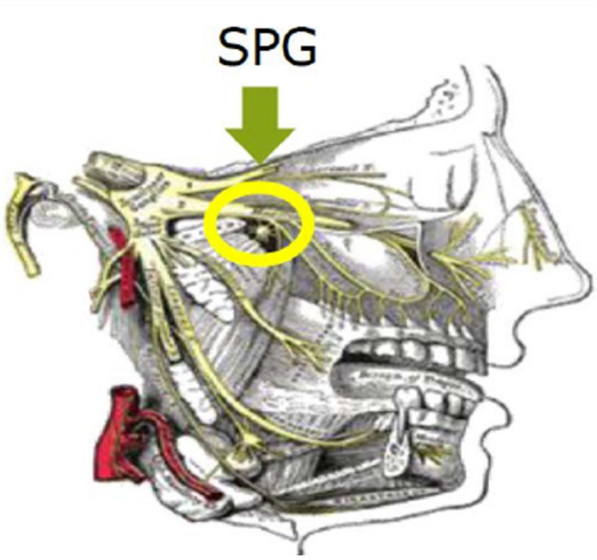
primary analysis just missed the formal significance level by 0.0008 (p=0.0258, compared to the p<0.025 multiplicity-adjusted type I error-rate threshold). (Note: There were two primary analysis populations in this pivotal study, and the overall type-I error was controlled at an overall 0.05 level using the Hochberg method, which requires p<0.05 in both populations or p<0.025 in one population).

ImpACT-24M was an exploratory, multicenter, single arm study. The primary goal of the study was to test the usability of the ISS500. The study focused on the implantation procedure, and correct setting of the stimulation level. Patients with mild acute ischemic stroke in the anterior circulation within 24 hours from stroke onset were recruited beginning May 2018, and the last follow-up visit was in September 2018.

2 Device Description

The ISS500 was evolved throughout the clinical studies used to support this marketing application. The Device Description section below provides descriptions on the final ISS500 device model that the sponsor intended to market in the US if the device is approved. More detailed information on the device evaluation history is provided in the "Regulatory History" section below.

The ISS500 is intended to treat acute ischemic stroke patients by stimulation of the Sphenopalatine Ganglion (SPG). In humans, there are two SPGs, one located behind each maxillary sinus; each innervates the ipsilateral hemisphere (see Figure 1).



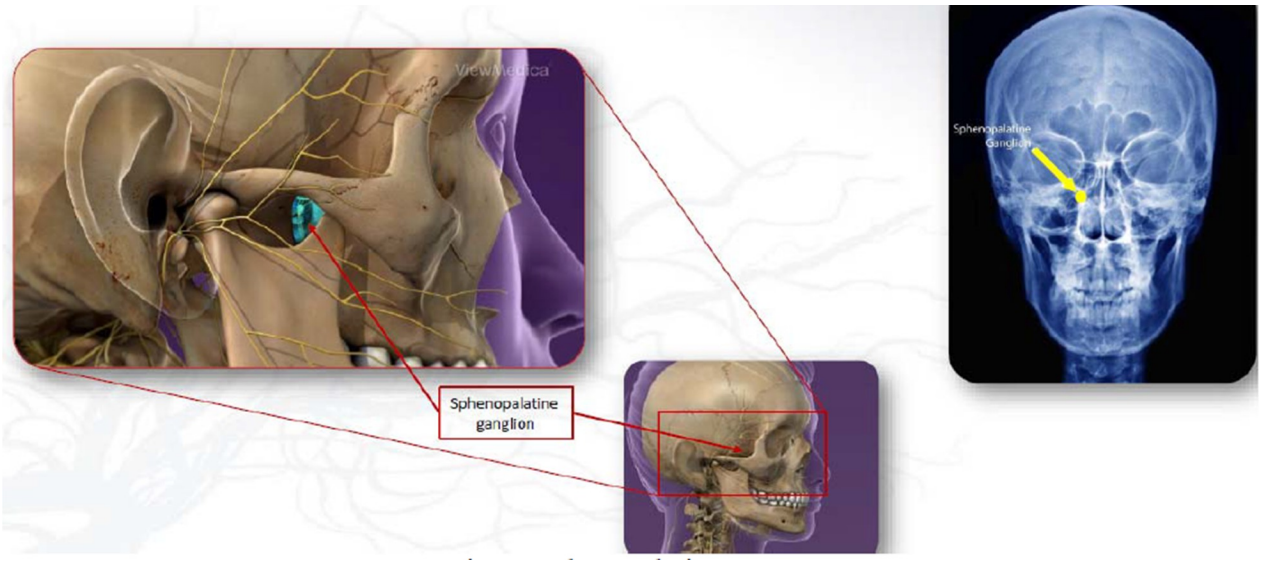


Figure 1 The Sphenopalatine Ganglion Anatomy

The ISS500 is comprised of a treatment subsystem and an implantation subsystem (see Figure 2):

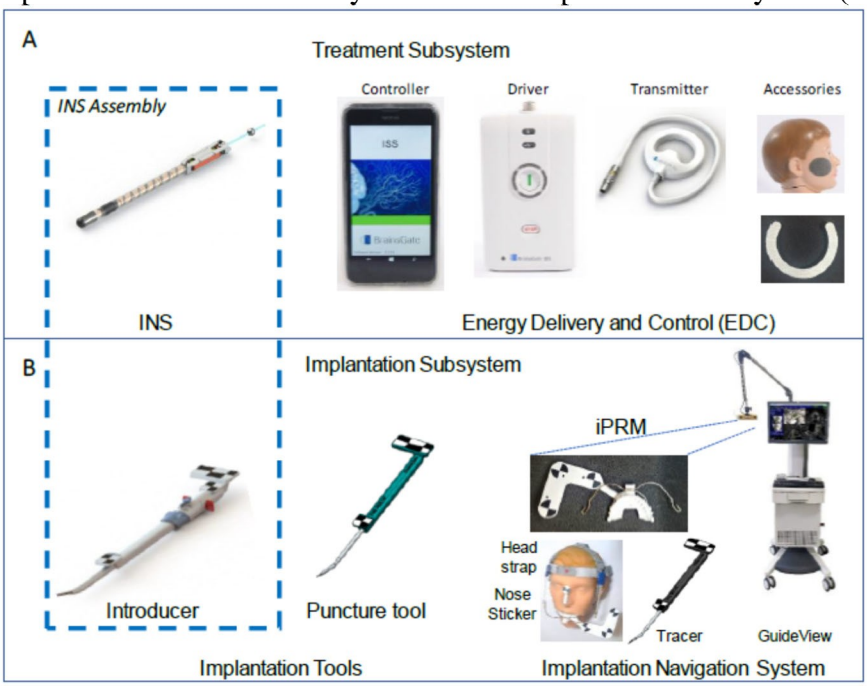


Figure 2 (A) Treatment and (B) Implantation Subsystems

2.1 Treatment Subsystem (Figure 2 A)

The role of the Treatment Subsystem is to deliver the stimulation to the patient during treatment. The Treatment Subsystem includes the following components:

- Injectable Neuro-Stimulator (INS), the INS is a single-use, disposable device and is provided sterile (Figure 3).

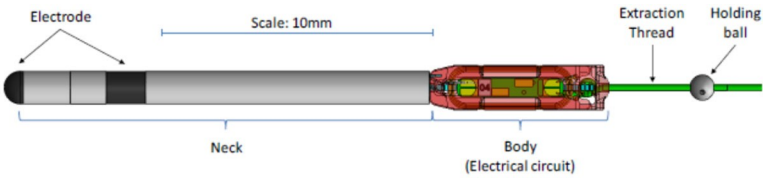


Figure 3 The Injectable Neuro-Stimulator (INS)

The INS structure is comprised of the following (see Figure 3):

1. Electrode – The bipolar electrode delivers the monophasic stimulation to the SPG.
2. Neck – The flexible neck structure consists of seven (7) vertebrae mounted on a Nitinol spine held in a tube (Figure 4). This neck structure allows the INS to follow the curved greater palatine canal pathways while ensuring it withstands the forces of implantation. The neck diameter (1.3 mm) and implant length (23 mm) allow for INS implantation regardless of anatomical variations of the greater palatine canal.

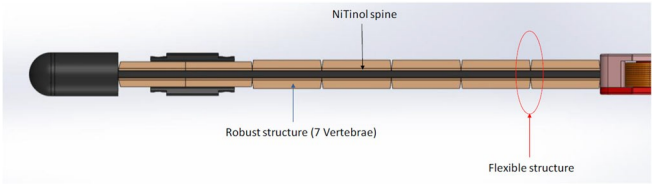


Figure 4 Flexible structure

3. Body (electrical circuit) – The body (Figure 3) houses the electronic components in a rigid, sealed bobbin structure.
4. Extraction thread with holding ball - The extraction thread is connected to the proximal end of the body, attached to the Nitinol spine in the bobbin (see Figure 3). A miniature stainless-steel ball is attached to the thread approximately 4 mm from the body. The ball is used to lock the INS in its place when inside the Introducer.

- Energy Delivery and Control (EDC) Set (Figure 5) delivers electrical energy to the INS, managing all treatment parameters. Energy is delivered using RF energy via a Transmitter that is attached to the patient's cheek. The EDC includes the following components:

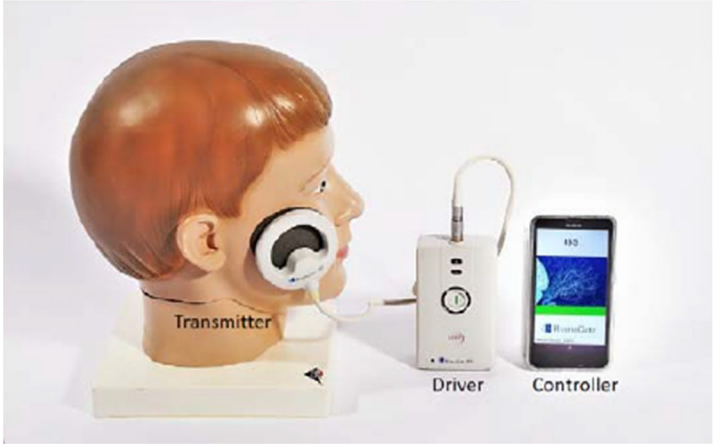


Figure 5 Energy Delivery and Control (EDC) Set

1. Controller – An off-the-shelf Nokia Lumia 635 running BrainsGate's Controller Software. It provides the Treatment Subsystem's graphical user interface.
2. Driver – An electronic microcontroller module which communicates with the controller, transmits RF energy through the Transmitter to the INS, monitors the treatment and generates treatment logs.
3. Transmitter – A RF antenna. Energy is transmitted wirelessly by magnetic inductance from a transmitter coil to the INS. The Transmitter has two sizes – regular and large (see Figure 6), which may be used depending on the size of the patient's face.

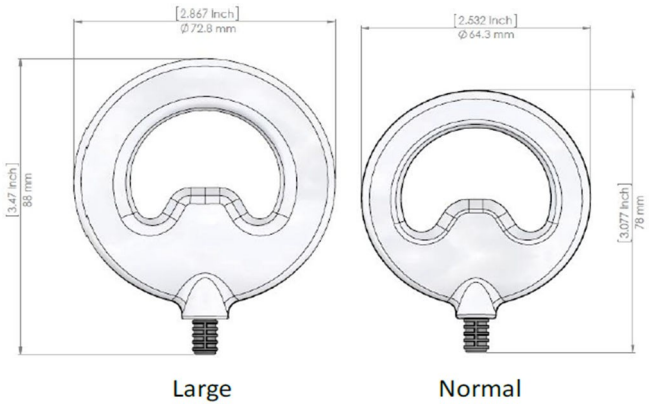


Figure 6 Transmitter Types

4. Patient sticker accessory (single-use, disposable) – Attaches the Transmitter to the patient's cheek during stimulation (see Figure 7, Left).
5. Transmitter sticker accessory (disposable) – Fixed to the Transmitter and used to attach the Transmitter to the Patient sticker accessory (see Figure 7, Right).

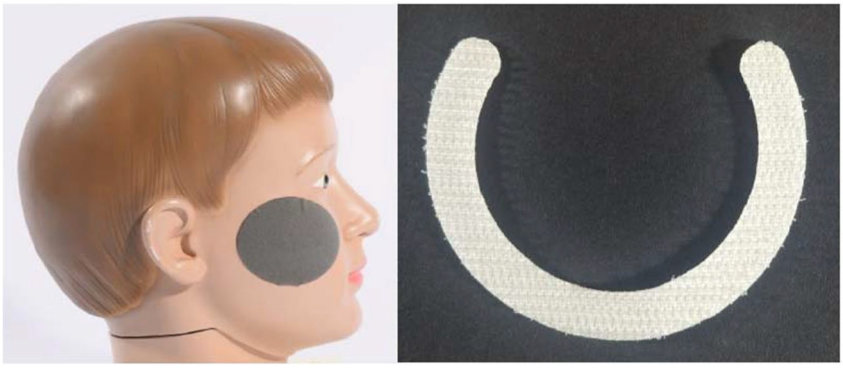


Figure 7 Patient sticker (left) and Transmitter sticker (right)

6. Isolation bag accessory (disposable) – Protects the Driver from dirt and contaminants during treatment.

2.2 Implantation Subsystem (Figure 2 B)

The role of the Implantation Subsystem is to guide the implanter to position the INS in its correct position. As illustrated in Figure 2 above, the primary components of the Implantation Subsystem consist of:

a. Implantation Navigation System
b. Implantation Tools

2.2.1 Implantation Navigation System

The image-based navigation system provides real time guidance to the implanter during implantation of the INS. It is based on Claronav's Navident system (K161406, CE marked), with a modified user interface to support the specific implantation in the greater palatine canal.

Using a stereoscopic camera, GuideView tracks the implantation tools and the Integrated Patient Reference Marker (iPRM), which represents the patient, and superimposes the tools' position on the patient's CT scan.

The Implantation Navigation System is comprised of the following components:

- GuideView: The GuideView software's user interface supports the implantation workflow and presents to the implanter navigation guidance during implantation. The GuideView software application is run on a PC based system placed on a cart equipped with an isolation transformer and connected to an optical tracking camera (MicronTracker). The camera is mounted on an articulated arm allowing its positioning above the patient. GuideView performs the following roles:

    - CT management (load, manipulate, change views of the patient's CT image);
    - Registration (matching between the patient and the patient's CT image);
    - Tools representation (symbolic representation of the implantation tools on the patient's CT image); and

- Implantation guidance (present tools positions relative to desired implantation path, guide implanter to correct tool's positioning and inform implanter when INS has reached its target location.)

The GuideView software receives inputs from two sources:

1. 3D Camera – The software receives from the MicronTracker 3D camera a video stream of the camera's field of view as well as position data of iPRM and implantation tools; and
2. Implanter – Using the mouse and keyboard, implanter performs implantation planning, confirms registration refinement, etc.

Figure 8 illustrates a typical GuideView screen.

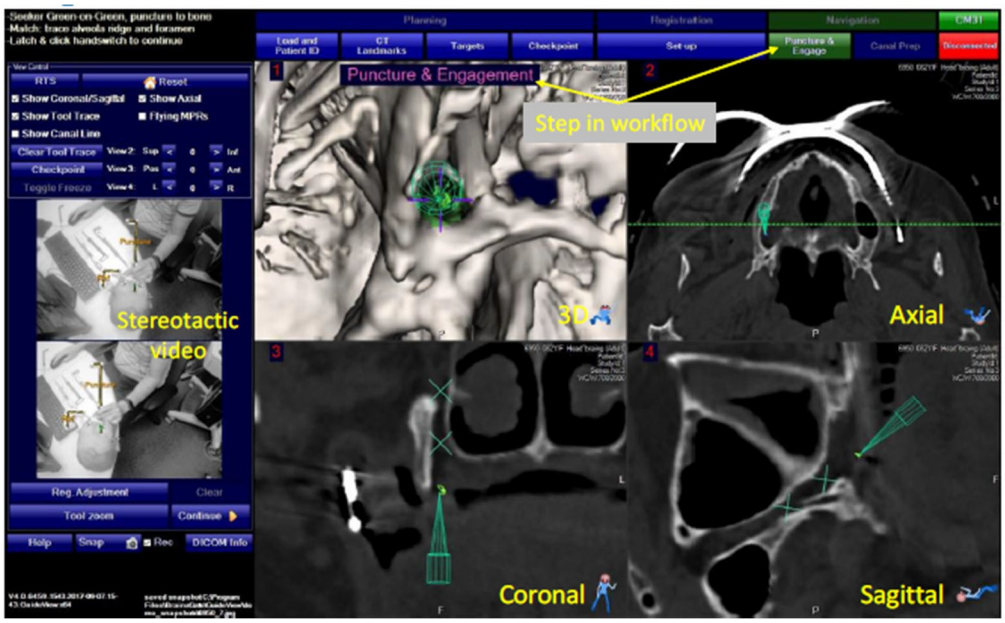


Figure 8 Typical GuideView Screen

- Integrated Patient Reference Marker (iPRM): The single-use, disposable iPRM (Figure 9) is a rigid polyamide white unit which includes an embedded CT visible metal insert ("CT Marker") and optical targets marker ("PRM"), mounted on a dental impression tray ("bite"). The optical targets are recognizable by the MicronTracker camera and used by GuideView to track the patient's head position and orientation.

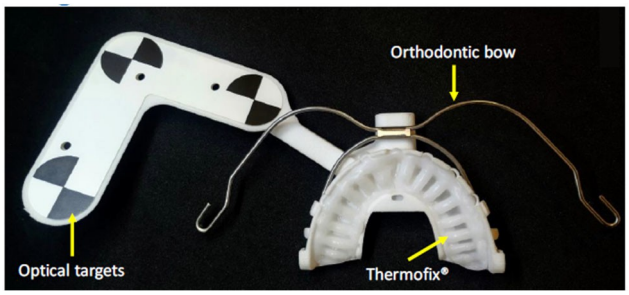


Figure 9 Integrated Patient Reference Marker (iPRM)

- Head strap (reusable): The Head strap is used to secure the iPRM in its location. An orthodontic bow connects the iPRM to the Head strap to prevent unintentional movements (Figure 10).

- Nose sticker: The Nose sticker is attached to the patient during the CT scan and implantation, and is used to aid in verifying the accuracy of registration using an optical marker. Prior to the CT scan, the iPRM and the Nose sticker are attached to the patient as shown in Figure 10. The Nose sticker is positioned with the round marker located above the sellion and the elongated channel running along the nose.

Figure 10 iPRM, Head Strap and Nose Sticker attached to the patient

- Tracer tool (reusable): The Tracer tool is used to create a trace along a CT-visible path to verify the quality of registration. The Tracer tool (Figure 11) is used as a virtual pen and moved along the Nose sticker on the patient to confirm registration accuracy.

Figure 11 Tracer Tool

2.2.1.1 Implantation Tools

Two tools are used during the implantation procedure:

2.2.1.1.1 Puncture Tool (reusable):

The Puncture Tool is used to puncture the mucosa and clear a path to the canal entrance and through the first 8mm of the canal itself. The Puncture Tool's distal part is shaped like the INS body (see Figure 12), preparing the canal entrance for the INS.

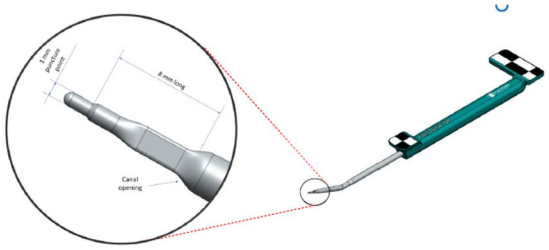


Figure 12 Puncture Tool

2.2.1.1.2 Introducer:

The single use, sterile Introducer (see Figure 13) is used to inject the INS in the greater palatine canal. The Introducer is preloaded with the INS.

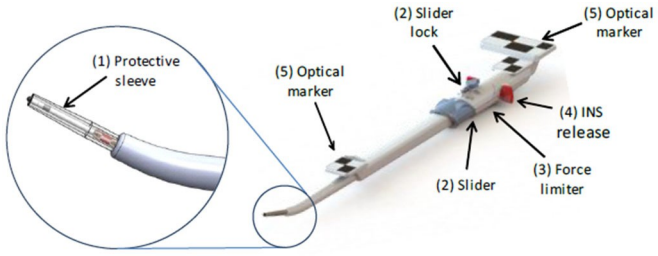


Figure 13 Introducer

The sponsor claimed the Introducer incorporates the following features:

1. Protective sleeve holding the INS during the penetration of the mucosa
2. Slider injector (with lock) used to advance the INS in the canal

3. Force limiter mechanism ensuring the force applied to the INS cannot exceed the designed forces
4. Release mechanism to release the INS once in its desired position in the canal
5. Optical markers identifiable by the 3D camera

The Panel will be asked to comment on a question about this topic area.

3 Proposed Indications for Use (IFU)

The sponsor proposes 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 8-24 hours from stroke onset (last known well).

The Panel will be asked to comment on questions about the unmet needs of this patient population.

4 Regulatory History

ImpACT-24A Study Timeline:

1. *July 2007 study approval:* The ImpACT-24A pivotal IDE study was approved with conditions in July 2007 for 660 patients and 15 sites in the United States.

2. *January 2010 change in device design (introduction of GuideView navigation system):* The GuideView CT-based navigation guidance system, an integral component of the device's Implantation Navigation System, was introduced to the study. The system is used during the implantation procedure and was intended to reduce the rate of device misplacement (initially 29% misplaced).

3. *October 2010 study halt and protocol revision:* The ImpACT-24A study was halted, in light of a high misplacement rate and following a planned interim analysis of the first 197 patients that (1) raised suspicion that the sham implantation procedure could cause mechanical activation of the SPG, and (2) revealed a large number of patients were enrolled into the study with transient ischemic attack (TIA), stroke mimic, or posterior stroke.

4. *June 2011 study resumption OUS and continued hold in the US:* The sponsor submitted an IDE supplement to FDA in April 2011 requesting approval of a revised protocol for their study sites in the US to resume study enrollment. The revised protocol incorporated the following primary modifications:

    a. Addition of baseline radiological evidence of stroke as an inclusion criterion.

    b. Addition of a sham procedure for control patients (refer to Section 8 of this Summary for a description of the sham procedure).

    c. A revised ratio of 1:1 between the treatment and control arms.

The study resumed OUS under the revised protocol in June 2011. FDA did not approve the revised protocol, recommending that the sponsor would need to demonstrate that the electrical stimulation provided by the device represents a potential for benefit on top of the suspected mechanical activation of the SPG by the implantation of the ISS500; otherwise, electrical stimulation would only represent an additive risk to mechanical activation without a known benefit. As a result, the study remained on enrollment hold in the United States.

ImpACT-24B study timeline:

- *April 2011 study resubmission, and July 2012 study resumption/approval of ImpACT-24B study:* As noted, the sponsor submitted a request to resume enrollment in both US and OUS in April 2011. FDA considered the changes to the protocol to be sufficiently significant such that the revised protocol would be considered a new study with a new IDE tracking number. The ImpACT-24B study received IDE approval in July 2012. Notably, the new study proposed a sham simulated surgical procedure, which just punctured the mucosa without implanting a sham device, as a control.

- *September 2012 to July 2018 study conduct -- changes to device design, study protocol, and statistical analysis:* During the course of the ImpACT-24B study, several changes to the device design, study protocol, and statistical analysis plan (SAP) were made.

    - Significant device design changes included:

        - Introduction of a new version of the device in April 2016 incorporating a different injectable neurostimulator design. The new injectable neurostimulator used the same stimulation protocol and pulse shape as the initial system but was more mechanically rigid to facilitate implantation.

        - Modification of components of the device, including the Bite iPRM, Puncture Tool, and Large Transmitter in June 2017. Notably, the new Bite PRM incorporated a dental impression tray, replacing a version of the PRM that was strapped around the patient's forehead. The version of the device introduced by this change represents the final marketed device hardware components.

        - Introduction of real time positioning in GuideView to shorten the implantation procedure in February 2018.

    - Significant changes to the study protocol and SAP included:

        - The addition of patients with confirmed cortical involvement (CCI) as a primary outcome.

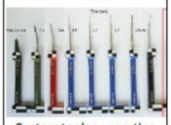
        - The re-definition of patients in the modified intent-to-treat (mITT) group to include only those in which the implant is placed within 5mm of the SPG (the previous definition was <15 mm).

- Analyses suggested by the sponsor's steering committee in June2018 including:

    - Dichotomy modified Rankin Scale (mRS) 0-2 as an outcome,
    - Dichotomy mRS 0-3 as an outcome,
    - Subgroup analyses by age, history of diabetes, and history of atrial fibrillation,
    - Clarification that covariates will not be stratified when performing the adjusted analysis (for covariates such as age, baseline NIHSS, baseline ASPECT score, time from stroke onset, etc.).

The sponsor provided summary images depicting the evolution of the device over the conduct of the ImpACT-24A and 24B clinical trials in the tables below:

Implantation System Changes

System	ISS400	ISS500L	ISS500L	ISS500M	ISS500M
Surgical tools	  Off the shelf tools Custom tools	(Minimally invasive procedure - no surgical tools needed)  Custom tools	 Custom tools supporting navigation	 Custom tools-reduced set	
Introducer		 "Zero insertion force" requirement	 Same as before with navigation support	 Injector (Slider Introducer)	
GuideView			 Navigation system		
Patient Reference Marker (PRM)			 Forehead mounted PRM		 Bite-PRM
First in human	4/2006	11/2007	11/2009	8/2016	6/2017

ImPACT-24B

ImPACT-24A

Table 6 Changs in the Implantation Subsystem During ImpACT-24A and ImpACT-24B

Treatment System Changes

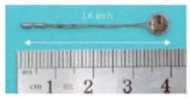
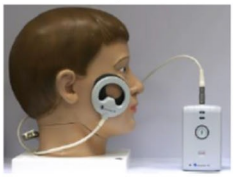
	ISS400	ISS500L	ISS500M
Implant	 Surgical (flap) procedure	 Minimal invasive procedure	 Injectable implant
Controller	 IPAQ		 Nokia Lumia Windows Phone
Driver & Transmitter	 Transmitter inside mouth (hard on patient)	 External transmitter Patient friendly	
First in Human	4/2006	11/2007	8/2016
		ImPACT-24B	
		ImPACT-24A	

Table 7 Changs in the Treatment Subsystem During ImpACT-24A and ImpACT-24B

ImpACT-24M

The ImpACT-24M study was not submitted to FDA for review prior to initiation, as the study did not involve US patients. ImpACT-24M was a prospective, multi-center, single arm usability study to validate the implantation procedure and demonstrate the ability to correctly identify a patient's stimulation level using physiological markers. This was the only study in patients that assessed cerebral blood flow. This study incorporated a device component (the Bite Patient Reference Marker) that was not utilized in ImpACT-24B but is a component of the ISS500 intended for marketing. The results of the study are included in the ISS500 PMA application.

Summary of all ImpACT studies

The initial device feasibility data was collected OUS. After analyzing the feasibility data, the sponsor submitted the ImpACT-24A study to FDA as a pivotal clinical trial to support the safety and effectiveness of the ISS500 in an IDE that was approved in 2007. Device design changes were made, and the study was placed on a hold following an interim analysis. Following significant study design changes, the ImpACT-24B was submitted to FDA and ultimately approved in 2012 under a different IDE. During the course of the ImpACT-24B study, significant changes to the device design and SAP were made during patient recruitment and data collection prior to the trial's end in 2018. The final device design was not studied in the ImpACT-24B pivotal clinical trial. The final device design was studied to assess the implantation procedure and stimulation levels in the ImpACT-24M trial in 2018, which was performed OUS and did not require IDE approval. As of the time of this Panel meeting, all IDE studies have been closed and all subject follow-up has been completed.

PMA submission

This current PMA was submitted on February 4, 2020. FDA issued a Major Deficiency letter on May 4, 2021, seeking additional information to address preclinical, clinical, and statistical deficiencies. The sponsor

provided additional information in an amendment dated July 28, 2021, and FDA is now seeking input from the Neurological Devices Panel on whether the data in the submission provide a reasonable assurance of the safety and effectiveness of the ISS500 for its intended use.

5 Non-clinical Testing

The sponsor provided pre-clinical testing to support marking of the subject device, including:

a) Sterility/Shelf Life/Reuse
b) Biocompatibility,
c) Software testing,
d) Mechanical, thermal, and electrical safety testing,
e) Electromagnetic compatibility (EMC) and wireless testing,
f) Magnetic resonance (MR) conditional testing,
g) Cybersecurity,
h) Design verification and validation testing – The GuideView navigation system.
i) Key design verification and validation testing – the INS and the EDC subsystems.
j) INS500 introducer assembly

The Panel will not be asked about the non-clinical information in this submission.

Please see Appendix I for additional details.

6 Overview of Ischemic Stroke

Primarily related to this submission are acute ischemic strokes (AIS), those that occur usually suddenly and that disrupt or cut off the cerebral blood flow to a portion of the brain, its associated vasculature, and other tissues. This is usually due to a thrombus or blood clot. Neurons begin to die within minutes of disrupted blood flow. Blood carries oxygen, glucose and other metabolites that allow the brain to function. The term "time is brain" is based on the limited amount of time it takes for brain tissue to begin dying and the rapidity that one act in order to save as much of that tissue as possible during an acute ischemic stroke and the resultant cerebral tissue infarction (permanent brain tissue damage and cell death). Multiple shifts in the stroke care paradigm and their systems have occurred at relatively fast pace. It should be noted that all the active acute stroke therapies available are time and amount of likely salvageable brain tissue based. There are additional portions of this overview that relate to the sponsor's claims regarding using the device and cerebral blood flow, reperfusion, and the blood brain barrier. This should all be taken into context of the acute ischemic stroke and the relation to the urgency of treatment. (Also see the figure below on cerebral blood flow time and cellular process/death).

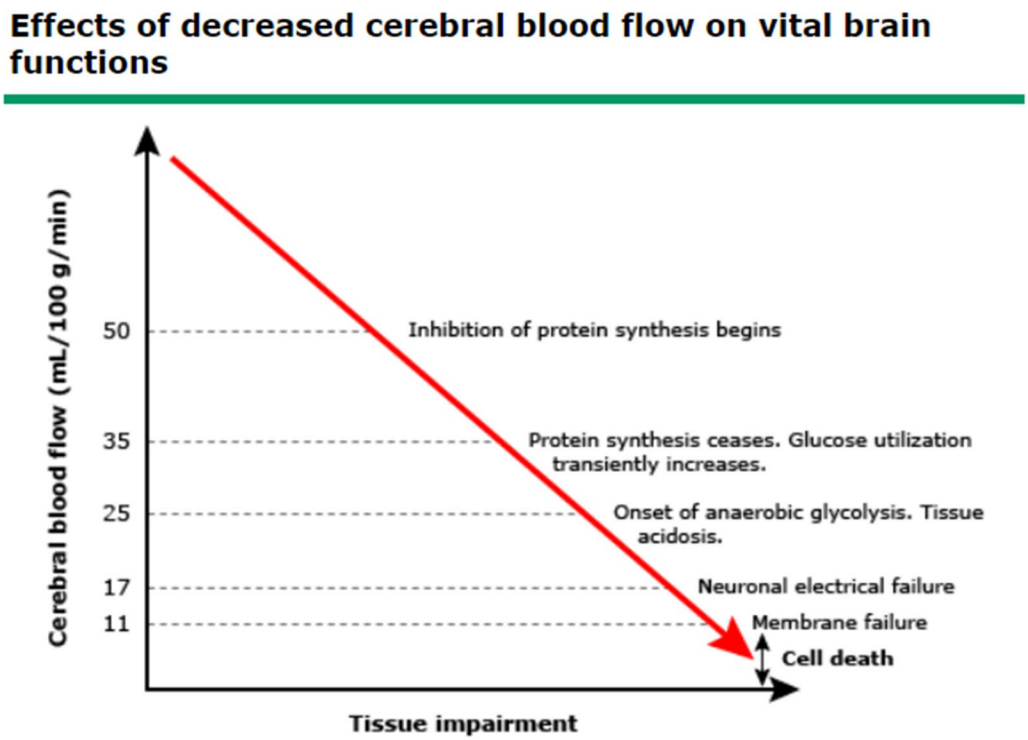


Figure 14 Effects of decreased cerebral blood flow on vital brain functions

6.1 General Clinical Aspects

Stroke is the clinical term for a loss of brain function due to a disturbance in the blood supply in a particular region of the brain. Stroke is subdivided into two types: ischemic (in which the blood supply is interrupted) or hemorrhagic (in which a blood vessel ruptures). The WHO in the 1970s defined stroke as a "neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours" to differentiate permanent damage from a transient or reversible deficit caused by a transient ischemic attack (TIA). The time frame of 24 hours was chosen somewhat arbitrarily. There are many well-defined risk factors for stroke and include age > 55, prior stroke or TIA, hypertension, diabetes, hyperlipidemia, cigarette smoking, atrial fibrillation, and migraine with aura.

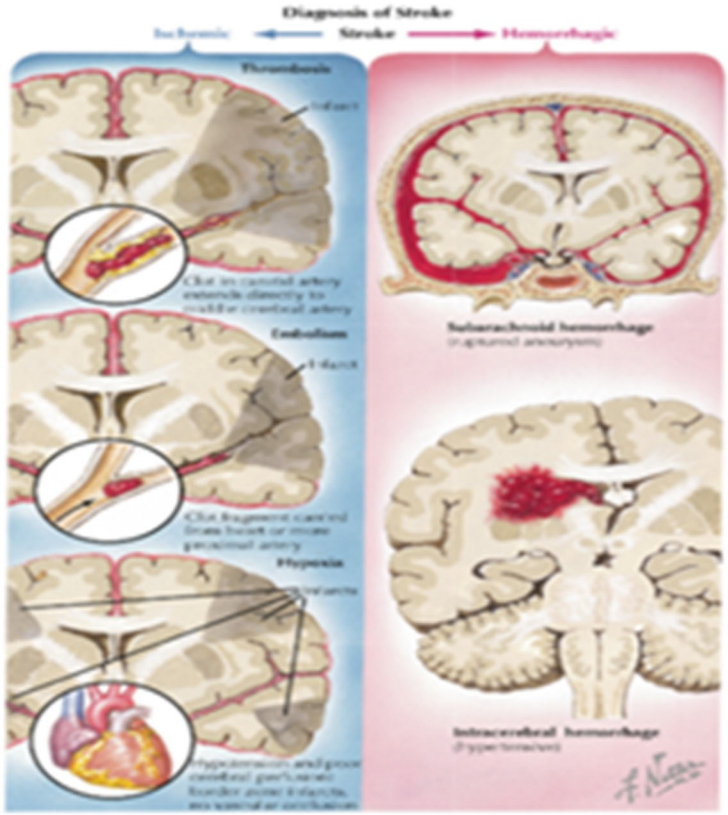


Figure 15 Stroke – Ischemic vs Hemorrhagic

From Neuroanatomy Frank Netter

Signs and symptoms of stroke are dependent on the area of the brain involved. The area of the brain involved in stroke is dependent on the particular blood vessels affected and the type of stroke that occurred (ischemic vs. hemorrhagic). Ischemic strokes or cerebral infarcts may be due to reduced flow or perfusion from multiple causes. These include decreased systemic perfusion (hypoperfusion) and cerebrovascular stenosis or occlusion (intracranial or extracranial); and the factors or conditions that may lead to them. An ischemic stroke involving the anterior circulation (the area of interest in this submission) may result in a variety of neurological deficits. Left (dominant) hemisphere major or branch cortical infarction may lead to the following impairments: aphasia, right hemiparesis, right-sided sensory loss, right-sided spatial neglect, right homonymous hemianopia, and/or impaired right conjugate gaze. Right (nondominant) hemisphere major or branch cortical infarction may lead to the following impairments: left hemiparesis, left-sided sensory loss, left-sided spatial neglect, left homonymous hemianopia, and/or impaired left conjugate gaze.

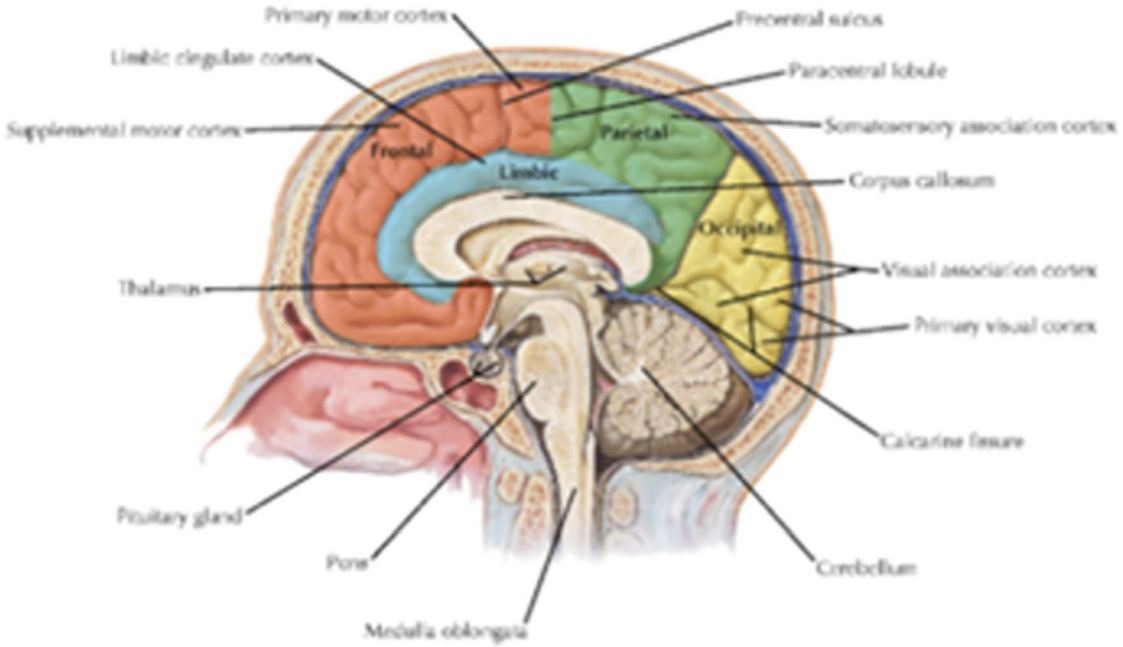


Figure 16 Lobes and functional areas of the brain

From Neuroanatomy Frank Netter

Pathophysiology

6.2 Cerebral Blood Flow

Cerebral blood flow (CBF) is the blood flow or circulation to and through the cereal vasculature. It is determined by vascular resistance and vessel diameter. Cerebral autoregulation is the process of how CBF is maintained at relatively constant level even with changes in cerebral perfusion pressure (CPP). Autoregulation appears to involve multiple pathways. There is evidence that the smooth muscle in vessels respond directly to changes in CPP as decreases in CBF leading to vasoactive chemicals being released and leading to dilation. CBF is generally maintained between mean arterial pressures of 60-150 mm Hg.

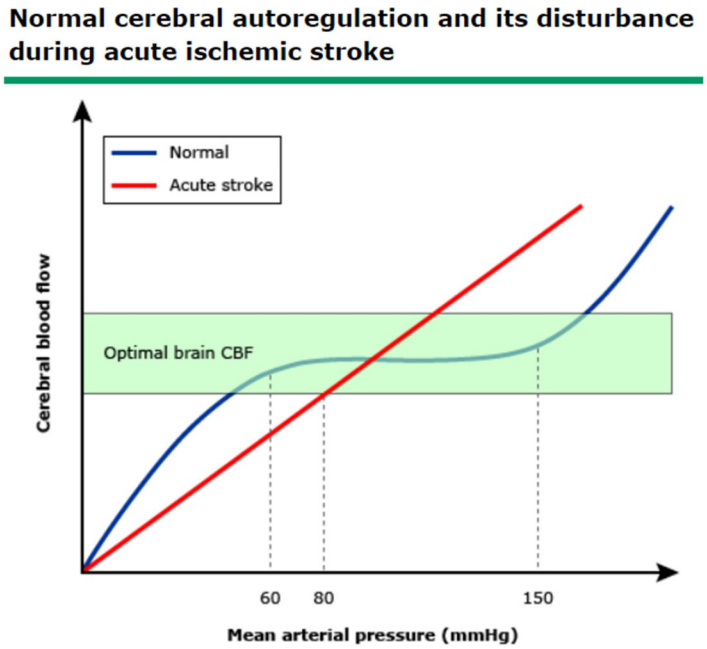


Figure 17 Normal Cerebral Autoregulation and Its Disturbance During Acute Ischemic Stroke

Dilation increases volume of blood > increase CBF
Constriction decreases blood volume > decrease in CBF

6.3 Cellular response to cerebral ischemia and penumbra

Not all cells in the region affected by the impaired blood supply die. There are two major zones of injury in the affected regions: the core area of ischemia and the ischemic penumbra. It is within the core area of ischemia that the blood flow is the most impaired (below 25%) and it is here that severe ischemia leads to cell death. However, the ischemic penumbra is typically a rim of injured but not dead brain tissue outside of the core ischemic zone. This area is supplied by collateral blood vessels and may remain viable for several hours. However, the collateral circulation is typically unable to supply enough oxygen and nutrients to the injured brain tissue; therefore, unless reperfusion is established these cells eventually die, as well. Currently, it is the area of the penumbra that is the primary focus of drug and device treatment of acute ischemic strokes.

Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acute Ischemic Stroke

	Neurons Lost	Synapses Lost	Myelinated Fibers Lost	Accelerated Aging
Per Stroke	1.2 billion	8.3 trillion	7140 km/4470 miles	36 y
Per Hour	120 million	830 billion	714 km/447 miles	3.6 y
Per Minute	1.9 million	14 billion	12 km/7.5 miles	3.1 wk
Per Second	32 000	230 million	200 meters/218 yards	8.7 h

Table 8 Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acuate Ischemic Stroke

Cell death following cerebral ischemia or stroke can occur by either necrosis or by apoptosis.

The process of necrosis is not well understood. In early stages, cellular chromatin becomes uniformly compacted, the endoplasmic reticulum is dilated, and ribosomes are dispersed. In later stages, swelling of the cell and mitochondria is followed by rupture of the nuclear, organelle, and plasma membranes, leading to the release of cellular material into the surrounding environment. This release of material results in the stimulation of inflammatory processes within the brain.

Apoptosis is highly regulated and has been studied in more detail than necrosis. As in necrosis, the chromatin begins to condense during early stages of apoptosis. Instead of cellular swelling, however, the contents of the cytoplasm also condense, and the mitochondria and other organelles remain intact. In later stages, the nucleus is broken into discrete fragments and the entire contents of the cell are divided into membrane bound bodies that are subsequently phagocytosed by macrophages.

There are three known pathways by which apoptosis can be initiated:

- Mitochondrial permeabilization
- Death receptor (Fas) pathway
- Endoplasmic reticulum stress

The most well-known pathway involves permeabilization of the mitochondria and release of cytochrome c into the cytoplasm. Activation of membrane-bound Fas, the so called "death receptor," and the accumulation of misfolded proteins at the endoplasmic reticulum during stress, can also lead to apoptosis. These initiators all lead to the activation of caspases that cleave cellular proteins and eventually cause cell death. Caspase-independent mechanisms of apoptosis have also been proposed.

Cerebral ischemia and infarction lead to loss of the structural integrity of the affected brain tissue and blood vessels. This process of tissue destruction and neurovascular disruption is mediated in part by the release of various proteases, particularly the matrix metalloproteases (MMP) that degrade collagens and laminins in the basal lamina. The loss of vascular integrity leads to a breakdown of the blood-brain-barrier and development of cerebral edema. Catastrophic failure of vascular integrity is postulated to cause hemorrhagic conversion of ischemic infarction by allowing extravasation of blood constituents into the brain parenchyma.

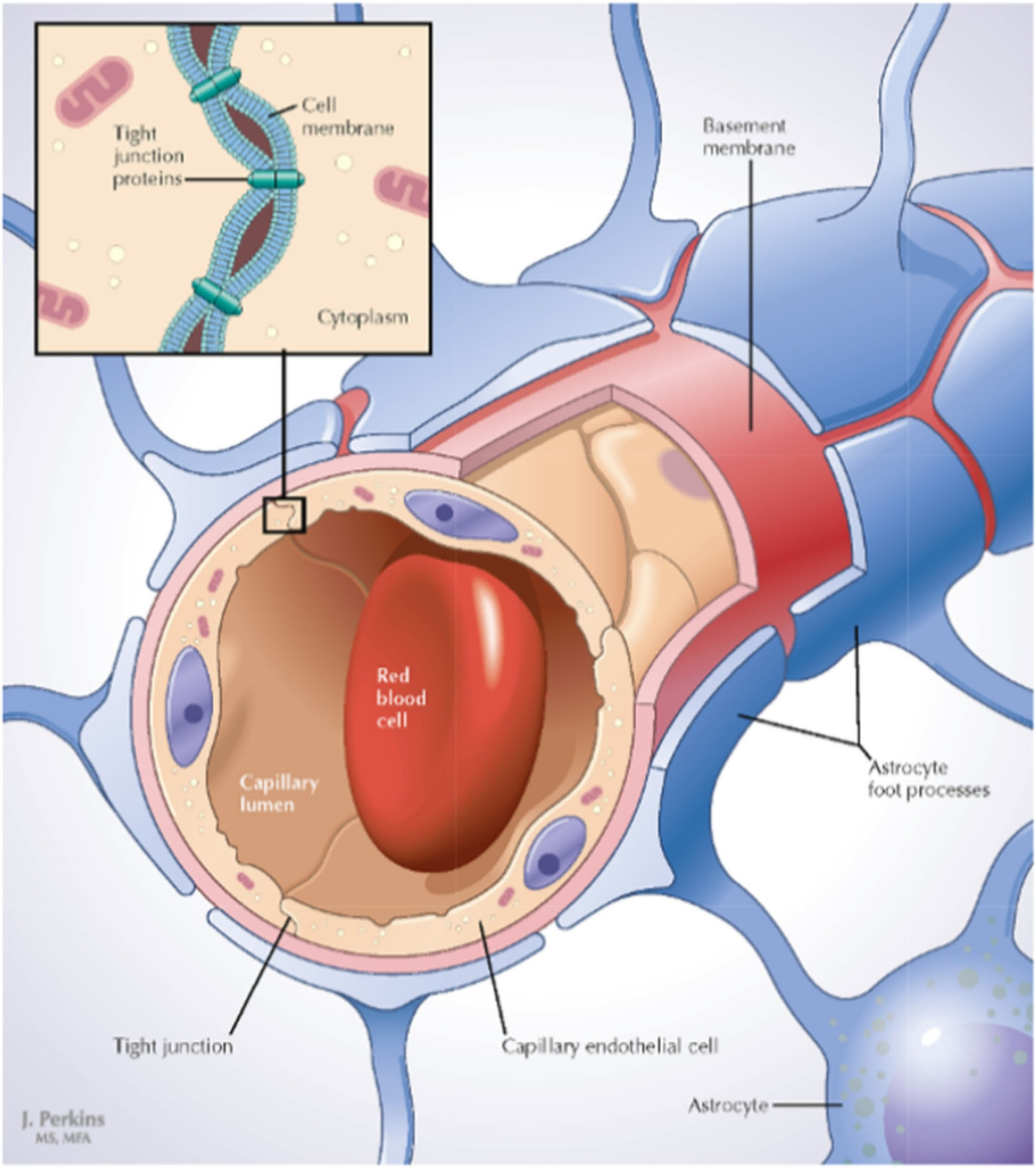


Figure 18 Capillary and cell structures that make up the BBB interface

Loss of cellular and Blood Brain Barrier integrity. BBB disruption plays a role in cerebral edema and exposure of the internal CNS to molecules in the peripheral circulation that it is usually protected from.
Cerebral edema complicating stroke can cause secondary damage by several mechanisms, including increased intracranial pressure, which may decrease cerebral blood flow, and mass effect causing displacement of brain tissue from one compartment to another (i.e., herniation), a process that can be acutely life-threatening.

Two types of cerebral edema can occur as a consequence of ischemic stroke:

- Cytotoxic edema is caused by the failure of ATP-dependent transport of sodium and calcium ions across the cell membrane. The result is accumulation of water and swelling of the cellular elements of the brain, including neurons, glia, and endothelial cells.
- Vasogenic edema is caused by increased permeability or breakdown of the brain vascular endothelial cells that constitute the blood-brain barrier. This allows proteins and other macromolecules to enter the extracellular space, resulting in increased extracellular fluid volume.

Roughly 10 percent of ischemic strokes are classified as malignant or massive because of the presence of space-occupying cerebral edema that is severe enough to produce elevated intracranial pressure and brain herniation.

6.4 Cerebral Ischemia and Intersection of Arterial, Venous, Glymphatic, Cerebrospinal and Blood Brain Barrier – Structures and Processes

The ischemia and the degenerative processes that occur effect the other structures in and that support the cerebral tissue and brain function. These include the cells, cellular processes, and flow in the cerebral microvasculature. Similarly, the BBB is affected, and its integrity diminished. The neurovascular unit (NVU) is described as being composed of the endothelia, pericytes, neurons, and astrocytes are involved in matching metabolic demand with blood flow. Metabolic end products such as lactate and adenosine as well as nitric oxide (NO) from the endothelium assist with that role by inducing vasodilation.

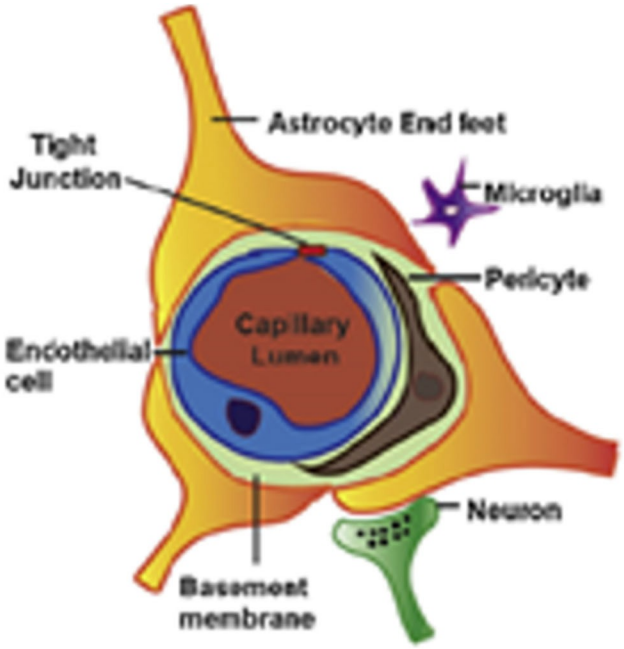


Figure 19 Capillary endothelium and the cells related to the specialized Blood Brain Barrier (BBB)

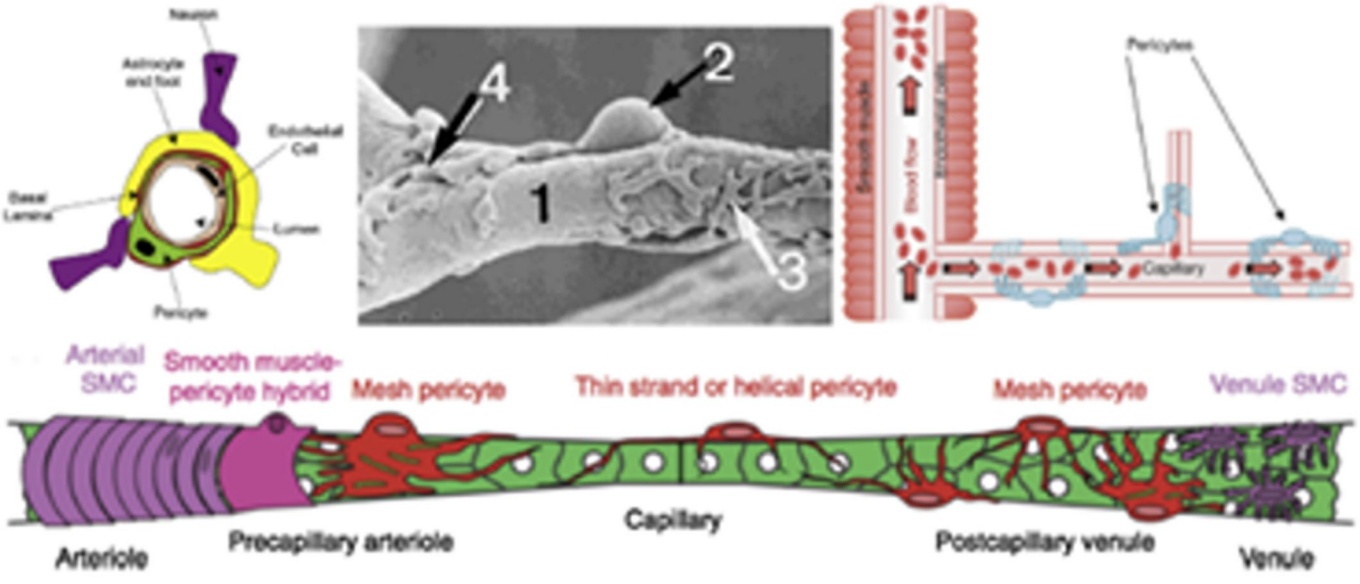


Figure 20 The associated cells and capillaries in the cerebral microvasculature

From: Hartmann et al., 2015

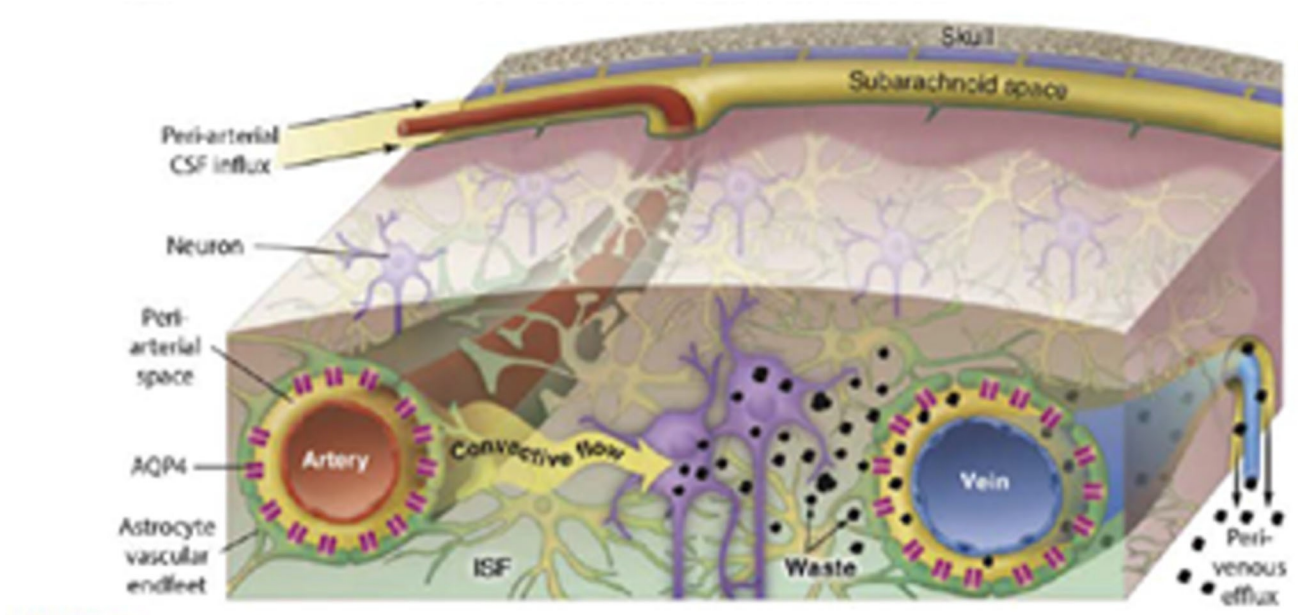


Figure 21 Perivascular Glymphatic Pathway

The phenomenon reported and described as "No Reflow" where blood flow slows or ceases in areas of the microvasculature in both cerebral and cardiac ischemia. It was first noted in global and focal cerebral ischemia the clinical literature over 50 years ago. In cerebral ischemia (AIS) it is hypothesized to be due to pericyte contraction and neutrophils facilitated by pro-inflammatory cytokines narrowing the vascular lumen hindering erythrocyte (red blood cells carrying oxygen) circulation. Some experimental and clinical evidence has been reported that the microvascular injury induced by ischemia/reperfusion also plays a critical role in determining tissue survival after recanalization by inducing microcirculatory clogging (no-reflow) [Del Zoppo and Hamann,2011; De Silva et al.,2009; Soares etal.,2010; Yemisci et al.,2009]. This reflow impairment is thought to be among the possible reasons along with cell death more progressed than anticipated related to less improvement after revascularization – including thrombolysis and endovascular thrombectomy (EVT)/neurothrombectomy. Recanalization or revascularization does not always equal reperfusion. In many clinical stroke trials, good outcome (mRS 0-2 at 90 days) is better correlated with reperfusion in patients treated with thrombolysis or EVT.

Both thrombolysis and EVT have been used to revascularize and restore perfusion to ischemic brain. Both have via randomized control trials have developed criteria for eligibility for use in AIS patients to maximize the benefit of their use and mitigate the risks to the amount possible. For example, for those two neurothrombectomy devices that have clearance indications for improving functional outcome (good outcome mRS 0-2 at 90 days) and revascularization (POL procode), additional studies have been done using criteria based upon time, comorbidities, and neuroimaging to extend eligibility in some patients 8-24 hours from last known well. The risks such as reperfusion injury, cerebral edema, hemorrhagic transformation, and other are a portion of the safety considerations that were used to develop the criteria and used in the clinical trials for those devices.

Collateral circulation plays a role in the penumbra and the ability to limit the core of cell death. Increasing collateral circulation and thus cerebral blood flow in those vessels in the cortex and possibly deeper structures

may have use in cerebral ischemia if both the clinical data in their use on the specified population on effectiveness reliable and the safety of the device's overall use are reliable and valid. It should be that benefit outweighs risk in the AIS population that it is intended for.

In the current instance of the subject device, there are concerns regarding uncertainties related to the clinical data, feasibility, and the safety related to not only the implantation procedure but also reperfusion injury (large, medium, small and micro vasculature) and cerebral edema related to the neurostimulation and reported increased cerebral blood flow. The current intended use of the device initiated within 8-24 hours after last known well and continued for the subsequent 4 days (total 5 days post ictus) with neurostimulation for 4 hours per day in patients that have not had revascularization (thrombolytic or EVT) or reperfusion assessment. If the device works as claimed, increasing cerebral blood flow raises concerns regarding the responses in the intracranial vasculature and tissues over that extended timeframe. The sponsor is not only intending the use the device within 8–24-hour time period which alone requires robust safety and effectiveness data, but also 4 more times in the 24-48-, 48-72-, 72-96- and 96–120-hour time periods after last known well (LKW).

6.5 Diagnosis/Initial Assessments

The immediate goals in acute stroke care include minimizing brain injury, treating medical complications, and moving toward uncovering the pathophysiologic basis of the patient's symptoms.

Stroke is diagnosed via history, physical and neurological examination, and neuroimaging; it is most diagnosed in an emergency room setting. It is highly important to differentiate between ischemic and hemorrhagic stroke quickly as the management of these conditions is very different and this is done primarily utilizing neuroimaging by CT or MRI. A recent study comparing the effectiveness of MRI and CT for the diagnosis of acute stroke in a suburban hospital found MRI to be more effective in identifying acute stroke of all types. [Moreau 2013, Vymazal 2012]. Additional neuroimaging techniques may be performed such as CTA/CTP or MRA/MR DWI in different combinations to ascertain thrombus location, thrombus burden and salvageable brain tissue that continue to be at risk – ischemic penumbra. The treatment of ischemic brain tissue is time dependent, particularly when considering the benefit vs risk as time passes.

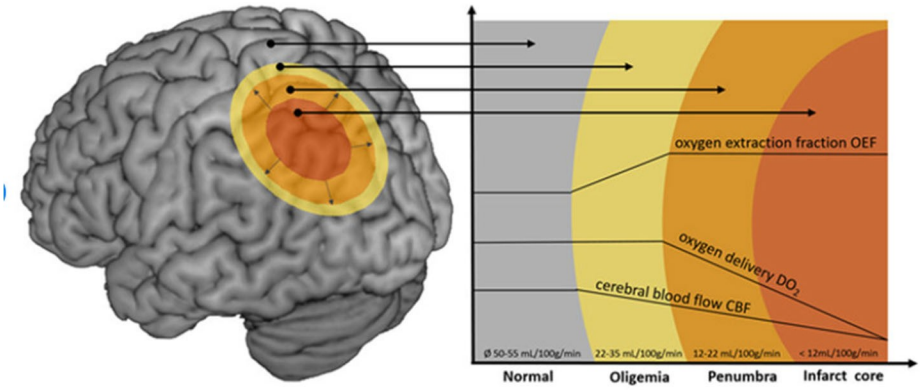


Figure 22 Diagrammatic Correlation of Areas of Infarct and Penumbra with Ischemia and Cell Processes

From presentation Rai, et al. 2013.

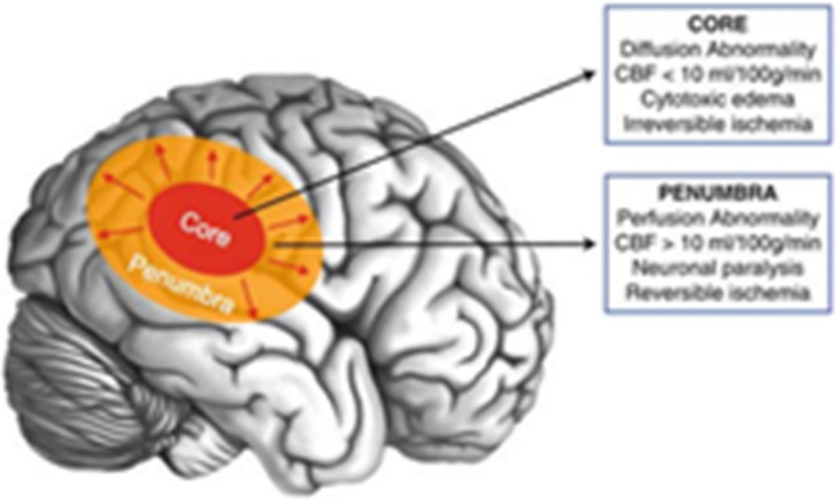


Figure 23 Illustration on Ischemic Infarct Core and Penumbra with CBF

From presentation Rai, et al. 2013.

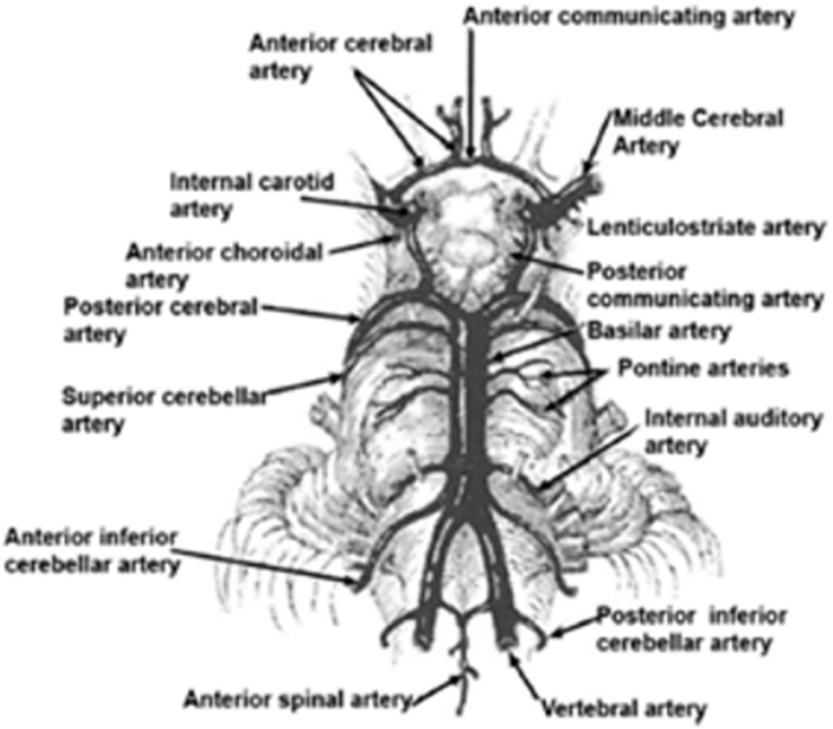


Figure 24 Major Cerebral Arteries and Circle of Willis

Stroke diagnosis aims at differentiating the types of stroke as well as the other causes of symptoms that may present similarly to stroke also called stroke mimics. Neuroimaging types and usual use in acute evaluation of AIS - NCCT/CTA/CTP; MRI/DWI MRI/MRA; cerebral angiography.

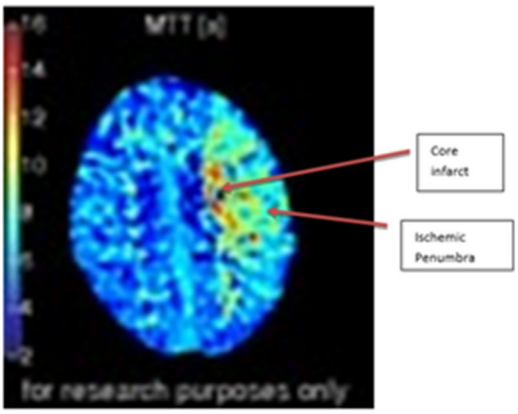
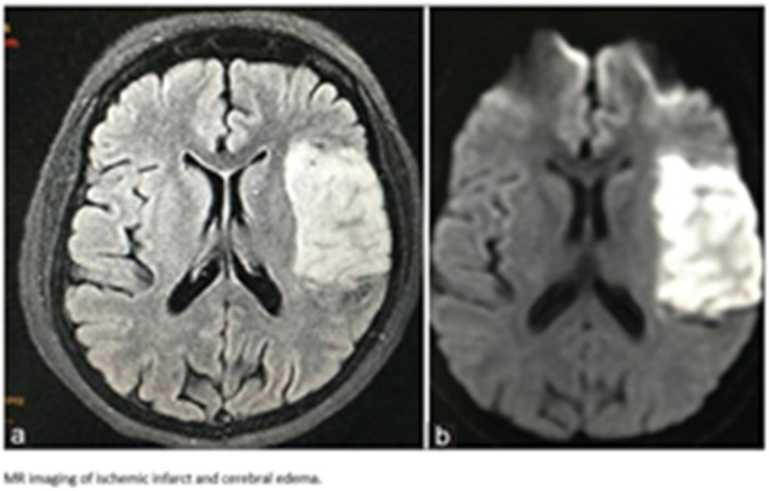


Figure 25 Example of CTP Imaging using MTT showing core infarct and ischemic penumbra
Computed Tomography Perfusion is CTP and Mean Transit Time is MTT



MR imaging of ischemic infarct and cerebral edema.

Figure 26 Example of MRI DWI of ischemic infarct and cerebral edema
Magnetic Resonance Imaging is MRI and Diffusion Weighted Imaging is DWI

Acute stroke differential diagnosis
Migraine aura
Seizure with postictal paresis (Todd paralysis), aphasia, or neglect
Central nervous system tumor or abscess
Cerebral venous thrombosis
Functional deficit (conversion reaction)
Hypertensive encephalopathy
Head trauma
Mitochondrial disorder (eg, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes or MELAS)
Multiple sclerosis
Posterior reversible encephalopathy syndrome (PRES)
Reversible cerebral vasoconstriction syndromes (RCVS)
Spinal cord disorder (eg, compressive myelopathy, spinal dural arteriovenous fistula)
Subdural hematoma
Syncope
Systemic infection
Toxic-metabolic disturbance (eg, hypoglycemia, exogenous drug intoxication)
Transient global amnesia
Viral encephalitis (eg, herpes simplex encephalitis)
Wernicke encephalopathy

Table 9 Acute Stroke Different Diagnosis

From: "UpToDate.com"

6.6 Treatment/Current Available Therapies

The FDA approved pharmacological treatment for acute ischemic stroke is limited to a single therapy – recombinant IV- tPA. Other pharmacologic therapies that are used in the acute and sub-acute stroke patient include antiplatelets, antithrombotics, and statins among others. Many are initiated in the first 24-48 hours after the stroke depending on the etiology of the stroke and other medical considerations.

In 2016, the FDA approved the De Novo application for Trevo ProVue and XP ProVue Retrievers (DEN150049; De Novo Summary) as prescription devices under 21 CFR Part 801.109 that are indicated "for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion, and smaller core infarcts who have first received intravenous tissue plasminogen activator (IV t-PA). The Trevo stent retriever devices are under product code POL, 21 CFR 882.5600 Neurovascular Mechanical Thrombectomy Device for Acute Ischemic Stroke Treatment as Class II devices. Subsequently, another stent retriever, Solitaire (K162539), has been cleared under the POL ProCode with indications for functional outcome with data from the SWIFT PRIME trial (G120142; 510(k) Summary). Both devices have been cleared with indication expansions by the FDA for use for up to 24 hours in a specific subset of patients based on clinical and neuroimaging criteria. Trevo (K173332; 510(k) Summary) was cleared with clinical data from the DAWN trial (G130223) and Solitaire (K181807; 510(k) Summary) was cleared with clinical data from DEFUSE 3 trial (G150028). Other stent retrievers and aspiration catheters have been cleared by the FDA under the product code NRY which is based on revascularization and not clinical functional outcomes.

The significant limiting factor for both treatments, thrombolysis and neurothrombectomy, is the time from

known onset to presentation to the ER. Although practice guidelines such as those by the American Heart Association state that under certain conditions, IV-tPA may be given up to 4 ½ hours after symptom onset they deviate from current FDA approval. Per FDA approval, IV-tPA should be administered within 3 hours of onset of stroke symptoms and the stent retrievers (Trevo or Solitaire) should be used within 24 hours of symptom onset depending on eligibility criteria.

Both the pharmacologic and device therapeutics with improved functional outcomes indications have presented data from randomized clinical trials. For the neurothrombectomy devices this was based on modified Rankin Scale (mRS) scores with good outcome defined as mRS 0-2 (fixed dichotomous scale). The fixed dichotomous mRS analysis has been used due to it having less variability from study to study and device to device. This contrasts with the shifting dichotomous (prognosis adjusted) and utility weighted (patient preference adjusted) versions and their analyses. It should be noted that although AIS clinical trials may have reported analyses using these other versions, to date for neurological devices such as neurothrombectomy devices that have indications for decreasing disability (improving functional outcomes at 90 days) have had to support the proposed IFU and submit analyses using the fixed dichotomous mRS as a primary endpoint. Data reported in clinical literature and that required for submission to the FDA for review may differ, with the data in the product labeling most likely being more related to the FDA review.

Device	mRS 0-2 Device Arm	MRS 0-2 Control Arm	File
Trevo (DAWN)	48.6%	13.1%	K173352 Extended use to 24 hours
Trevo MR CLEAN	29.6%	19.3%	DEN150049
Solitaire DEFUSE 3	31.2%	15.3%	K181807 Extended use to 24 hours
Solitaire SWIFT PRIME	MM, IVtPA + Solitaire 62.7%	MM, IVtPA alone 36.8%	K162539

mRS 0-2 at 90 days

modified Rankin Scale (mRS)
Medical Management (MM)

Table 10 Fixed dichotomous mRS 0-2 in Trevo and Solitaire Stent Retriever Devices

From DEN150049, K173352, K162539, and K181807. These results come from the public regulatory approval or clearance summaries of the devices at that time. These numbers may differ from those reported in clinical literature.

6.7 Stroke Continuum of Care in the US – Acute Ischemic Stroke

The objective in acute stroke patients is to assess and evaluate to provide the best and most appropriate care and treatment in the fastest manner possible.

The typical acute stroke accesses the prehospital system one of two ways – either via emergency medical services (EMS/ambulance) or is brought directly to the hospital by private vehicle. If the patient is brought by EMS, there is communication usually between the EMS team and the hospital emergency room (ER) about the patient, what identifies them as a possible stroke patient and alerts the stroke team/ER to be prepared. The patient is assessed by obtaining history, performing neurological/physical exam, laboratory studies, and neuroimaging. This assessment is done to determine if the patient is having a stroke, what type of stroke (ischemic vs hemorrhagic), and whether the patient is eligible for current available proven therapies (IV thrombolysis or neurothrombectomy). In order to not delay care, most of these are done in tandem to decrease the amount of time it takes. [See stroke algorithm chart in Figure 27 to see simplified version of immediate acute stroke evaluation through to this step.]

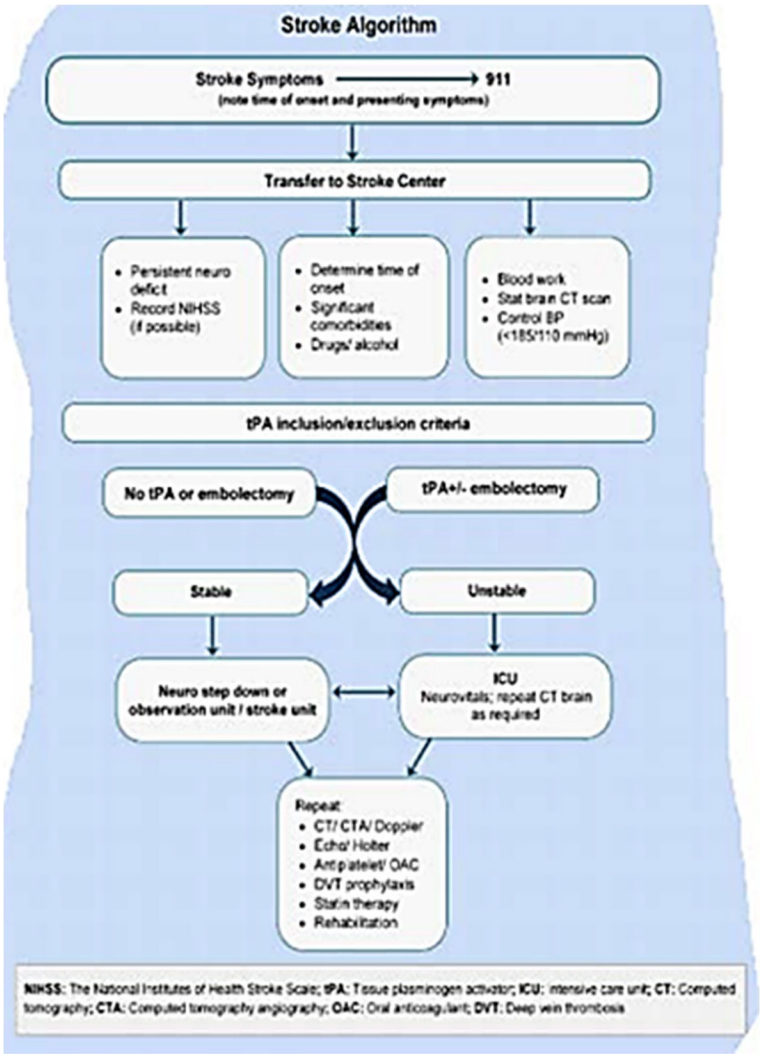


Figure 27 Stroke Algorithm Chart
From AHA Guidelines 2015

The two FDA cleared acute therapeutic options – thrombolysis and EVT are currently the only "active" acute ischemic stroke treatments. The acute ischemic stroke treatment paradigm does not end with those more active evaluable therapies. The current AIS systems of care and the acknowledgement that with or without these two therapies being used in a patient's treatment, the care that has evolved over the past 20 years and particularly the past 5 years has improved patient outcomes. The care that a patient receives in an acute stroke unit has been shown in clinical literature to improve patient outcomes over those care for in a non-stroke unit or center. Evaluation, assessment, and treatments for either new stroke related impairments (like dysphagia/swallowing difficulty) and co-morbidities along with treating and managing the direct effects of cerebral ischemia (edema, hemorrhage) have benefited this population. A patient having had a stroke 10 years ago with the same lesion and symptoms would find significant differences in approach and care now.

There are some issues with this paradigm shift. Not all patients have equal access to the specialized hospitals/centers and medical staff. In order to decrease some of the access gaps, there has been an increase in specialized teleneurology, telestroke, and teleradiology services as well as larger comprehensive centers and smaller hospitals developing a hub and spoke model relationship.

6.8 AIS Treatment Issues

The treatment of acute stroke patients and particularly acute ischemic stroke patients has improved. There are still issues that are trying to be addressed including the number of patients eligible for available AIS treatments that do not receive them and those that are ineligible for those available.

- Issues with education of population and arrival for time limited therapies
- Access to available therapies (geographical barriers, staff, cost) is not equally available across the US
- Access to qualified physician and surgical specialty staff (disparities)

A brief walk through a typical patient first 24 hours
In the US,probable acute stroke patients are evaluated in the Emergency Room. Assessed initially by neurologic exam and history and to determine if the suspected stroke is ischemic or hemorrhagic via neuroimaging (usually CT scan). Labs, history, and additional neurovascular imaging (CTA/CTP or MRA/MRI DWI) to ascertain further information about the stroke – size, location, vessels involved, perfusion, etc. If it is an acute ischemic stroke (AIS) – in parallel with that assessment is finding if the patient is eligible for IV thrombolysis and the neurovascular imaging provides information on whether there is a thrombus amenable to endovascular thrombectomy or neurothrombectomy. The two are not exclusive. If the patient is not at a level of care facility that they need they are usually transferred to a facility with the appropriate care. After receiving thrombolysis, EVT or both or none, the patient is usually treated in an acute stroke unit or neuro ICU where maximal medical management and care are provided.

	ASRH	PSC	TSC	CSC
Location	Likely rural	Likely urban/suburban	Likely urban	Likely urban
Stroke team accessible/available 24 h/d, 7 d/wk	Yes	Yes	Yes	Yes
Noncontrast CT available 24 h/d, 7 d/wk	Yes	Yes	Yes	Yes
Advanced imaging (CTA/CTP/MRI/MRA/MRP) available 24 h/d, 7 d/wk	No	Yes	Yes	Yes
Intravenous alteplase capable	Yes	Yes	Yes	Yes
Thrombectomy capable	No	Possibly	Yes	Yes
Diagnoses stroke pathogenesis/manage poststroke complications	Unlikely	Yes	Yes	Yes
Admits hemorrhagic stroke	No	Possibly	Possibly	Yes
Clips/coils ruptured aneurysms	No	Possibly	Possibly	Yes
Dedicated stroke unit	No	Yes	Yes	Yes
Dedicated neurocritical care unit/ICU	No	Possibly	Possibly	Yes

ASRH indicates acute stroke-ready hospital; CSC, comprehensive stroke center; CT, computed tomography; CTA, computed tomography angiography; CTP, computed tomography perfusion; ICU, intensive care unit; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MRP, magnetic resonance perfusion; PSC, primary stroke center; and TSC, thrombectomy-capable stroke center.

Table 11 Levels and Capabilities of Hospital Stroke Designation
From Adeoye, et al. 2019

The use and treatment of an AIS patient with the subject device (implantation and subsequent neurostimulation) is likely to require a facility with a Neuro ICU or ICU with 24 hour in house neurological/neurosurgical coverage in the US. This device would likely give it the same issues regarding access to facilities and staff as thrombolysis, thrombectomy, and acute stroke care services in general. Unfortunately, the study that has US patients is small sample size and does not provide sufficient feasibility data that would provide evidence of its use in the current paradigm.

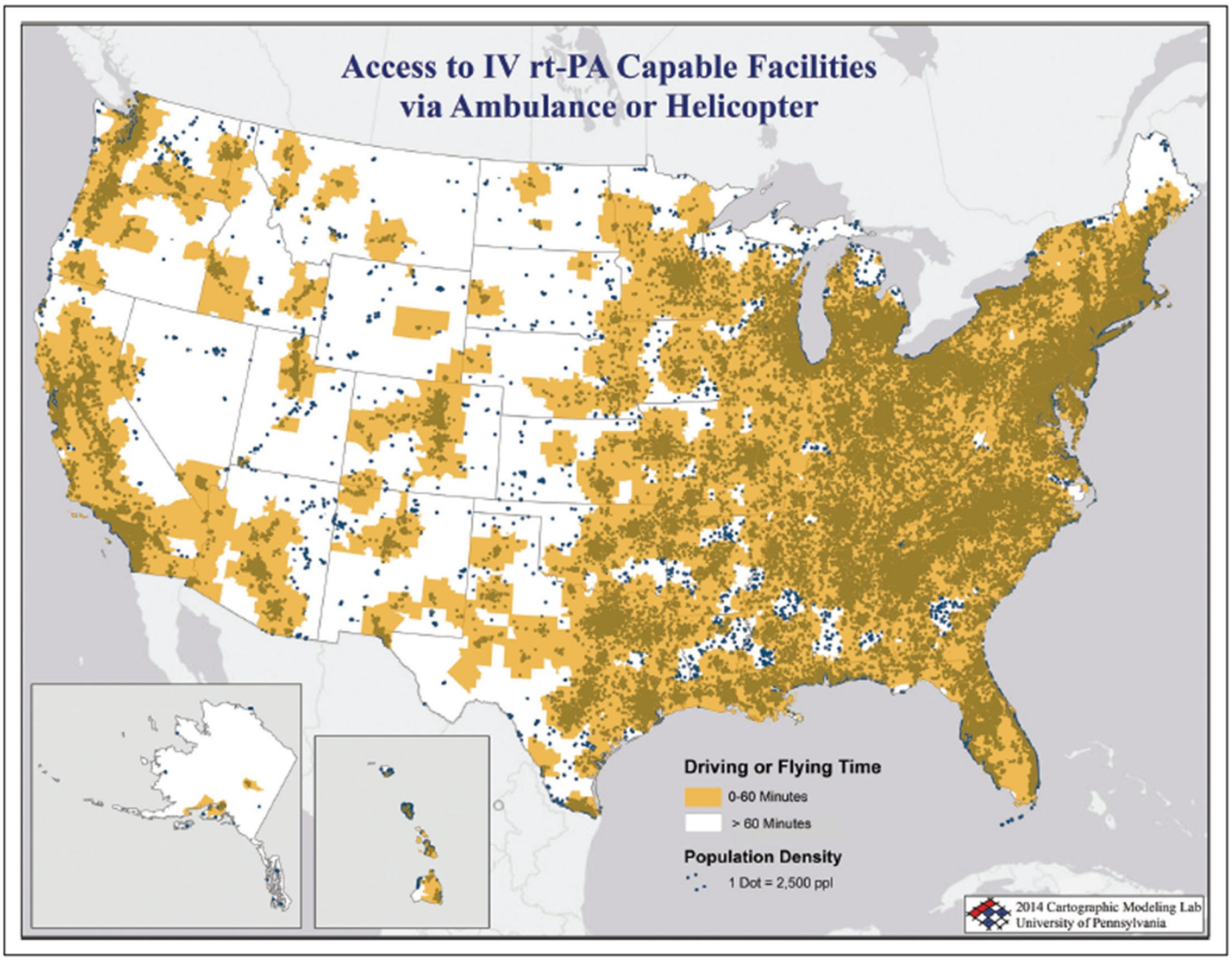


Figure 28 Access by Ground or air to intravenous (IV) alteplase-capable hospitals within 60 minutes
ppl indicates people; and rt-PA, recombinant tissue plasminogen activator. From Adeoye, et al. 2019.

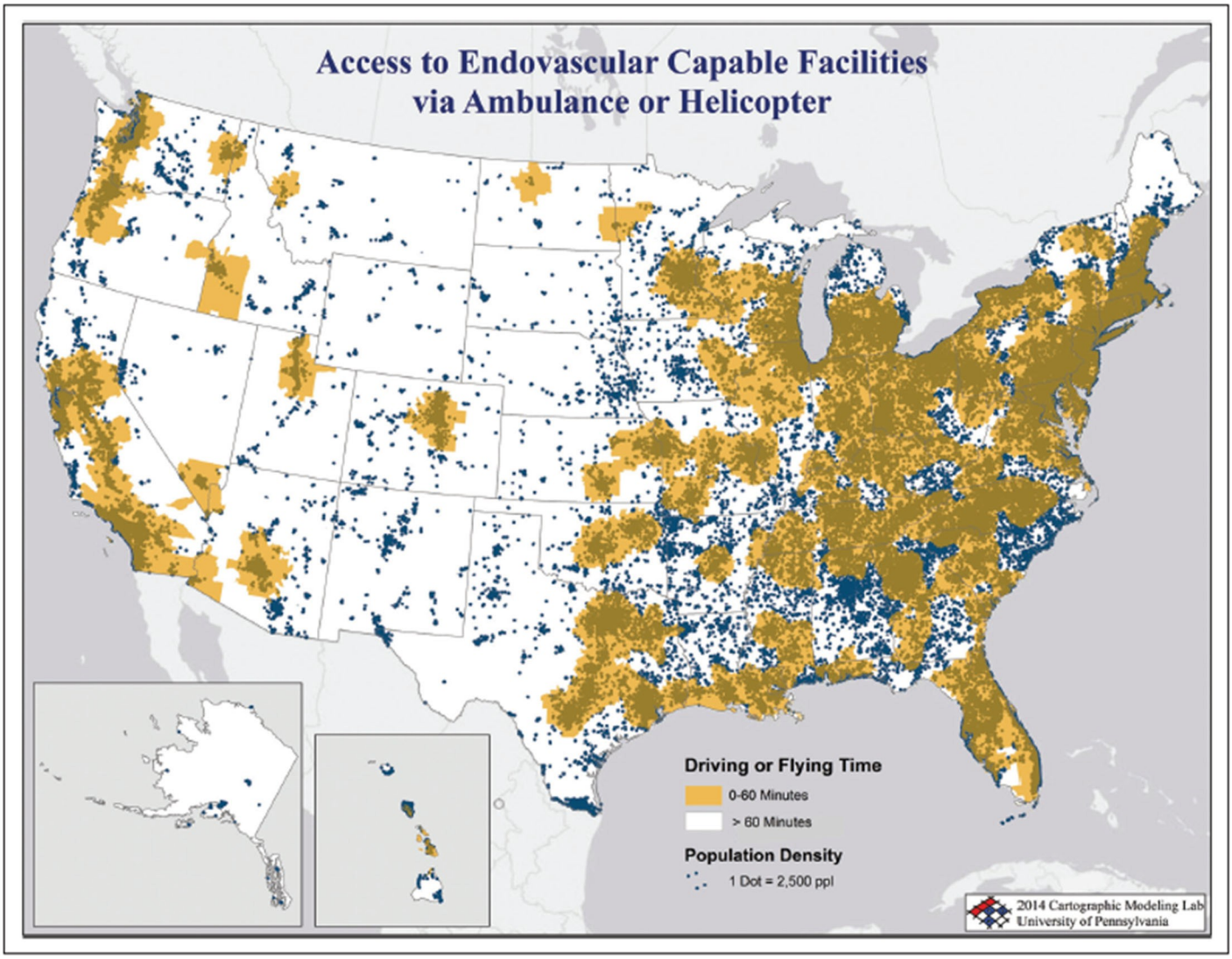


Figure 29 Access by ground or air to endovascular- capable hospitals within 60 minutes
ppl indicates people. From Adeoye, et al. 2019.

7 Implantation Procedure

As mentioned in the Device Description section, the INS is injected via an image-guided procedure using the Implantation Navigation System, comprised of the GuideView optical navigation system and its associated positioning, tracking, and implantation tools. The INS is placed in the greater palatine canal with its electrode in the SPG fossa (Figure 30). The GuideView optical navigation system tracks and superimposes the position of the implantation tools and the INS on the pre-procedure CT image of the maxilla and greater palatine canal.

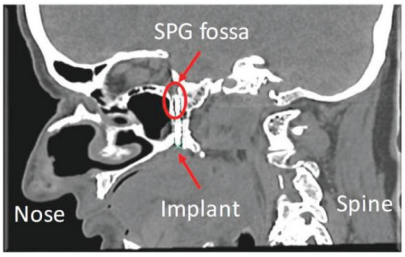


Figure 30 An implant Placed in the Greater Palatine Canal

Figure 31 below shows the upper palate of the mouth. The dotted yellow line marks the hard-soft palate border. The entrances of the left and right canals and the corresponding left and right puncture points (which are determined by the canal orientation and mucosa thickness) are located anterior to the yellow line, in the hard palate.

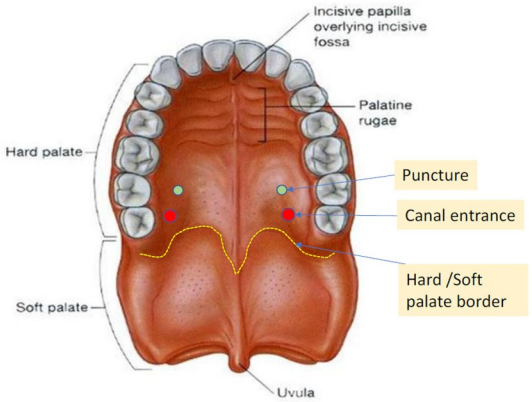


Figure 31 The Upper Palate

Figure 32 shows the relative positions of the hard-soft palate border, the canal entrance, and the puncture point, in a sagittal view.

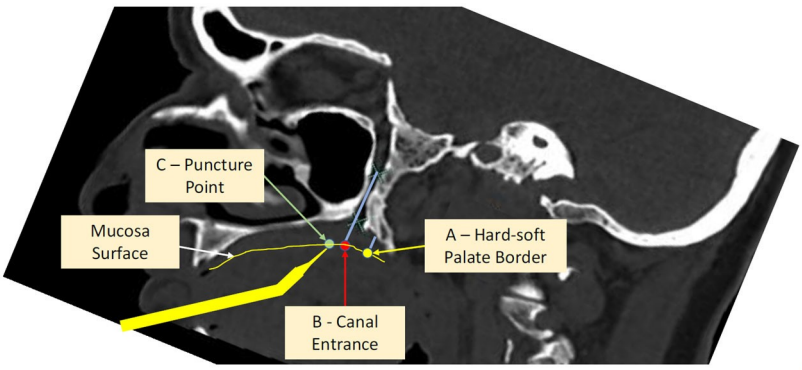


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Figure 32 The Upper Palate – Sagittal View

The goal of the implantation procedure is to inject the INS to the greater palatine canal (GPC) with its

electrodes in the Pterygopalatine Fossa (PPF), as shown in Figure 33.

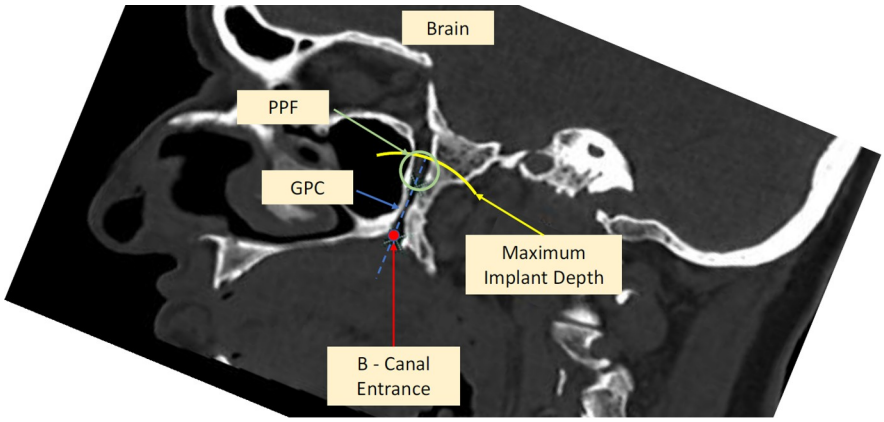

Figure 33 The Greater Palatine Canal and Fossa

The maximum INS depth is 30mm from the canal entrance (marked in yellow in Figure 33), in the middle of the PPF.
Note: A spepareate document is included in the panel pack for the implantation procedure.

The Panel will be asked to comment on a question about this topic area.

7.1 Correct Implantation Position

The sponsor claimed the following that both the INS and the navigation system were changed during the clinical trials to minimize implantation-related risks and complications. The initial INS used in ImpACT-24A was fragile and not flexible, and users were cautioned not to attempt to insert it to the canal without dilating the canal first using a set of rigid trocars (up to 2mm diameter) and to apply zero force when inserting the INS. The rigid trocars were determined to cause INS misplacements in the range of 5-15mm. In some cases where patients had curved canals or the trocars were misaligned, the thin canal wall was breached, and the electrodes reached the maxillary sinus or the nasal cavity.

As a result, the final INS was redesigned to increase flexibility while maintaining mechanical integrity, and trocars were no longer used in the implantation procedure in ImpACT-24B. The correct INS position definition was redefined to be less than 5mm after the sponsor gained experience with the final INS and verified that its mechanical design allowed it to be inserted without trocars.

7.2 Training of the Implanter

The sponsor indicated the implanter would be trained to prevent the following errors or adverse events, which might contribute to further clinical complications or device misplacement:

a. Aspiration – During the procedure, it is important to perform suction and after puncturing the mucosa. It is also important to stop minor bleeding by applying pressure with the finger for a few seconds.

   Failure to perform suction as instructed might lead to patient agitation and even aspiration (see

section 2.2, section 10.1, and section 10.2 in the Implantation Procedure Manual provided with this Summary).

b. Airway obstruction – Identification of patients at risk and management of airway obstruction was added to the manual and will be added to the training syllabus. Note that the device is to be used only in conscious, cooperative patients.

c. Use errors – Several use errors were noted during the trial that could complicate the procedure. Most of these use errors were addressed by the new INS and navigation system, but a few continue to depend on the implanter:

    1. Registration accuracy verification – If the iPRM moves, the system detects such movements automatically by tracking a fixed marker on the patient's nose. The implanter must pay attention to the accuracy indication and correct the registration as needed. Otherwise, the INS might be misplaced, and the patient will not be treated.

    2. Moving the introducer from the canal opening – The role of the introducer is to bring the INS, protected, to the canal opening. Moving the introducer from the opening when the INS is half-way in the canal and half still inside the introducer might damage the INS. Although this step only takes a few seconds, this mistake did occur once (1/197) during the trial. To prevent similar errors, the documentation and training were updated, and the final implantation system warns the implanter when it detects that the introducer is moved. Moving the introducer when the implant is half-way in and ignoring the system notification might lead to damage to the implant. In such a case, the damaged INS would have to be removed and a new implant would have to be placed.

    3. Failure to cut excess thread at the end of implantation – If the thread is not cut as instructed, the patient might remove the INS and will require re-implantation.

The sponsor states that the Implanter training and qualification are an important part of the mitigation of the above complications. Therefore, the sponsor proposed the following certification process:

1) The first 5 implantations per implanter will be performed under remote guidance by BrainsGate.
2) The following 3 additional procedures for accreditation will be supervised by BrainsGate.
3) Implanters that have not performed an implantation for a period of more than 6 months will need to request assistance in their next procedure (either by BrainsGate or by a qualified colleague).

In addition, all procedures are recorded (similar to an airplane's "black box") and if misplacements occur in clinical practice, the procedures will be debriefed to identify the root cause and prevent it from repeating itself. Note: A spepareate document is included in the panel pack for the training materials.

7.3 The Implanter Qualifications:

In ImpACT-24B, among the 481 mITT patients allocated to active SPG stimulation, 306 (63.6%) of the implant procedures were performed by neurologists and the remaining 175 (36.4%) implantation procedures

were performed by neuroradiologists, surgeons, and anesthesiologists. The sponsor claims that the main requirement from the implanter is to be attentive to the patient's condition and stroke symptoms.

On the technical side, the implanter would be required to be a medical physician, qualified by BrainsGate, and would be required to understand the principles of the navigation system and be able to correlate between the tactile feeling and the image on the screen.

The implantation training used a head model with various replaceable canals. The implanters perform simulated procedures using the model (including procedures with simulated registration errors) and are required to notice the system's indications when such errors occur.

The use of the models is intended to allow the instructor to assess the implanter's ability to use the navigation system as intended.

The need for suction and the main factors for correct preparation of the dental impression were also emphasized during training.

The sponsor stated that the same head model and the same training methodology were used in the clinical trials with the exception of the procedure itself being simplified by the final INS and navigation system).

More detailed information can be found in the Implantation Procedure Manual provided.

The Panel will be asked to comment on questions about this topic area.

8 Treatment Procedure

Every treatment session with the ISS500 is divided to 3 phases (Table 12). Each phase is explained below.

Phase	Description
Positioning	Ensures that the transmitter is well positioned, and the implant receives sufficient amount of energy. During this phase there is no stimulation to the patient.
Adaptation	Finds the correct stimulation level for the patient. During the adaptation process the INS' output current is controlled by the controller.
Treatment	Delivers pulses of current to the patient. The system verifies the position of the transmitter between treatment pulses to ensure uninterrupted treatment.

Table 12 – Treatment Phases

Positioning Phase

The objective of the positioning phase is to identify the position for the Transmitter on the patient's cheek; this is intended to ensure maximal energy transfer between Driver and INS. Positioning mode may be initiated from either the Controller or the Driver.

Controller – Instructs the Driver to enter positioning mode, and then displays to the caregiver the coupling

quality information it receives from the Driver. This phase ends when the caregiver confirms the Transmitter is attached to the patient and that they are ready to proceed to adaptation.

Driver – Sends data to the INS and senses the feedback level to determine the quality of coupling. The Driver continuously provides the Controller the quality of coupling information. Audible indication is provided by the Driver if no feedback is detected.

INS – Receives data from the Driver and provides feedback to the Driver. No treatment current is supplied to the patient.

Caregiver – Searches for the maximal coupling position of the Transmitter on the patient's cheek based on the coupling quality reading on the Controller. Once the maximal coupling position is found, the Caregiver attaches the Patient sticker to the patient and places the Transmitter at that position.

Adaptation Phase

The objective of the adaptation phase is to identify the patient's Comfortable Tolerance Level (CTL) that will be used in the treatment phase. The CTL is determined based on a specific biological marker for SPG activation – lacrimation.

Controller – Instructs the Driver to enter adaptation mode and manages the adaptation process by sending to the Driver instructions of gradually increasing stimulation levels. Following each increased increment, the Controller waits for the Caregiver's feedback on patient's response. The system monitors the Caregiver's feedback and uses the information to set the patient's CTL.

Driver – Responsible for delivering the required stimulation level to the patient. The Driver receives instructions from the Controller to deliver the next stimulation level, which it translates to low-level instructions to the INS. The Driver monitors the feedback from the INS to verify the stimulation was delivered as instructed.

INS – Receives commands from the Driver to set the new stimulation level. The INS returns feedback to the Driver indicating if the new stimulation level was delivered. Throughout the adaptation phase, the Driver monitors the feedback from the INS to verify that the transferred energy is sufficient, and the Controller indicates to the Caregiver if the Transmitter needs to be re-positioned.

Caregiver – Monitors the patient in search of specific physiological markers – sensation, unilateral lacrimation, and discomfort – and provides input to the Controller.

Patient comfortable tolerance level (CTL) determination – CTL is determined based on specific biological markers – sensation and/or unilateral lacrimation.

In the adaptation phase, the Controller gradually increases the stimulation level delivered to the patient, allowing the Caregiver to monitor the patient and provide feedback if and when sensation or unilateral lacrimation is noticed. Stimulation level is increased until the earlier of (i) unilateral lacrimation is noted, (ii) maximal stimulation level is reached, or (iii) patient feels discomfort. CTL is determined by the Controller based on Caregiver's feedback during the adaptation phase.

Treatment phase

The objective of the treatment phase is to stimulate the patient's SPG at the patient's CTL determined during the adaptation phase for the duration of the treatment session.

Under no circumstances should the patient feel pain during treatment. If pain is felt by the patient, the Caregiver uses the Controller to decrease stimulation level to a lower CTL to prevent pain reoccurrence.

Treatment is initiated by the Caregiver using the controller and ends automatically when the full treatment duration has been reached. It may also be paused and resumed at any time by the Caregiver (using either the Controller, or by removing the Transmitter from the patient).

The Treatment phase is repeated over five (5) consecutive days. Table 13 lists the treatment regimen parameters as further illustrated in Figure 34 Treatment Regimen.

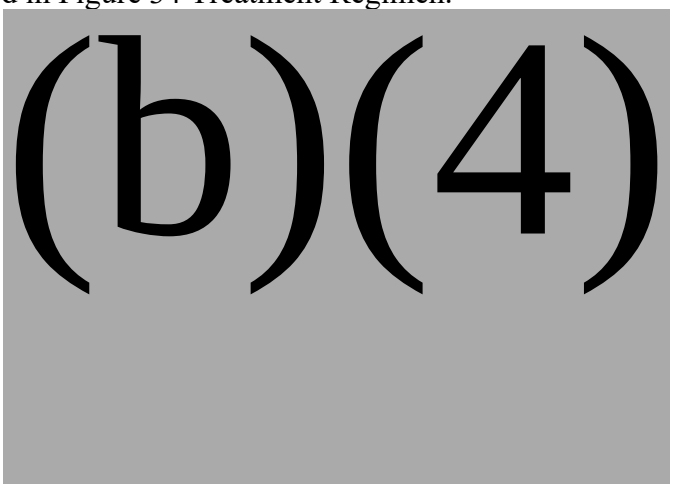

Table 13 Treatment Regimen

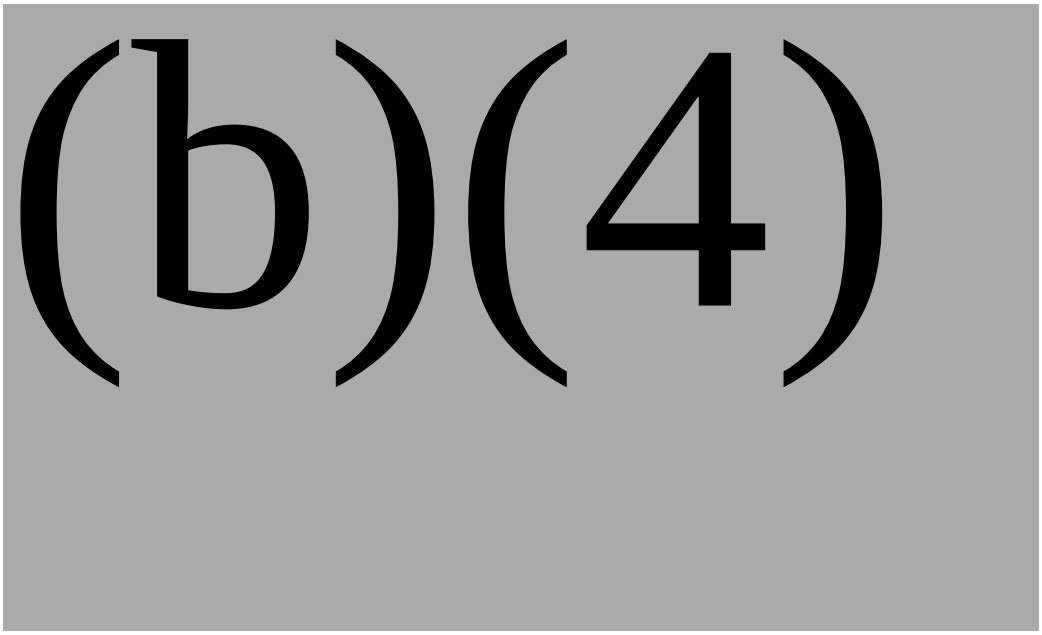

Figure 34 Treatment Regimen

Controller – Responsible for the daily treatment delivery, ensuring the patient receives four (4) hours of treatment per day. The Controller instructs the Driver to commence treatment phase providing the stimulation level (at the CTL) and the required treatment duration. Following treatment commencement, the Controller monitors the Driver's function and displays to the Caregiver the quality of coupling, stimulation level, and remaining duration of the treatment session. The Controller does not have an active role once the treatment mode has commenced, however, the Caregiver can use the Controller to interrupt the treatment session (pause/stop) in which case the Controller instructs the Driver accordingly.

Driver – Responsible for delivering the correct stimulation level to the patient as dictated by the Controller. The Driver gradually increases the stimulation level to the required level, avoiding abrupt, large changes. If the Caregiver does not provide input to change the stimulation level during the treatment session, the Driver continues to deliver the stimulation in accordance with the initial instructions from the Controller to the treatment session's completion. The treatment session ends automatically when the full treatment duration has been reached.

During treatment, the feedback from the INS to the Driver confirms that the INS is sufficiently powered to deliver the required stimulation level, and the Controller indicates to the Caregiver if the transmitter needs to be re-positioned. The Driver continuously monitors this feedback allowing it to optimize battery utilization by adjusting the transmission power to actual needs. If the Driver detects an error or a disconnect in the INS during treatment, it issues an audible and visible notification to the caregiver.

Caregiver – Instructs the Controller to commence treatment, monitors the patient during treatment and intervenes if needed.

9 Overview of Clinical Studies

Three studies (as shown in Table 5), ImpACT-24A, ImpACT-24B and ImpACT-24M, were provided to support this PMA. ImpACT-24A was intended to be a prospective, double-blind, sham-controlled, multi-center randomized pivotal trial; however, was halted at half the planned sample size due to a high rate of INS misplacement. Therefore, it did not achieve adequate power to either support or reject the study hypotheses. ImpACT-24B was a prospective, double-blind, sham-controlled, multi-center randomized pivotal trial, which provides the primary clinical evidence to support this PMA. ImpACT-24M was a prospective, multi-center, single arm usability study to validate the implantation procedure and demonstrate the ability to correctly identify a patient's stimulation level using physiological markers.

9.1 ImpACT-24A

The ImpACT-24A study was intended to be a prospective, randomized, double-blind, sham-controlled, multicenter study. The primary objective of the study was to assess the safety and effectiveness of SPG stimulation with the ISS device. The first patient was enrolled in January 2009 and the last follow-up visit was in January 2011. The planned enrollment was 660 subjects, but terminated early after 303 subjects were randomized due to a high rate of device misplacements, thus underpowered to confirm or reject the hypothesis. During the study, the GuideView navigation system was introduced to reduce the rate of misplacement. The ISS model used was different compared to the models used in ImpACT-24B and ImpACT-24M. Post-hoc analysis probed a signal of potential benefit with confirmed cortical infarct. Appendix E includes a figure with the breakdown of subject enrollment and accountability and several tables which includes demographics and baseline characteristics of the study populations.

9.2 ImpACT–24B

The ImpACT-24B study was a multicenter, randomized patient-blinded and evaluator-blinded, sham controlled, parallel arm trial to assess the safety and effectiveness of the ISS500 as an adjunct to usual care in subjects with acute ischemic stroke ineligible for thrombolysis and endovascular treatment. Treating investigators were not blinded. Multiple protocol revisions were made following several interim analyses and after the trial randomized most of the subjects.

Patients were recruited beginning June 10, 2011. The last follow-up visit was on June 6, 2018

9.2.1 Pivotal Study Objectives

The purpose of this study was to evaluate the safety and effectiveness of SPG stimulation within 24 hours from onset, using the ISS500, in patients with acute ischemic stroke in the anterior circulation, in all eligible patients and in patients with confirmed cortical involvement (CCI).

9.2.2 Pivotal Study - Eligibility Criteria

Subject had to sign the informed consent prior to any study activity and had to meet all inclusion and exclusion criteria in order to be eligible for the study. Compared to the Inclusion Criteria of ImpACT-24A, imaging findings demonstrating signs of ischemia in the anterior circulation was added to the inclusion criteria. The following are the key Inclusion/Exclusion criteria (see full list in Appendix C – Pivotal Study Inclusion/Exclusion Criteria):

9.2.2.1 Inclusion Criteria

- Age: ≥ 40 years and ≤ 80 years for male and 85 for female subjects.
- Clinical diagnosis of an acute ischemic stroke in the Carotid, Middle or Anterior Cerebral Artery territories based on general physical examination and neurological examination.
- Imaging findings demonstrating signs of ischemia in the anterior circulation, consistent with the clinical diagnosis.
- Baseline NIHSS ≥ 7 and ≤ 18 within 2 hours prior to implantation.
- Ability to initiate treatment within 8- 24 hours from stroke onset.
- Signed informed consent from patient him/herself or legally authorized representative if applicable.

9.2.2.2 Exclusion criteria

1. Treated with intravenous (IV)-tPA, intra-arterial (IA)-tPA or neurothrombectomy devices forthe current stroke.

9.2.3 Pivotal Study - Safety Endpoints:

Adverse events were classified by the investigators as related to the implantation, treatment, or unrelated.

The following were the pre-specified safety endpoints:

1. Incidence of serious adverse events
2. Incidence of neurological deterioration as defined by an increase of 4 or more points on the NIHSS related to any neurological event within the first 10 days after the stroke onset
3. Implantation complications
4. Stimulation adverse events
5. Proportion of failed implantations (%)
6. 90-day mortality
7. MoCA assessment at 90 days (US patients, for regulatory purposes only).

Pain during implantation and stimulation, used to determine stimulation dosage, was not documented as an adverse event.

The Panel will be asked to comment on questions about this topic area.

Additionally, the rates of symptomatic intracranial hemorrhages and pneumonia SAEs are reported, as the risk of these events was identified in the risk analysis and the rates of these events were reviewed routinely by the DSMB.

To assess the cumulative evidence after study completion, cumulative safety analysis was also performed (pooled individual patient data from ImpACT-24A and ImpACT-24B).

9.2.4 Pivotal Study – Effectiveness Endpoint

9.2.4.1 Primary Effectiveness Endpoint:

The primary effectiveness endpoint was a favorable global disability outcome, assessed using sliding dichotomy analysis of the mRS evaluated by the site on day 90, in the two primary analysis populations – the mITT population and the CCI population. Initially, mITT was the only primary analysis population. The CCI patient population analysis was added during the last year of the study.

The DAWN acute ischemic stroke trial results were presented at a scientific meeting in May 2017 and published online in November 2017. The DAWN study showed treatment benefit in an 8-24 hour window. The sponsor identified similarities in the inclusion criteria for the DAWN trial and the ImpACT-24B trial CCI population and thus proposed the CCI population as an additional primary analytic population in January 2018.

As noted above in the Overview of Ischemic Stroke section, after the initial De Novo for Trevo (DEN150049; De Novo Summary) and 510(k) for Solitaire (K162539) in 2016, both devices have been cleared with indication expansions by the FDA for use for up to 24 hours in a specific subset of patients based on clinical and neuroimaging criteria. Trevo (K173332; 510(k) Summary) was cleared with clinical data from the DAWN trial (G130223) and Solitaire (K181807; 510(k) Summary) was cleared with clinical data from DEFUSE 3 trial (G150028).

Both the pharmacologic and device therapeutics with improved functional outcomes indications have presented data from randomized clinical trials. For the neurothrombectomy devices this was based on modified Rankin Scale (mRS) scores with good outcome defined as mRS 0-2 (fixed dichotomous scale). The fixed dichotomous mRS analysis has been used due to it having less variability from study to study and device to device. This contrasts with the shifting dichotomous (prognosis adjusted) and utility weighted (patient preference adjusted) versions and their analyses. It should be noted that although AIS clinical trials may have reported analyses using these other versions, to date for neurological devices such as neurothrombectomy devices that have indications for decreasing disability (improving functional outcomes at 90 days) have had to support the proposed IFU and submit analyses using the fixed dichotomous mRS as a primary endpoint.

The inclusion exclusion criteria from DAWN (and DEFUSE 3) are based in part on neuroimaging criteria to ascertain in that extended 8-24 hour time period that there was salvageable tissue present prior to using the device (stent retrievers). The sponsor of the current device did not use such. The type of neuroimaging reading and scoring was not pre-specified in the initial versions of the investigation plan and statistical analysis plan. The sponsor applied ASPECTS scores on patients that already been enrolled and did not adjudicate the previous neuroimaging reading.

Data reported in clinical literature and that required for submission to the FDA for review may differ, with the data in the product labeling most likely being more related to the FDA review.

9.2.4.2 Secondary/Additional Effectiveness Endpoints

The following additional endpoints were assessed in both mITT and CCI populations:

- mRS 0-2 (Functional independence) at day 90
- mRS 0-3 (Capable of self-care or better) at day 90
- SIS-16 (Stroke-related quality of life) at day 90
- Covariate analysis of the primary and secondary effectiveness parameters
- Longitudinal analysis of ordinal mRS
- RIKS-Stroke assessment at 180 and 360 days.

A newer version of the INS was introduced during the study.

In addition, the following commonly analyzed outcomes in acute stroke trials were assessed as post-hoc, exploratory effectiveness endpoints:

- Utility-weighted mRS (Disability-related quality of life) at day 90
- Growth in infarct signs on the ASPECTS scale at day 5

Correct implant position was assessed based on implant position distance to the fossa on day-5 imaging using the GuideView System. Following the introduction of the newer device design and implantation procedure, the definition of "Correct Implant Position" was updated from within 15mm to within 5mm from the fossa, while within 15 mm was used as an auxiliary analysis. Learning curve effects were assessed using this definition of correct INS position excluding the first three (3) patients in each site.

9.2.5 Data Analyses

9.2.5.1 Safety Analysis

Safety analysis was performed on the Safety Analysis Set which included all patients in whom the implantation procedure was initiated.

9.2.5.2 Primary Effectiveness Analysis

According to the updated SAP, the primary effectiveness analysis was performed on the mITT cohort (see definition below) and on the CCI population (a subset of mITT patients with confirmed cortical involvement).

Initially, the mITT population was pre-specified as the primary analysis population. CCI was added as an additional primary analysis population as one of the two primary analysis populations during the last year of the study (2018). Two interim analyses were conducted before June 2016.

The mITT population included all randomized patients who were correctly implanted (within ≤5mm from the fossa) and received at least one SPG stimulation session or sham stimulation. The CCI population was defined as subjects in mITT who had baseline NIHSS ≥ 10 and signs of cortical involvement on baseline NCCT imaging (at least one of the following ASPECTS regions: M1-M6, Insular Cortex). If ASPECTS was not

available, patients with NIHSS ≥ 10 and total occlusion of a large anterior circulation vessel on CTA were also considered to have CCI. The sponsor indicated that this approach was taken in part because of results of ImpACT-24A, and in part due to the results of the DAWN study (Nogueira RG, 2018) late-window mechanical thrombectomy clinical trial, which found benefit of late treatment in patients likely to harbor extensive cortical ischemia due to presence of severe neurologic deficit (baseline NIHSS ≥ 10) and large vessel occlusion.

9.2.5.3 Secondary Effectiveness Analysis Set

A secondary analysis was performed on the Per Protocol cohort which included all subjects who were correctly implanted, and were exposed to at least 4 treatment sessions, and had no major protocol violation potentially affecting outcome, and for whom there was at least a 30-day follow-up evaluation of the effectiveness parameters (mRS and NIHSS).

9.2.6 Study Design

9.2.6.1 Study Overview and Plan

The following figure shows the overall study schematic diagram:

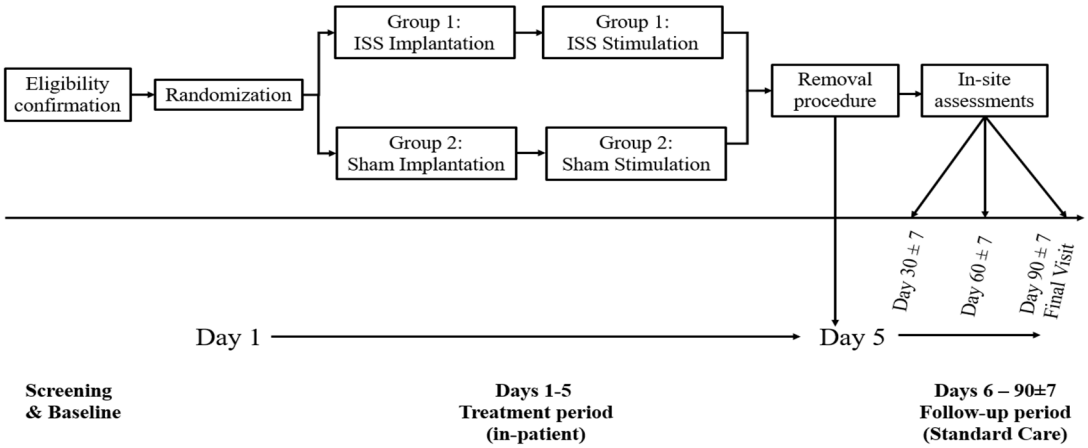

Figure 35 Study Schematic Diagram

The study was comprised of the following periods:

1. **Screening (Eligibility Confirmation and Informed Consent):** up to 24 hours from stroke onset
2. **Treatment:**

   Period I: INS or Sham implantation, 5 Days of ISS500 or Sham Stimulation

   Period II: 85±7 days follow-up
3. **Final Visit:** 90±7 days after randomization

Investigators treated subjects during the trial following accepted clinical guidelines for the treatment of acute

stroke. The protocol stipulated that treatment according to guidelines included the use of antiplatelets, management of secondary stroke, dyslipidemia, hypertension, diabetes and counseling regarding smoking cessation.[10]

Screening (Eligibility Confirmation and Informed Consent)

Subjects with Acute Ischemic Stroke were screened upon arrival to the hospital. Since the treatment must be initiated between 8 and 24 hours from stroke onset, the screening window was limited and all procedures were performed as soon as possible. All screened patients were identified by patient number and signed the informed consent prior to any study procedure initiation.

The last time a patient was seen asymptomatic was determined by the investigator by interviewing the patient's relative (or any other relevant person) who was the last one to have seen the patient asymptomatic.

The following were performed during the Screening Visit:

1. Informed consent procedure which included detailed verbal description of all study aspects as described in the informed consent.
2. Ensured eligibility as per inclusion/exclusion criteria.
3. Ensured availability of implanting physician.
4. Assignment of Patient Number.
5. Notified Implantation Facility to prepare for implantation procedure

Period I - Day 1-5

Day 1

Randomization

Eligible subjects were randomized in a 1:1 ratio into one of the following groups:

Group 1: Implantation and ISS Stimulation during five consecutive days

Group 2: Sham Implantation and Sham Stimulation during five consecutive days

Randomization was performed through a computer-generated randomization scheme. A randomization service utilizing an Interactive Web Based Randomization System (IWRS) provided an implantation and treatment code. This code was entered into the ISS500, which was programmed to determine the implantation/treatment assignment.

To qualify for implantation and be enrolled, the patient must meet the following requirements at the time of implantation:

[10] Guidelines were those of the American Stroke Associafion and the European Stroke Organization. Early ImPAC 24B Protocol, June 20, 2012, Section 8.5, page 53.

Ability to initiate treatment within the 8-24 hours following stroke onset or since last seen without symptoms.

An NIHSS score evaluated no longer than 2 hours prior to implantation (repeat screening evaluation if needed).

All other eligibility criteria had been met (including coagulation profile).

Implantation Procedure

Implantation was performed by a trained physician as explained in the Implantation Procedures Manual. Implantation was guided by a navigation system based on a pre-operative CT. Patients for whom the screening CT did not comply with the navigation system requirements underwent a dedicated, region specific, NCCT before implantation.

The following were performed:

- Ensured availability of pre-operative CT that complies with navigation system requirements (for subjects in the Treated arm).
- Measured vital signs (blood pressure, heart rate).
- Applied continuous monitoring electrodes.
- Transferred the patient to the implantation facility (if applicable).
- Administered antibiotic prophylaxis.
- Induced sedation if needed.
- Performed implantation.
- Recorded all adverse events that occurred prior, during and after the implantation procedure.
- Recorded all medications/treatments administered to the patient during this procedure.
- For post operative pain management, it was recommended to use NSAIDs, to be administered on a per need basis (pain related to implantation) provided there were no contra-indications for the use of NSAIDs.

Following completion of the implantation procedure, the patient was transferred to the stroke unit/neurological department/other facility for first treatment initiation. Re-implantation was permitted only once per subject and only if misplacement into the Nasopharynx had been ascertained.

The first stimulation was initiated within 24 hours since stroke onset, after the implantation was completed. The protocol required that investigators treat all subjects according to accepted practice guidelines for treatment of cute ischemic stroke.

Post Implantation Procedures
Following implantation, the treatment was initiated with one of the following treatment modalities, based on the code mentioned above:

- Group 1: ISS Stimulation.
- Group 2: Sham Stimulation.

First Day of Treatment (Day 1): Treatment Initiation

- The treatment was initiated as soon as possible and within 8-24 hours since stroke onset.
- Treatment was not initiated if patient had received IV-tPA, IA-tPA or neurothrombectomy before the first treatment (after implantation).
- In the event a patient had received neurothrombectomy at any time during the treatment period (day 1-5), or suffered from a life threatening condition or intracranial hemorrhage, treatment was stopped.
- Assessed patient for adverse events.
- Measured vital signs (blood pressure, heart rate) prior to treatment initiation.
- Entered randomization code received through IWRS into ISS500.
- Initiated first treatment session (ISS500/Sham Stimulation) and continued for 4 hours (initial treatment must commence within 24 hours from stroke onset).
- Recorded all medications/ treatments administered to the patient.
- Recorded all adverse events that had occurred prior to, during and after treatment.

Day 2-4
ISS500/Sham Stimulation treatment sessions were repeated daily on Days 2-4 after stroke onset. Each treatment was initiated within 18-26 hours from the preceding treatment.

- All efforts were made to initiate daily stimulation within 18 to 26 hours from the previous treatment initiation.
- Assessed patient for adverse events.
- Measured vital signs (blood pressure, heart rate) prior to treatment initiation.
- Recorded all concomitant medications/therapies given to the patient.
- Evaluated implantation site and oropharynx.
- Initiated treatment session and continue for 4 hours.
- Recorded all adverse events that have occurred prior to, during and after treatment.

Day 5/ Day of Discharge
Following completion of the last ISS500/Sham Stimulation treatment session, imaging was performed for assessing INS positioning and/or lesion assessment. The removal procedure was then performed by a trained physician. Subsequently, patients were evaluated for safety and effectiveness.

After hospital discharge the protocol specified that treating investigators follow accepted clinical practice guidelines.

In the event of early discharge from the hospital (before 5 days of treatment have been completed), the Investigator ensured device removal prior to discharge upon completion of treatment.

Period II - Day 6-89±7 days

As warranted by their clinical condition, subjects were released to home or rehabilitation center and were continued to be followed-up for an additional 85±7 days.

Rehabilitation destination and type were decided by the investigator.

The patient returned to the study site on day 30±7 and day 60±7. During these visits, neurological and effectiveness assessments, adverse events, vital signs (blood pressure, heart rate) and subject's general medical condition were assessed.

Final Visit - Day 90±7 days

The patient returned to the study site on day 90±7 days for the final visit. During this visit neurological and effectiveness assessments, adverse events, vital signs (blood pressure, heart rate) and an interview about the patient's general medical condition were performed. The mRS assessment on day 90 was videotaped and sent to a central reading facility, intended to ensure the blinding (and quality) of the assessment.

Follow Up-Telephone Interviews- Day 180±7 and 360±7 days

Patients were contacted by study personnel via telephone on day 180±7 and on day 360±7 in order to assess their quality-of-life status.

9.2.6.2 Selection of Doses in the Study

The sponsor stated, that the first clinical sign of stimulation is a tingling sensation, then lacrimation, and then, if stimulation further increases, pain appears. In ImpACT-24A and ImpACT-24B, stimulation was gradually increased until the patient reported mild facial discomfort and then it was decreased to a CTL. However, it is unclear how blinding was maintained if patients in the intervention group experienced pain whereas the sham group did not.

In some cases, stimulation exceeded the CTL and was delivered in the sub-optimal painful range, reflected by patients reporting facial discomfort during a treatment session.

The physiologic method of setting the CTL (based on ipsilateral lacrimation or tingling sensation) was validated in ImpACT-24M, a subsequent 50-patient single-arm study (described in section 8.3, below).

9.2.6.3 Blinding

The sponsor stated the ImpACT-24B Trial was a randomized double-blind study, where patient and outcome assessors were blinded to treatment allocation. They included the following elements to help ensure the

blinding was maintained throughout all the periods of the study.

a. Patient Blinding: All patients (Treated and Control) underwent a procedure using the GuideView image-guided navigation system, including a puncture in the mucosa of the upper palate under local anesthesia.

   The control patients underwent simulated implantation (without placing an actual INS). The same ISS500 stimulation device was used for both groups. It delivered either active treatment or sham treatment, such that the patients remained blinded to the treatment assignment.

   Blinding features were integrated into the device to prevent unblinding, including vibration of the transmitter, lights, beeps, etc. All these device elements were executed in both the treated and control arms.

   Following the last treatment session, the INS was removed. Patients in the control arm underwent sham-removal procedure.

b. Blinded Assessment of Effectiveness Outcomes: Effectiveness assessments were performed by blinded evaluators, who were not present during the patient's treatment sessions, did not enquire or seek information regarding any adverse event, assessments performed or other symptoms which had occurred during the treatment phase, and did not to discuss with patient/family any events related to the treatment period. The blinded evaluator did not have access to the patient's case report form (CRF) or study-related documents, except for pre-stroke disabilities and medical history which were needed for correct assessment of disabilities due to the stroke itself.

   The last mRS interview, on day 90, was videotaped and was sent for central assessment, intended to ensure the blinding (and quality) of the assessment.

c. Sponsor Blinding: Sponsor personnel were blinded to outcome data. Activities related to quality assurance of outcome assessment and interaction with the central mRS assessors were carried out by external endpoint-managers, who were not physically located in the Sponsor’s facilities, and had no access to implantation-related information or any other information which might have revealed patient allocation.

   A data visibility scheme was implemented in the eCRF system to prevent Sponsor access to outcome information and to prevent endpoint-manager and central mRS assessor access to data which might expose patient allocation.

The principles and analyses of blinding are referenced in the Appendix E.

9.2.7 Results

9.2.7.1 Subject Accountability

Patients were enrolled from June 10, 2011 through March 7, 2018. Of the 1,078 patients randomized, 1,000 received at least 1 active/sham treatment and entered the mITT population, including 520 in the CCI population. Among the 1,000 mITT: in the SPG stimulation group, 478 (99.4%) of 481 completed the 90-day follow-up and 3 (0.6%) had last observation carried forward; and in the sham stimulation group, 514 (99.0%) of 519 completed the 90-day follow-up, 3 (0.6%) had last observation carried forward, and 2 (0.4%) had worst case mRS 6 imputed when no follow-up available.

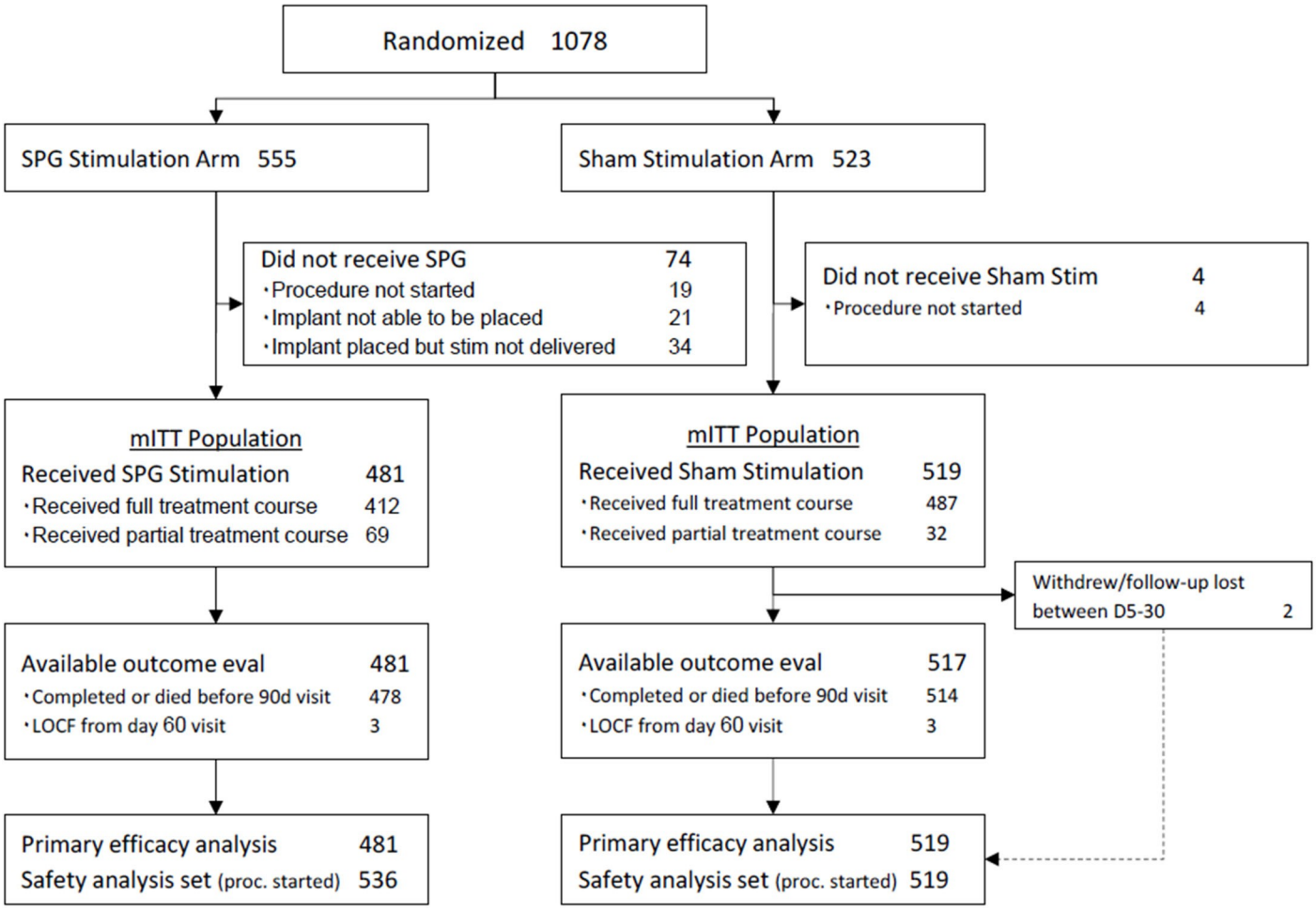

Figure 36 CONSORT Chart – All Patients

Among initially randomized patients, 481/555 (87%) allocated to SPG stimulation and 519/523 (99%) allocated to sham stimulation received at least one treatment and entered the mITT. Leading reasons for not receiving a stimulation treatment were implant misplacement (32 cases) and incomplete implantation procedure (21 cases). Patients entering the mITT and patients not entering the mITT were similar in baseline characteristics, except for a lower frequency of history of hypertension among non-mITT patients

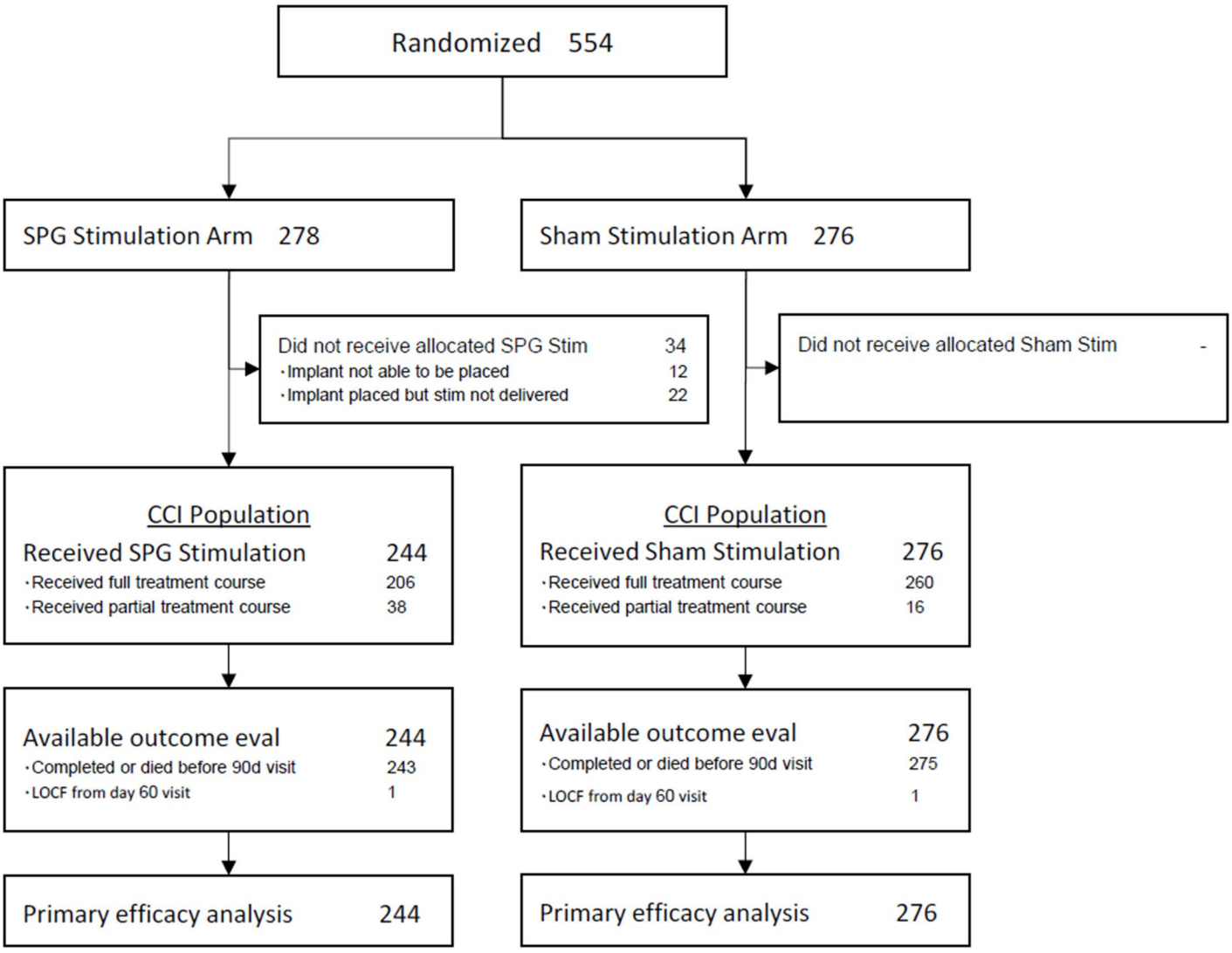

Figure 37 CONSORT Chart – CCI Patients

9.2.7.2 Demographics and Baseline Characteristics

Most baseline characteristics were balanced between treatment groups in both populations (Table 70). However, a few random imbalances were noted:

1) There were more left-hemisphere strokes than right-hemisphere strokes in the study in general (53%) and specifically in the treated group (57%).
2) There were nominally more patients in the SPG stimulation group with pre-existing non-zero mRS (9% vs. 6%) and with previous residence other than "home without assistance" (2% vs. 1%).
3) There were also statistically significant differences between SPG- and sham group patients in INR and aPTT in the CCI population (1.08 vs. 1.05 and 28.8 vs. 27.4 respectively).

In both the mITT and CCI populations, time from last known well to randomization was not statistically different, and time from last known well to first stimulation/sham treatment was longer in the active treatment group, by a mean of 56 minutes. Appendix E includes a tables on demographics and baseline characteristics of the mITT and CCI, mITT vs. non-mITT, CCI vs. non-CCI, and the Per Protocol and Safety populations. The CCI population, compared to non-CCI patients, had more severe neurologic deficits (median NIHSS 13 vs. 10, $p<0.0001$), more extensive infarct signs on imaging (mean ASPECTS 6.4 vs. 8.1, $p<0.0001$), and more frequent history of atrial fibrillation (32.1% vs. 18.1%, $p<0.0001$).

9.2.7.3 Enrollment by Country and Region

The sponsor indicated that during the 8-year trial period, there have been several important changes in stroke care which affected the study in both patient mix and recruitment rate. The most notable change is the growing use of mechanical thrombectomy in clinical trials and in routine use in comprehensive stroke centers and research centers in western countries, including the US.

The growth in the use of mechanical thrombectomy affected ImpACT-24B in two ways:

1. Patient Mix – In some countries, patients with moderate-severe stroke and large penumbra were candidates for thrombectomy. ImpACT-24B patient mix shifted toward patients with contra-indications for thrombectomy (milder strokes, lack of penumbra, patients with comorbidities and other contra-indications).

2. Recruitment Rate – Recruitment rate dropped in Western Europe and North America and recruitment shifted to countries in Eastern Europe (especially Serbia and Georgia).

The following table shows the distribution of patients by country:

#	Country	Patients
1	Georgia	290
2	Serbia	213
3	Spain	167
4	United States	60
5	Poland	57
6	Germany	30
7	Czech Republic	30
8	Israel	30
9	Finland	25
10	Hong Kong	21
11	France	18
12	Portugal	18
13	The former Yugoslav Republic of Macedonia	12
14	Canada	9
15	Slovakia	9
16	Italy	7
17	Denmark	2
18	Ukraine	2
	Total	1000

Table 14 Recruitment by Country – mITT

9.2.7.4 Clinical Investigational Plan Compliance

9.2.7.4.1 Protocol Deviations

The following table lists the most common protocol deviations (deviations that occurred in ≥3% of the patients).

	Category	Deviation Description by Category	Rate	% T	% C
1	Treatment	Time between treatments not done according to protocol specifications	7%	7%	8%
2	Follow-Up	D-90 Visit out of window	6%	5%	6%
		D-30/60 Visit out-of-window	5%	5%	5%
3	Inclusion	First treatment done more than 24 hours from stroke onset	5%	7%	1.7%
4	Implantation	Antibiotic prophylaxis not administered	4%	0.4%	8%

Table 15 Frequent Protocol Deviations

Notes:

1. Treatment – The specified time between treatment sessions is 18-26 hours. There are 5 sessions per patient and >98% of the sessions were in the specified time. The median deviation time is 1 hours.
2. Follow-up – The protocol specifies a time window of ±7 days around days 30, 60, 90 for follow up visits. The median deviation was 3 days in both the treated and sham-control arms. The rate of deviations in both arms is similar too. This small deviation is unlikely to influence the results of the study.
3. Inclusion – First treatment was late (beyond 24 hours from onset) in 7% of the treated arm and 1.7% of the sham-control arm. This difference is due to the longer implantation (compared to the sham procedure). The average deviation was 67 minutes. Since the introduction of the modified INS, both the rate of deviations (1.0%) and their average duration (31 min.) were lower.
4. Implantation – Antibiotic Prophylaxis was intended to minimize the risk of infection due to implantation. No implant-site infections resulted from this deviation.

9.2.7.4.2 Major Violations

A routine monitoring visit in one of the sites revealed that required source data was not kept for the first 24 patients recruited to the study[i]. Without reliable source data, the validity of the data entered into the EDC (the electronic data collection system) cannot be verified.

In the study's primary analysis (Favorable Outcome on mRS sliding dichotomy), patient classification as success or non-success is dependent in part on baseline prognostic characteristics (NIHSS, age, stroke side) in addition to the mRS score at 90 days. The lack of reliable source records for these 24 patients puts the validity of their baseline data in question and may affect their outcome determination.

As a result, the SAP definition of "Major Protocol Violations Potentially Affecting Outcome" was updated to include this violation. This change resulted in the exclusion of these 22 patients from the secondary analysis set (Per Protocol analysis set)[ii].

[i] The audit results have been reported to the relevant ethical committee. The study team was re-trained and that the issue did not repeat itself.
[ii] Two additional patients had other violations.

9.2.7.5 Treatment Tolerability

The number of patients who had their treatment stopped due to a SAE is similar between the groups. The breakdown of these SAEs is shown in the following table:

Event type		SPG	Sham	Total
Nervous system disorders	Stroke deterioration	13	13	27
	Seizure	0	1	
Respiratory	Pneumonia	1	1	4
	Respiratory failure	1	1	
Cardiac	Cardiac failure	3	0	4
	Acute myocardial infarction	1	0	

Table 16 Serious Adverse Events Leading to Treatment Stop

9.2.7.6 Analysis of Efficacy

9.2.7.6.1 Primary Effectiveness Endpoint

The primary Effectiveness endpoint was favorable global disability outcome on the 90-day mRS analyzed using sliding dichotomy in the mITT population and the CCI population. Multiplicity adjustment was performed using the Hochberg procedure.

Population	SPG stim	Sham stim	Odds ratio (95% CI)	p-value
mITT	48.6%	45.5%	1.14 (0.89–1.46)	0.31
CCI	49.6%	39.9%	1.48 (1.05–2.10)	0.0258

Table 17 Primary Effectiveness Results

Note: The multiplicity-adjusted thresholds are 0.05 for the larger p-value (mITT) and is 0.025 for the smaller one (CCI).

The figure below shows the entire mRS distribution on the two cohorts:

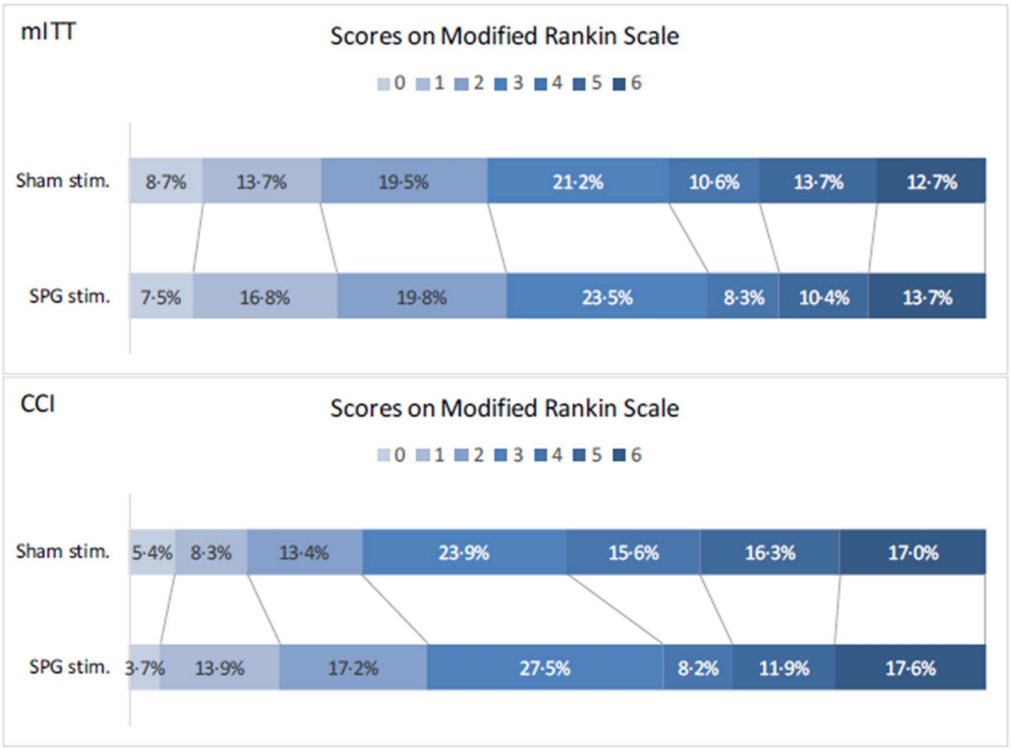

Figure 38 mRS Distribution (Day 90) - ImpACT-24B

9.2.7.6.2 Secondary Clinical Effectiveness Endpoints

Outcome	mITT Population				CCI Population			
	SPG stim (N=481)	Sham stim (N=519)	Odds ratio (95% CI)	p-value	SPG stim (N=244)	Sham stim (N=276)	Odds ratio (95% CI)	p-value
mRS 0–2	44.1%	41.8%	1.10 (0.86–1.41)	0.47	34.8%	27.2%	1.43 (0.99–2.08)	0.06
mRS 0–3	67.6%	63.0%	1.22 (0.94–1.59)	0.13	62.3%	51.1%	1.58 (1.11–2.25)	0.01
	SPG stim mean (SD)	Sham stim mean (SD)	Difference (95% CI)	p-value	SPG stim mean (SD)	Sham stim mean (SD)	Difference (95% CI)	p-value
SIS-16	57.7 (38.2)	54.7 (38.7)	3.0 (-1.8–7.8)	0.23	52.2 (38.5)	43.9 (38.1)	8.3 (1.6–14.9)	0.01
UW-mRS	55.8 (35.4)	53.2 (36.2)	2.7 (-1.8-7.1)	0.24	50.0 (35.7)	43.9 (35.6)	6.1 (-0.0-12.3)	0.05

Table 18 Secondary Clinical Effectiveness Endpoints

9.2.7.6.3 180-Day and 360-Day Follow-Up

This section presents the results of the RIKS phone-questionnaire at 180 days and 360 days after stroke onset in the mITT and CCI populations.

Data availability is presented in the following Table 19.

	Follow-up	SPG	Sham	Total
mITT	180	473/481 (98.3%)	511/519 (98.5%)	984/1000 (98.4%)
	360	472/481 (98.1%)	507/519 (97.7%)	980/1000 (98.0%)
CCI	180	240/244 (98.4%)	273/276 (98.9%)	513/520 (98.7%)
	360	241/244 (98.8%)	271/276 (98.2%)	512/520 (98.5%)

Table 19 - RIKS Data Availability

Patients who died were assigned the worst possible outcome in all questions and are included in the availability numbers.

Table 20 below shows the 180-day and 360-day mortality in the two primary populations.

	Follow-up	SPG	Sham	OR	p-value
mITT	180	76/473 (16.1%)	77/511 (15.1%)	1.08 (0.76-1.52)	0.67
	360	86/472 (18.2%)	84/507 (16.6%)	1.12 (0.81-1.56)	0.50
CCI	180	48/240 (20.0%)	57/273 (20.9%)	0.95 (0.62-1.46)	0.81
	360	54/241 (22.4%)	61/271 (22.5%)	0.99 (0.66-1.51)	0.98

Table 20 Mortality Rates at 180 Days and 360 Days from Onset

The following charts present the results of the RIKS questionnaire at 180 days and 360 days after stroke onset in the mITT and CCI populations. Odds ratios and p-values were calculated using ordinal logistic regression.

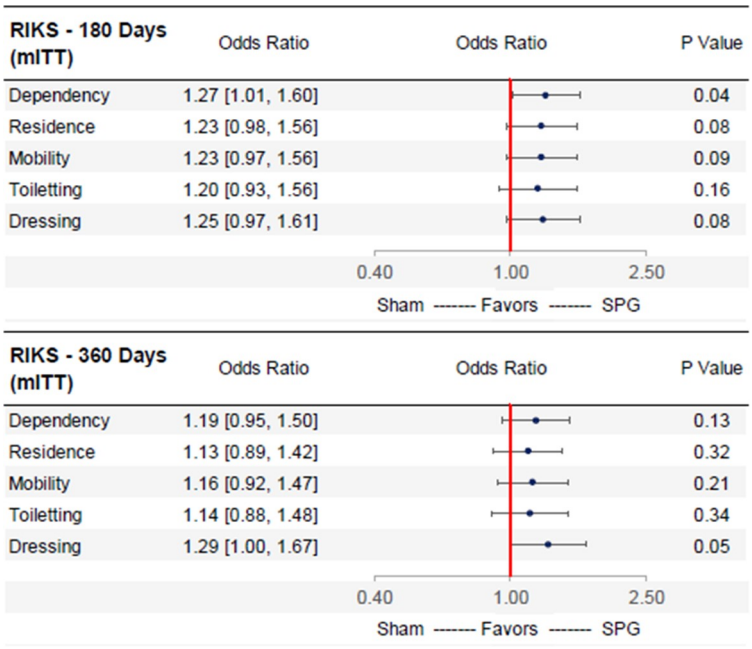

Figure 39 180-day and 360-day Follow-Up – mITT

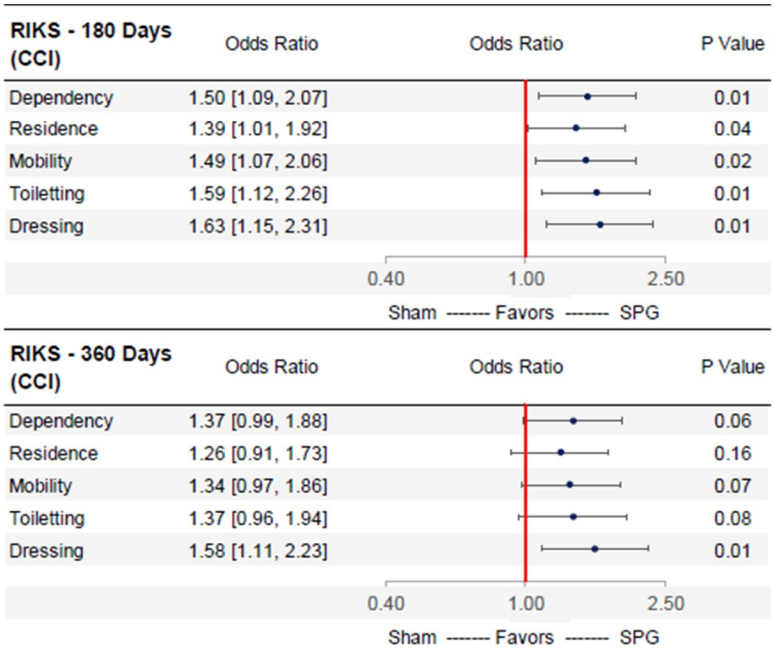

Figure 40 180-day and 360-day Follow-Up – CCI

9.2.7.6.4 Poolability Analysis

ImpACT-24B had low CCI enrollment in many countries. In the US, with 19 patients in the active group and

12 patients in the sham group. This ranked the 4th highest in the countries enrolled. The sponsor conducted a country-poolability analysis by fitting a logistic regression model using Firth's method on the primary endpoint with covariates for treatment arm, country, and a treatment arm by country interaction. They reported that in both the mITT and CCI analyses, "the interaction term joint test p-value was >0.15, a commonly used significance level for evaluating poolability of data (P-value = 0.74 and 0.52 for mITT and CCI, respectively)." However, the validity of such poolability analysis and the corresponding p-values is questionable because there were many low-enrollment countries. Moreover, FDA conducted an exploratory analysis by dividing the countries into two groups. The high-enrollment group consisted of the 4 countries with more or the same CCI enrollment as the US whereas the low-enrollment group included the remaining 14 countries. The high-enrollment group had 381 total CCI patients and had responder rates of 50% (active) and 43.8% (sham), with a nominal p-value of 0.244 (Chi-squared test). The low-enrollment group appeared to have much better results with 139 patients, with responder rates of 48.4% (active) and 29.3% (sham), with a nominal p-value of 0.0208. This noticeable difference and the concern about the poolability by country further increases the uncertainty of applying OUS data to the US population.

As an additional exploratory analysis, FDA split the high-enrollment countries (top k rows) and low-enrollment countries (the rest rows) and compared the results on the primary endpoint. The definition of "high-enrollment" was arbitrary; therefore, FDA varied the number of countries enrolled (k = 4, 5, and 6). The nominal p-values were calculated by applying the Chi-squared test to the corresponding cohorts as done in the primary analysis.

K	Cohort	#Patients	Trt_Success_Rate	Sham_Success_Rate	p_value
6	GEORGIA – POLAND (High Enrollment)	426	49%	41.6%	0.125
6	FRANCE – UKRAINE (Low Enrollment)	94	52.3%	32%	0.0465
5	GEORGIA – CZECH (High Enrollment)	402	48.7%	42.2%	0.19
5	POLAND – UKRAINE (Low Enrollment)	118	52.8%	32.3%	0.0244
4	GEORGIA – US (High Enrollment)	381	50%	43.8%	0.224

4	CZECH – UKRAINE (Low Enrollment)	139	48.4%	29.3%	0.0208

In terms of the primary endpoint, it appeared that the treatment group was generally better than the sham group, but the gaps between the two groups were larger in the low-enrollment groups. This leads to uncertainty about the claims of overall treatment effect and particularly that for US patients because the homogeneity of a treatment effect involving low-enrollment countries cannot be determined with high confidence due to the lack of data. However, when only considering high-enrollment countries, the treatment effect appeared diminished.

9.2.7.6.5 Endpoint Analysis by Stimulation Level (Dose Response)

ImpACT-24B included different versions of the INS component along with changes to how the stimulation level was applied.

The changes in the user interface of the device initially caused more frequent deviations from the recommended stimulation ramp-up profile, with patients being treated with higher average stimulation levels than were seen with the original device. As a result, the DSMB noted an increase in the number of nonserious facial pain adverse events occurring during treatment in some eastern European sites. Study sites were retrained to ensure the ramp up profile was followed (See Table 21).

Period	Start Date	N	Stimulation Level Mean		Pain AE	
			Mean (SD)	p-value	%	p-value
First implant model	June 10, 2011	293	Base level	Reference	18.8%	Reference
Modified implant, before retraining	August 25, 2016	134	140% of base level	<0.0001	47.8%	<0.0001
Modified implant, after retraining	October 1, 2017	54	Base level	0.50	1.9%	0.002
p-values are relative to first implant						

Table 21 Stimulation Levels and Pain Adverse Events over Time (Treated Patients)

Overstimulation can lead to pain. Pain can subsequently be a source of unblinding. Because of the range of stimulation levels delivered, analyses of endpoints by stimulation levels (dose response analysis) and by implant model were undertaken. Figure 41 shows the rates of favorable outcome (and associated 95% CI) on the mRS sliding dichotomy at 90 days across different stimulation levels (the Dose Response).

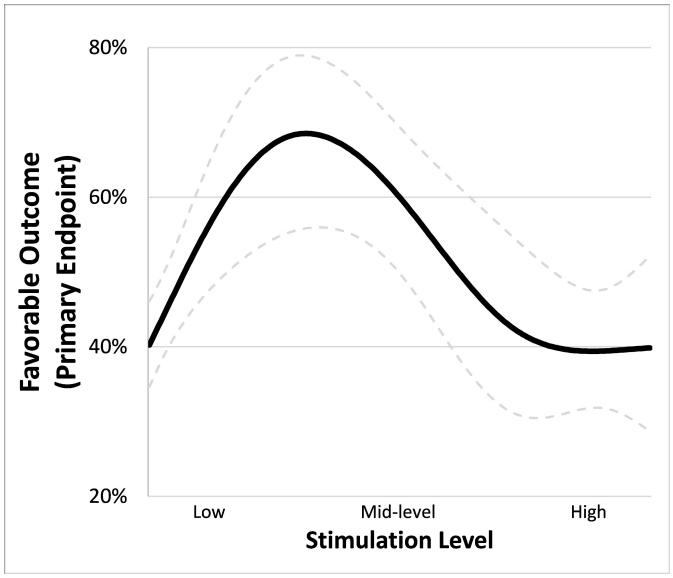

Figure 41 Restricted Cubic Spline Model of the Primary Effectiveness Effect in CCI Population as a Function of Stimulation

Significance level for the presence of a dose-response relationship was calculated using the likelihood ratio test. Stimulation level was associated with the rate of favorable outcome (p=0.0006). As delineated in Figure 41, the rate of favorable outcome at zero stimulation (control patients) is 40%, with an upper confidence limit of 46%. Current levels ranging from in the low-medium range yielded favorable outcome rates higher than those observed at a current level of zero, as evidenced by the lower confidence bounds across this range being above 46%.

In contrast, covariate analysis showed that implant model was not associated with outcome (p=0.28). The outcomes of mRS 0-2, mRS 0-3, SIS and utility-weighted mRS were also evaluated using RCS models.

	Covariate Adjustment		
Endpoint	**Unadjusted**	**Adjusted for Implant Type**	**Adjusted for all pre-specified covariates**
Sliding Dichotomy	0.0006	0.0005	0.004
mRS 0-2	0.0007	0.0002	0.02
mRS 0-3	0.0006	0.0006	0.01
SIS-16	0.002	0.0015	0.03
Utility Weighted mRS	0.001	0.0007	0.03

Table 22 Significance of Association between Stimulation Level and Outcome

The likelihood ratio test showed significant dose-response relationships between all the Effectiveness outcomes and stimulation level, with and without adjustment for all pre-specified covariates, independent of the which implant model was used.

No significant dose-response relationship between stimulation level and outcome was found in the complementary non-CCI population.

9.2.7.6.6 Effectiveness Results – Per Protocol Analysis Set

The following table shows the results of the primary and additional clinical Effectiveness endpoints analyzed in the Per Protocol Population.

Outcome	mITT Per-Protocol Population				CCI Per-Protocol Population			
	SPG stim (N=417)	Sham stim (N=481)	Odds ratio (95% CI)	p-value	SPG stim (N=206)	Sham stim (N=252)	Odds ratio (95% CI)	p-value
Sliding Dichotomy	49.2%	45.5%	1.16 (0.89-1.50)	0.28	51.5%	40.9%	1.53 (1.06-2.22)	0.02
mRS 0–2	45.6%	42.2%	1.15 (0.88-1.49)	0.31	37.4%	28.2%	1.52 (1.03-2.26)	0.04
mRS 0–3	68.6%	63.6%	1.25 (0.95-1.65)	0.12	65.0%	52.0%	1.72 (1.18-2.51)	0.005
	SPG stim mean (SD)	Sham stim mean (SD)	Difference (95% CI)	p-value	SPG stim mean (SD)	Sham stim mean (SD)	Difference (95% CI)	p-value
SIS-16	58.7 (38.0)	55.0 (38.6)	3.7 (-1.4-8.8)	0.15	54.7 (38.3)	44.8 (38.0)	9.9 (2.8-16.9)	0.01
UW-mRS	56.9 (35.1)	53.6 (36.1)	3.3 (-1.4-8.0)	0.17	52.4 (35.1)	44.7 (35.7)	7.7 (1.2-14.2)	0.02

Table 23 Per Protocol Analysis Set

9.2.7.6.7 Subgroup Analysis

The following figures show evaluation for heterogeneity of SPG stimulation effect upon the primary endpoint of favorable outcome (mRS sliding dichotomy) in pre-specified subgroups, in the mITT and CCI populations:

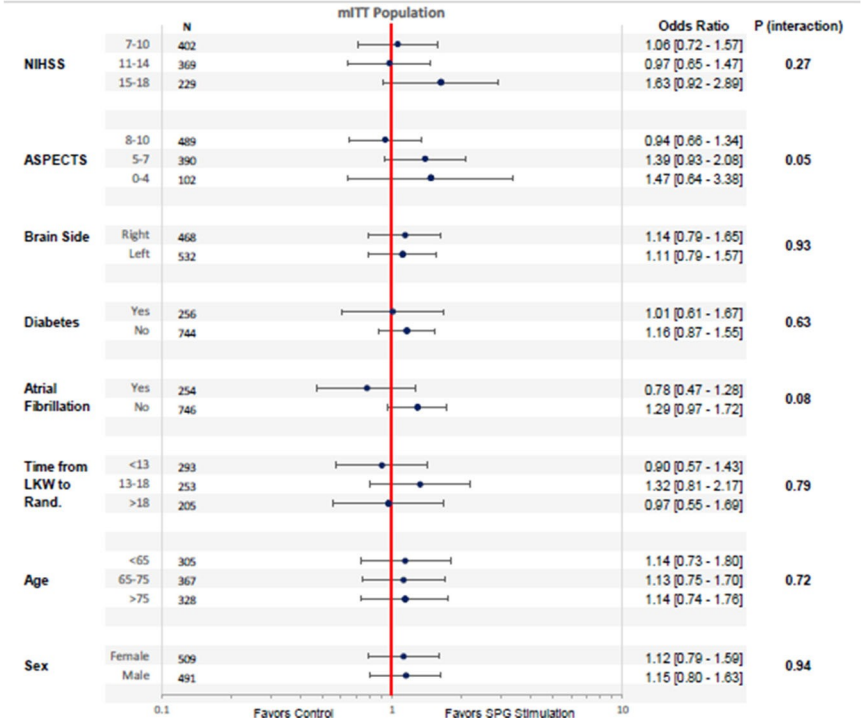

Figure 42 Subgroup Analysis – mITT

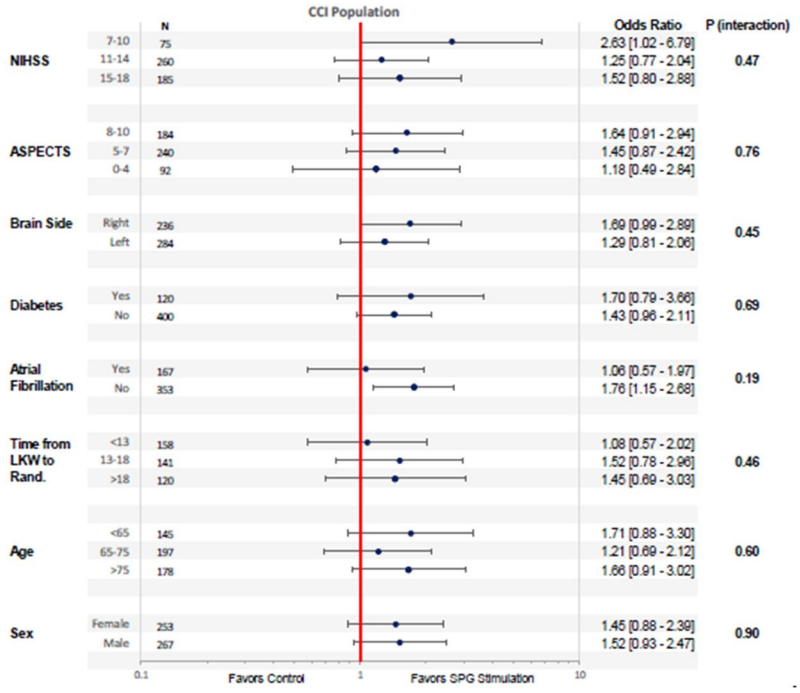

Figure 43 Subgroup Analysis – CCI

In the mITT population, there was interaction between the treatment effect and the baseline ASPECTS score (infarct size), with higher benefit in patients with larger lesions (lower ASPECTS).

In the CCI population, there is no significant interaction between treatment effect and any of the prespecified covariates, including the ASPECTS score.

9.2.7.6.8 Effectiveness Analysis with Adjustment for Baseline Prognostic Factors

The following table shows the results of analysis of the primary and additional clinical Effectiveness endpoints with adjustment for baseline prognostic factors:

Outcome	mITT Population		CCI Population	
	Odds ratio (95% CI)	p-value*	Odds ratio (95% CI)	p-value*
Sliding Dichotomy	1.13 (0.86,1.48)	0.37	1.47 (1.00,2.17)	0.05
mRS 0–2	1.02 (0.76,1.37)	0.92	1.43 (0.92,2.23)	0.11
mRS 0–3	1.14 (0.83,1.55)	0.41	1.55 (1.02,2.36)	0.04
	Mean Difference (95% CI)	p-value*	Mean Difference (95% CI)	p-value*
SIS-16	0.7 (-3.3,4.8)	0.72	5.6 (-0.1,11.3)	0.05
UW-mRS	0.8 (-3.0,4.6)	0.69	3.5 (-1.7,8.8)	0.18

Table 24 Effectiveness Analysis Adjusted for Baseline Prognostic Factors

*Adjusted for 9 pre-specified baseline features: age, sex, NIHSS, stroke brain side, ASPECTS, time from stroke onset to study treatment, diabetes, atrial fibrillation, and predicted mRS mean-median difference

9.2.7.6.9 Longitudinal mRS Analysis

The mRS was evaluated in a longitudinal manner to characterize the average shift across the total ordinal outcome scale due to the treatment. A repeated measures logistic regression was used to produce a common odds ratio at each visit and overall. Results for each analysis population are provided below.

	OR [95% CI]	p-value ¥
Overall Treatment Effect	1.11 [0.91,1.36]	0.2902
Day 5	1.09 [0.90,1.32]	
Day 30	1.08 [0.87,1.34]	
Day 60	1.15 [0.92,1.44]	
Day 90	1.14 [0.89,1.44]	
¥ P-value based on repeated measures ordinal logistic regression model (mRS at days 5, 30, 60 and 90). Fixed effects include treatment arm, visit, and a treatment by visit interaction term.		

Table 25 Longitudinal Analysis – mITT

	OR [95% CI]	p-value ¥
Overall Treatment Effect	1.31 [0.99,1.74]	0.0551
Day 5	1.15 [0.90,1.47]	
Day 30	1.25 [0.92,1.69]	
Day 60	1.42 [1.03,1.96]	
Day 90	1.46 [1.03,2.06]	
¥ P-value based on repeated measures ordinal logistic regression model (mRS at days 5, 30, 60 and 90). Fixed effects include treatment arm, visit, and a treatment by visit interaction term.		

Table 26 Longitudinal Analysis – CCI

9.2.7.6.10 Infarct Size Growth Analysis

Imaging was performed at baseline (prior to randomization) and after 5 days of treatment. Mean time from imaging to first treatment was 6.6±4.3 hours in the SPG stimulation group and 5.9±3.8 hours in the sham-control group, limiting the value of this analysis.

Table 27 shows the change in ASPECTS score between baseline imaging and day 5.

	SPG mean (SD)	Sham mean (SD)	Difference (95% CI)	p-value
mITT	1.0 (2.0)	1.2 (2.1)	-0.2 (-0.4-0.1)	0.25
CCI	1.3 (2.2)	1.5 (2.2)	-0.2 (-0.6-0.2)	0.24

Table 27 Change in ASPECTS Score (BL-D5), Lower change indicates smaller infarct growth

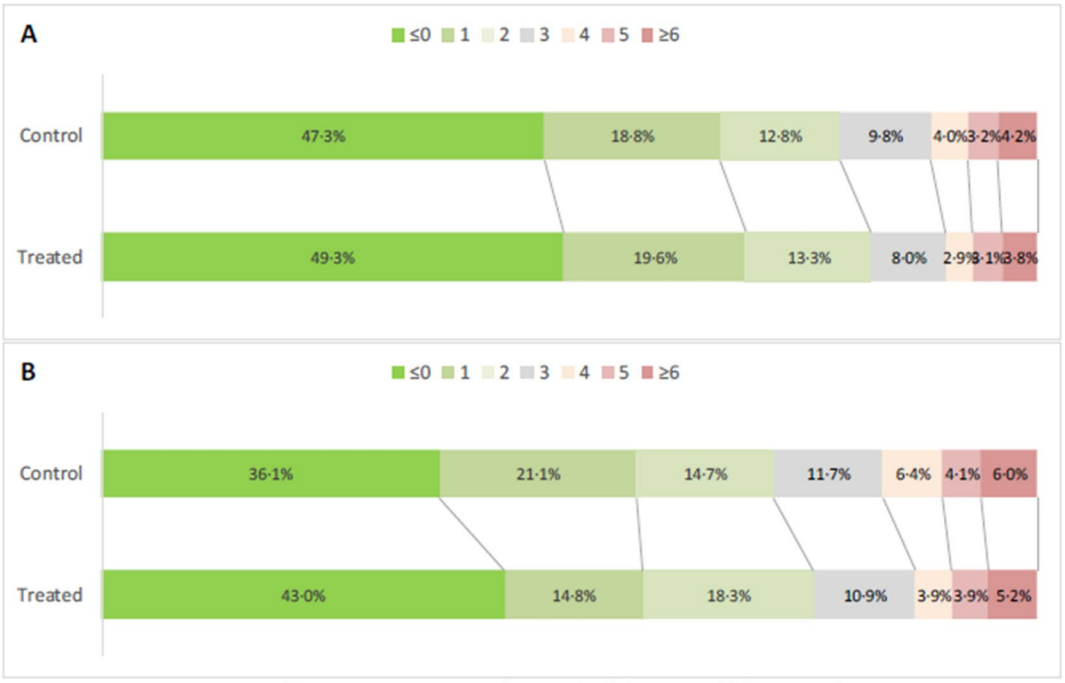

Table 28 Change in ASPECTS Score (BL – D5) in (A) mITT and (B) CCI Populations

9.2.7.6.11 Sensitivity Analysis

The following sensitivity analysis shows the clinical effectiveness endpoints analyzed using a broader definition of correct implant position (within 15mm from the fossa) for entry into the mITT and CCI populations:

Outcome	mITT Population				CCI Population			
	SPG stim (N=501)	Sham stim (N=519)	Odds ratio (95% CI)	p-value	SPG stim (N=256)	Sham stim (N=276)	Odds ratio (95% CI)	p-value
Sliding Dich.	48.1%	45.5%	1.11 (0.87 - 1.42)	0.40	48.0%	39.9%	1.40 (0.99-1.97)	0.057
mRS 0–2	43.7%	41.8%	1.08 (0.84 - 1.39)	0.54	33.6%	27.2%	1.36 (0.94-1.96)	0.11
mRS 0–3	66.9%	63.0%	1.18 (0.92 - 1.53)	0.20	60.5%	51.1%	1.47 (1.04-2.07)	0.03
	SPG stim mean (SD)	Sham stim mean (SD)	Difference (95% CI)	p-value	SPG stim mean (SD)	Sham stim mean (SD)	Difference (95% CI)	p-value
SIS-16	57.3 (38.4)	54.7 (38.7)	2.6 (-2.1-7.4)	0.28	51.0 (38.7)	43.9 (38.1)	7.2 (0.6-13.7)	0.03
UW-mRS	55.3 (35.6)	53.2 (36.2)	2.2 (-2.3-6.6)	0.34	48.8 (35.9)	43.9 (35.6)	4.9 (-1.2-11.0)	0.12

Table 29 Sensitivity Analysis - <15mm from Fossa

Outcome	mITT Population				CCI Population			
	SPG stim (N=275)	Sham stim (N=519)	Odds ratio (95% CI)	p-value	SPG stim (N=118)	Sham stim (N=276)	Odds ratio (95% CI)	p-value
Sliding Dich.	51.3%	45.5%	1.26 (0.94-1.69)	0.12	58.5%	39.9%	2.13 (1.37-3.29)	0.0007
mRS 0–2	50.2%	41.8%	1.40 (1.05-1.88)	0.02	44.1%	27.2%	2.11 (1.35-3.31)	0.001
mRS 0–3	74.2%	63.0%	1.69 (1.22-2.33)	0.001	72.9%	51.1%	2.57 (1.61-4.11)	<.0001
	SPG stim mean (SD)	Sham stim mean (SD)	Difference (95% CI)	p-value	SPG stim mean (SD)	Sham stim mean (SD)	Difference (95% CI)	p-value
SIS-16	63.1 (37.1)	54.7 (38.7)	8.4 (2.8-14.1)	0.003	59.7 (36.2)	43.9 (38.1)	15.8 (7.5-24.1)	0.0002
UW-mRS	61.2 (33.7)	53.2 (36.2)	8.0 (2.8-13.2)	0.002	57.8 (33.3)	43.9 (35.6)	13.9 (6.2-21.5)	0.0003

Table 30 Sensitivity Analysis - <15mm from Fossa – Physiologically Selected CTL Range

Learning-curve effects were assessed using the same broader definition of correct implant position (within 15mm from the fossa), but excluding the first 3 patients in each site:

Outcome	mITT Population				CCI Population			
	SPG stim (N=422)	Sham stim (N=427)	Odds ratio (95% CI)	p-value	SPG stim (N=217)	Sham stim (N=230)	Odds ratio (95% CI)	p-value
Sliding Dich.	49.8%	45.7%	1.18 (0.90-1.54)	0.23	47.5%	37.8%	1.49 (1.02-2.16)	0.04
mRS 0–2	44.8%	41.9%	1.12 (0.86-1.47)	0.40	33.2%	26.1%	1.41 (0.94-2.12)	0.10
mRS 0–3	67.3%	62.5%	1.23 (0.93-1.64)	0.15	60.4%	49.6%	1.55 (1.07-2.26)	0.02
	SPG stim mean (SD)	Sham stim mean (SD)	Difference (95% CI)	p-value	SPG stim mean (SD)	Sham stim mean (SD)	Difference (95% CI)	p-value
SIS-16	58.2 (38.5)	54.7 (38.4)	3.5 (-1.7-8.7)	0.19	50.7 (38.8)	43.3 (37.7)	7.4 (0.3-14.6)	0.04
UW-mRS	55.9 (36.0)	53.1 (36.3)	2.9 (-2.0-7.7)	0.25	48.6 (36.4)	43.3 (35.5)	5.3 (-1.4-12.0)	0.12

Table 31 Sensitivity Analysis – Learning Curve

Outcome	mITT Population				CCI Population			
	SPG stim (N=227)	Sham stim (N=427)	Odds ratio (95% CI)	p-value	SPG stim (N=99)	Sham stim (N=230)	Odds ratio (95% CI)	p-value
Sliding Dich.	54.2%	45.7%	1.41 (1.02-1.94)	0.04	59.6%	37.8%	2.42 (1.50-3.93)	0.0003
mRS 0–2	51.5%	41.9%	1.47 (1.07-2.04)	0.02	43.4%	26.1%	2.18 (1.33-3.57)	0.002
mRS 0–3	74.4%	62.5%	1.75 (1.22-2.49)	0.002	72.7%	49.6%	2.71 (1.63-4.53)	0.0001
	SPG stim mean (SD)	Sham stim mean (SD)	Difference (95% CI)	p-value	SPG stim mean (SD)	Sham stim mean (SD)	Difference (95% CI)	p-value
SIS-16	64.4 (36.9)	54.7 (38.4)	9.7 (3.5-15.9)	0.002	59.5 (35.9)	43.3 (37.7)	16.2 (7.4-25.0)	0.0003
UW-mRS	61.9 (33.8)	53.1 (36.3)	8.9 (3.1-14.6)	0.002	57.8 (33.5)	43.3 (35.5)	14.5 (6.2-22.8)	0.0006

Table 32 Sensitivity Analysis – Learning Curve – Physiologically Selected CTL Range

9.2.7.6.12 Subgroup Effectiveness Analysis US vs. OUS and West vs. East

This section compares the effectiveness results between US and OUS and between the two regions (West vs. East), focusing on the CCI population by including the covariate US/OUS or West/East in a statistical model for each outcome, for example, a logistic regression model for the sliding dichotomy of 90-day mRS.

Given the small number of US patients in ImpACT-24B (31 CCI patients), pooled results of ImpACT-24A and ImpACT-24B are presented (46 US patients).

The following figures summarize the results of the Effectiveness subgroup analysis for US vs. OUS (Figure 44) and West vs. East (Figure 45).

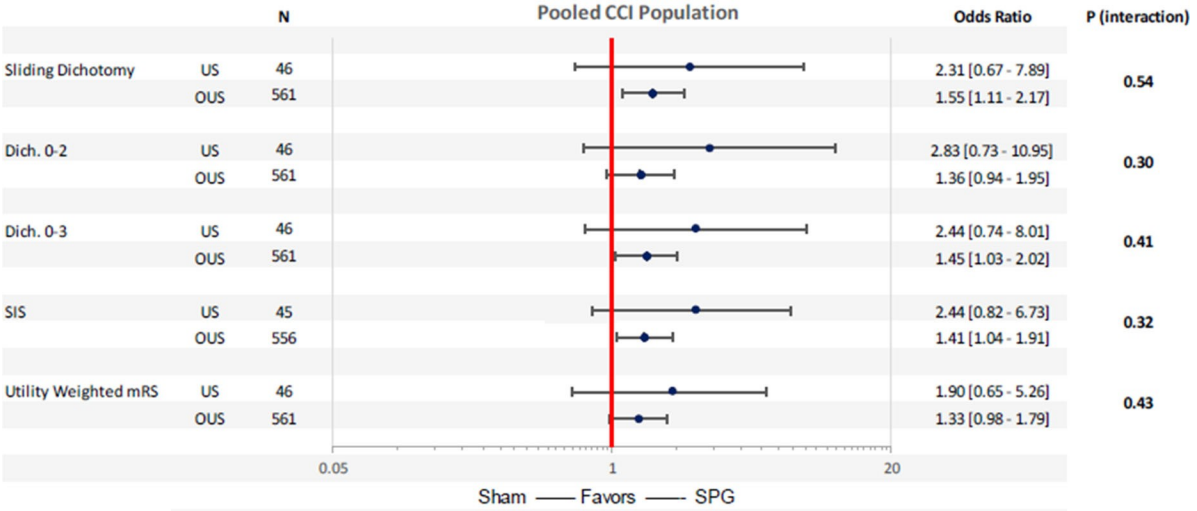

Figure 44 Pooled Subgroup Effectiveness Analysis - US vs. OUS - CCI Population

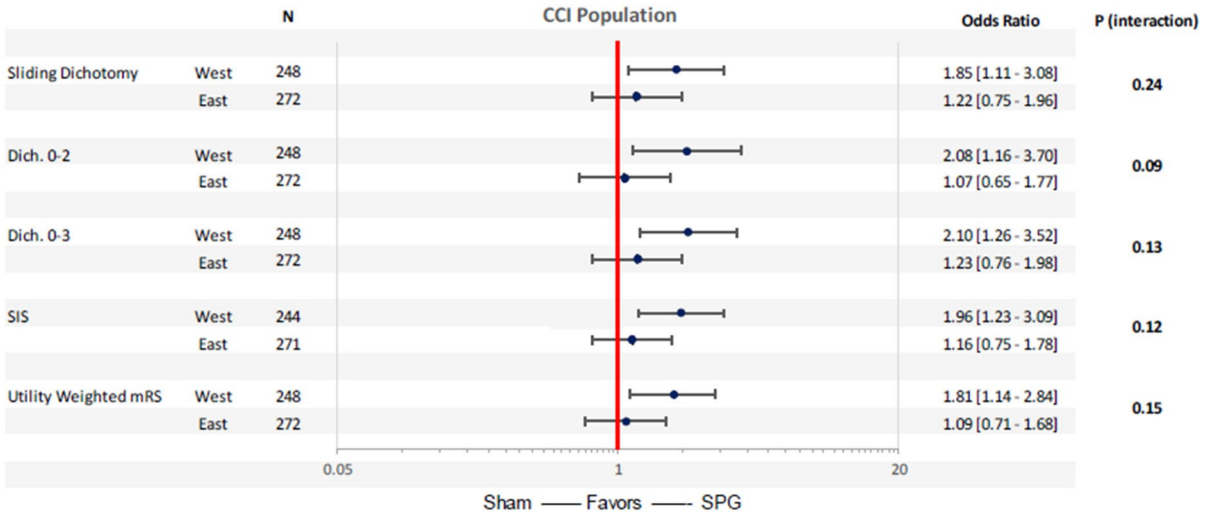

Figure 45 Subgroup Effectiveness Analysis - West vs. East - CCI Population

The confidence intervals in the US subgroup are too wide to draw any conclusions, but there is a trend towards higher treatment effects in western countries in all endpoints.

Despite differences in some pre-specified baseline characteristics, covariate analysis showed that treatment heterogeneity by geographic region is not associated with differences in any of the pre-specified variables.

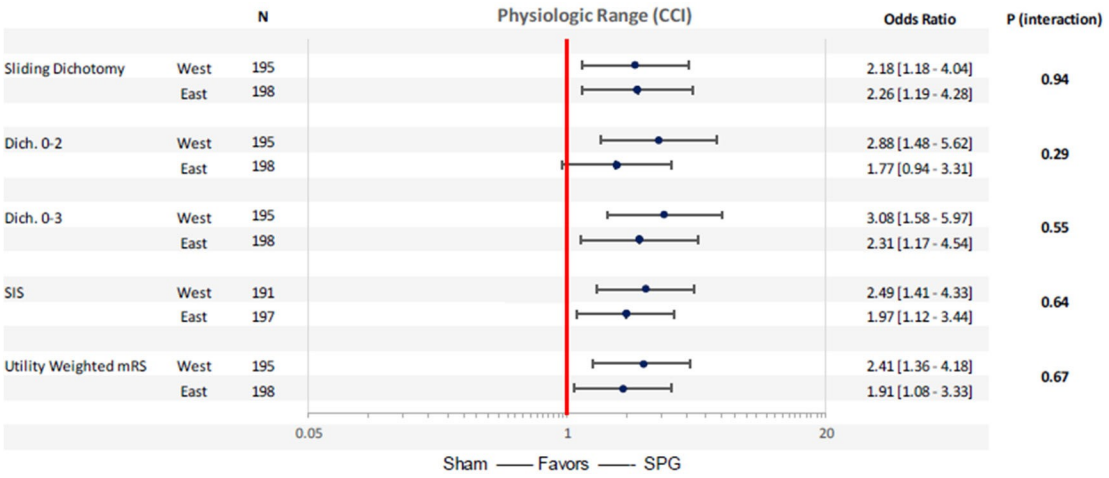

Figure 46 West vs. East – Physiologically Selected Stimulation Range

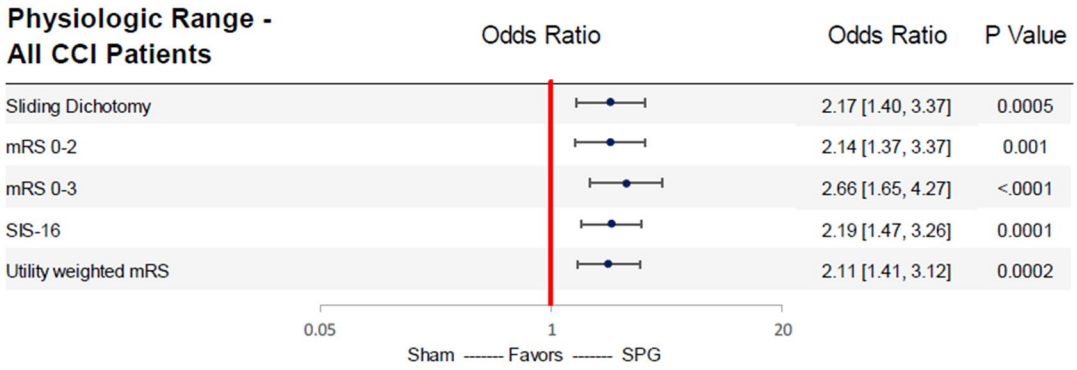

Figure 47 East and West Combined – Physiologically Selected Stimulation Range

The sponsor concluded the lower treatment benefit in countries with low IV-tPA and mechanical thrombectomy rates is likely due to the higher proportion of patients who were stimulated at sub-optimal levels in these countries (57% vs 46%).

9.2.7.7 Statistical/Analytical Issues

9.2.7.7.1 Handling of Dropouts or Missing Data

The primary effectiveness analysis was performed in the mITT population which included all patients who received at least one full active/sham stimulation session. Seventy-eight (78) patients did not receive at least one full treatment and were not included in this analysis, including 23 patients among whom the implantation procedure was not started, 21 cases of incomplete implantation procedure, 32 cases of implant

misplacement, one case of electrode disconnection, and one patient who completed implantation but did not receive one full treatment.

Ninety nine percent (99%) of the mITT patients completed their follow up according to the protocol. The remaining 1% (3 treated and 5 control patients) had their effectiveness data imputed using the last observation carried forward (LOCF) method as specified in the protocol, which assigns the worst possible outcome if no carry-forward data is available. While the day 30, day 60, and day 90 mRS ratings were performed by blinded assessors, the day 5 mRS was performed by an unblinded assessor. Therefore, day 5 assessments were not carried forward. Only mRS ratings performed by blinded assessors (on days 30, 60, and 90) were used (affecting two of the eight patients with missing day 90 data).

The following table shows sensitivity analyses using alternative missing data handling techniques for these two patients:

Missing Data Handling Technique	mITT Population (N=1000)				CCI Population (N=520)			
	SPG stim (N=481)	Sham stim (N=519)	Odds ratio (95% CI)	p value	SPG stim (N=244)	Sham stim (N=276)	Odds ratio (95% CI)	p value
Assign worst possible outcome (mRS = 6)	48.6%	45.5%	1.14 (0.89-1.46)	0.31	49.6%	39.9%	1.48 (1.05-2.10)	0.0258
Assign best possible outcome (mRS = 0)	48.6%	45.9%	1.12 (0.87-1.43)	0.38	49.6%	39.9%	1.48 (1.05-2.10)	0.0258
Complete case analysis (Censor the 2 missing cases)	48.6%	45.6%	1.13 (0.88-1.45)	0.34	49.6%	39.9%	1.48 (1.05-2.10)	0.0258
Last observation carried forward (Carry forward the day 5 mRS)	48.6%	45.7%	1.13 (0.88-1.45)	0.34	49.6%	39.9%	1.48 (1.05-2.10)	0.0258

Table 33 Sensitivity Analysis - Missing Data Handling Techniques

9.2.7.7.2 Interim Analyses

The results of the first interim analysis indicated that a sample size of 800 patients would be adequate if 100% treatment delivery yield going forward was achieved (The treatment delivery yield was defined as proportion of patients receiving full treatment). However, under a conservative assumption that the treatment delivery yield going forward was not improved any further, up to 200 additional patients may be required, for a total of up to 1,000 patients enrolled in the study.

The minimum sample size of 800 patients would be comprised of:

1. 604 patients (non-diluted Interim Analysis result,i.e., the interim analysis resulted in no alpha spending)
2. 200 patients (treatment delivery yield to-date, i.e., treatment delivery yield is an ongoing improvement process, and it does not affect the Type I Error)

Eight hundred (800) patients sample size detection and power:

3. Power: 80% (assuming 11% effectiveness)

4. Detection: 7% or higher (in mITT) with overall p-value<0.05

The final sample size in the range of 1,000 patients was determined in a linear way based on the treatment delivery yield. At the same interim analysis, an assessment of futility under H1 hypothesis was conducted as the basis for determining whether there should be a recommendation for early termination of the study due to lack of evidence of a beneficial effect. According to the SAP, the decision to recommend termination of the trial would be based on an assessment of the conditional power (CP), defined as the conditional probability that the final result will exceed a critical value given the data observed to that point in the study. That is, the decision to terminate for futility will be expressed in terms of the probability of a statistically significant outcome at the final analysis, after adjusting the sample size, conditional on the interim test statistic. If that conditional probability falls below the predefined threshold, the results suggest stopping the study for futility.

The SAP defined that the futility threshold would be documented by the DSMB and/or Sponsor prior to conducting the interim analysis. This threshold was set at 10%. It also defined that the interim analysis would be conducted on both the mITT and PP study populations, and the study would be stopped due to futility only if the interim effects in both populations fell below the threshold.

The first interim analysis was planned. Following that, unplanned changes in the overall study objectives were made. The second interim analysis was a futility analysis only (no possibility of termination on success and no sample size adjustment) and was found to be non-futile.

9.2.7.7.3 Multiple Comparison/Multiplicity

The study had two primary analysis populations. Multiplicity was handled with a pre-specified method using the Hochberg step-up procedure. In this procedure, the population with the largest p-value is assessed first with p-value threshold 0.05. If the largest p-value is larger than 0.05, the smaller p-value is assessed with a threshold of 0.025. In this study, the mITT p-value was 0.3146 (neutral) and the CCI p-value was 0.0258, marginally higher than the formal Hochberg threshold (by approximately ¼ of a patient).

9.2.7.7.4 Blinding Analyses

Six-hundred-ninety-six (696) patients answered the questionnaire (the additional 304 were unable to answer due to their condition). The following table shows the patient-blinding analysis results

	SPG	Sham	Total
Patient Blinding Success	350/350 (100.0%)	334/346 (96.5%)	684/696 (98.3%)

Table 34 Patient Blinding Analysis (mITT)

Central mRS assessment was available in 843 of 870 mITT patients without known mortality before day 90. Of the remaining 27 patients, 8 patients were lost to follow-up before day 90, and 19 assessments were not filmed due to technical reasons.

The following table shows the assessor-blinding analysis results.

	SPG	Sham	Total
Assessor Blinding Success	377/403 (93.5%)	435/440 (98.9%)	812/843 (96.3%)

Table 35 Local Blinded Assessor Blinding Analysis (mITT)

9.2.7.8 Safety Evaluation

The pre-specified safety analysis population includes all patients in whom the implantation/sham procedure was initiated (536 patients in the SPG stimulation group, 519 patients in the sham control group). Safety results are also presented for the two primary Effectiveness analysis populations, all patients in whom the implantation/sham procedure was initiated and the CCI population.

Results from the safety evaluation did not find significant differences in the safety endpoints, including Incidence of Serious Adverse Events (% of patients with at least one event), 90-day Mortality, Incidence of neurological deterioration as defined by an increase of 4 or more points on the NIHSS related to any neurological event within the first 10 days after stroke onset, Incidence of Symptomatic Intracranial Hemorrhages, and Incidence of Pneumonia SAEs between the SPG stimulation and the sham group for all patients in whom the implantation/sham procedure was initiated and the CCI population.

9.2.7.8.1 Safety endpoints - ImpACT-24B

9.2.7.8.1.1 Incidence of Serious Adverse Events

	SPG Stim.	Sham	OR (95% CI)	p
All	161/536 (30.0%)	146/519 (28.1%)	1.10 (0.84 - 1.43)	0.50
CCI	94/278 (33.8%)	100/276 (36.2%)	0.90 (0.63 - 1.27)	0.55

Table 36 Incidence of Serious Adverse Events (% of Patients with at Least One Event)

Table 36 above indicates that there are no significant differences in the Incidence of Serious Adverse Events between the SPG stimulation and the sham group for all patients in whom the implantation/sham procedure was initiated and the CCI population.

9.2.7.8.1.2 90-day Mortality

	SPG Stim.	Sham	OR (95% CI)	p
All	76/536 (14.2%)	64/519 (12.3%)	1.17 (0.82 - 1.68)	0.38
CCI	51/278 (18.3%)	47/276 (17.0%)	1.09 (0.71 - 1.69)	0.68

Table 37 90-day Mortality

Table 37 above indicates that there are no significant differences in the 90-Day Mortality between the SPG stimulation and the sham group for all patients in whom the implantation/sham procedure was initiated and the CCI population.

9.2.7.8.1.3 Incidence of Neurological Deterioration

Neurological Deterioration (ND) was defined by an increase of 4 or more points on the NIHSS related to any post-randomization neurological event within the first 10 days after stroke onset.

	SPG Stim.	Sham	OR (95% CI)	P
All	41/536 (7.6%)	35/519 (6.7%)	1.15 (0.72-1.83)	0.57
CCI	24/278 (8.6%)	26/276 (9.4%)	0.91 (0.51-1.63)	0.75

Table 38 Neurological Deterioration

Table 38 above indicates that there are no significant differences in the Neurological Deterioration between the SPG stimulation and the Sham group for all patients in whom the implantation/sham procedure was initiated and the CCI population.

9.2.7.8.1.4 Incidence of Symptomatic Intracranial Hemorrhages (sICH)

sICH was defined as any ICH event within the first 5 day, associated with NIHSS deterioration (at least one point), and clinician-investigator judgment that the ICH caused the worsening.

	SPG Stim.	Sham	OR (95% CI)	P
All	4/536 (0.7%)	11/519 (2.1%)	0.35 (0.11 - 1.10)	0.06
CCI	2/278 (0.7%)	8/276 (2.9%)	0.24 (0.05 - 1.15)	0.05

Table 39 Symptomatic ICH

Table 39 above indicates that there is a trend toward lower rate of sICH in the treated arm. This trend replicated that seen in the ImpACT-24A study and reaches statistical significance in the pooled analysis.

9.2.7.8.1.5 Incidence of Pneumonia SAEs

Pneumonia was defined as any of the following events: respiratory tract infection, respiratory failure, lower respiratory tract infection, aspiration, respiratory arrest, and bronchitis.

	SPG Stim.	Sham	OR (95% CI)	P
All	23/536 (4.3%)	28/519 (5.4%)	0.79 (0.45-1.38)	0.40
CCI	14/278 (5.0%)	20/276 (7.2%)	0.68 (0.34-1.37)	0.28

Table 40 Pneumonia SAEs

Table 40 above indicates that the implantation procedure does not increase the risk of pneumonia SAEs, which is a typical complication of stroke.

9.2.7.8.1.6 Implantation Complications

As mentioned in the Section 7 (Implantation Procedure) above, two models of the implant were used in the study. The sponsor stated the first generation of the implant was fragile and required the implanter to prepare the canal using a set of rigid trocars before inserting the implant. With the old implant, various levels of resistance occurred in curved and narrow canals (approximately 25% of the procedures). The new implant was designed to mitigate these concerns. The sponsor claimed that the implantation success rate had reportedly reduced the procedure time by 50%. The sponsor also claimed that the additional improvements in the implantation technique shortened the skin-to-skin time even further to <5 minutes on average. Table 41 summarizes the complication rates and procedure duration with the final device (submitted in this PMA), compared to the previous generations.

	Final Device	Final Implant/ Old Navigation	Old Implant/ Old Navigation
Study	ImpACT-24M	ImpACT-24B	
N	50	197	339
Skin-to-skin Median (IQR) [min.]	4 (3-7)	17 (12-23)	35 (25-52)
Resistance (estimated)	0% (0)	0% (0)	~25% (~85)
SAE	0% (0)	0.5% (1)	0.6% (2)
AE	0% (0)	7.6% (15)	36.9% (125)
Misplacements	0% (0)	2.0% (4)	8.3% (28)
Incomplete Procedures	0% (0)	2.0% (4)	5.0% (17)

Table 41 Implantation Complications Rate

Figure 48 shows that procedure duration with the final system was significantly reduced to 4 minutes skin-to-skin time (IQR 3 – 7 minutes), as detailed in the following graphs:

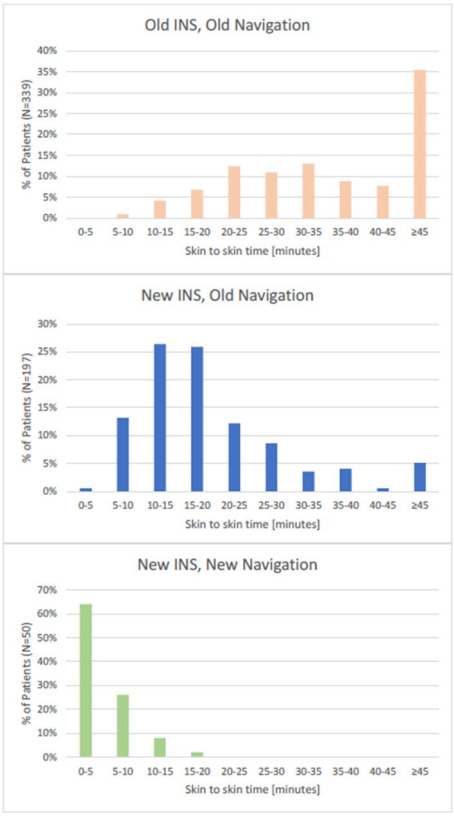

Figure 48 Skin to Skin Time by Implant Type and Registration

Table 42 details the number and frequency of the different types of device deficiencies related to the implant or the implantation in ImpACT-24B. Percentages are calculated relative to the number of implantations (including failed implantations, Treated group only):

Device Deficiency / Model	Old (N=339)	Modified Implant (N=197)	Total (N=536)
Torn Thread	11 (3.2%)	1 (0.5%)	12 (2.2%)
PCB Break	3 (0.9%)	-	3 (0.6%)
Electrode Shear	-	1 (0.5%)	1 (0.2%)
Electrodes Disconnected	1 (0.3%)	-	1 (0.2%)
Implant Crack	1 (0.3%)	-	1 (0.2%)
Unintentionally removed [i]	4 (1.2%)	1 (0.5%)	5 (0.9%)
Expiry Date	1 (0.3%)	-	1 (0.2%)
Total	**21 (6.2%)**	**3 (1.5%)**	**24 (4.5%)**

Table 42 Device Deficiencies (Treated group)

[i] Unintentional implant removal might occur by the patient if the implanter does not trim the extraction thread as instructed.

The sponsor claimed that the modified implant proved to resolve the deficiencies that triggered its

development, namely, torn threads, printed circuit board breakage, cracks and electrodes disconnection. One case of torn thread occurred with the modified implant – the thread was torn at its designed "weak spot", leaving enough remaining thread to extract the implant without additional consequences. Electrode shear was a new failure mode, unique to the modified implant.

Table 43 lists serious adverse events that occurred during the study and were related or possibly related to the implantation or implant removal procedures.

PT	Old Implant (N=339)	Modified Implant (N=197)	All Treated (N=536)
Complication of device removal	1 (0.3%)	1 (0.5%)	2 (0.4%)
Device breakage	1 (0.3%)	-	1 (0.2%)
Total	2 (0.6%)	1 (0.5%)	3 (0.6%)

Table 43 Implantation / Implant Removal SAEs by Implant Type

The Panel will be asked to comment on questions about this topic area.

9.2.7.8.1.7 Proportion of Failed Implantations

Table 44 reports the portion of failed implantations in ImpACT-24B (compared to the more recent ImpACT-24M study).

	Initial Implant	Modified Implant	All ImpACT-24B	ImpACT-24M
Incomplete Procedures	5.0% (17/339)	2.0% (4/197)	3.9% (21/536)	0.0% (0/50)
Misplacements	8.3% (28/339)	2.0% (4/197)	6.0% (32/536)	0.0% (0/50)
Total Failed Implantations	13.3% (45/339)	4.1% (8/197)	9.9% (53/536)	0.0% (0/50)
Skin to skin time, Median (IQR)	35 (25-52)	17 (12-23)	25 (16-40)	4 (3-7)

Table 44 –Implantation Success Rate and Skin-to-skin Time (Treated Patients) – ImpACT-24B vs. ImpACT-24M

The long procedure time caused, in some cases, the implantation procedure not to be completed due to patient agitation. The sponsor claimed that as the procedure became shorter and more accurate with the modified implant and with improvements in the navigation, the rates of both the incomplete procedures and the misplacements reduced, and the total proportion of failed implantation dropped from 13.3% to 4.1%. However, the sponsor suggests that procedure duration is not the only factor that contributed to the reduced complications rate. The final implant has a rigid-flexible neck that was intended to allow it to pass through narrow and curved canals with no resistance (the force required to slide the implant into the canal is less than 400gr) and without having to dilate the canal using rigid trocars (the use of rigid trocars was one of the main reasons for misplacements, prolonged procedures, and complications). The only required preparation for the final device is an initial puncture of the mucosa and clearing the first 8mm of the canal using the Puncture

Tool. As a result, the sponsor claimed that no difficulty in injecting the implant was reported in any of the 247 procedures using this implant. The sponsor stated that another key feature of the final implant is that its body and extraction thread are much stronger than the old implant, addressing the difficulties in implant removal.

9.2.7.8.1.8 Adverse Events Related to Implantation/Removal using the New Implant in ImpACT-24B

The sponsor reported that there were no complications using the final implant and navigation system.

9.2.7.8.1.9 Non-Serious Adverse Events Related to Implantation or Implant Removal

Table 45 lists all non-serious adverse events classified by the investigators as related or possibly related to the implantation or implant removal procedures

SOC	PT	Old Implant (N=339)	Modified Implant (N=197)	Total SPG (N=536)	Sham (N=519)
Injury, poisoning and procedural complications	Implant site pain	32 (9.4%); 36	2 (1.0%)	34 (6.3%); 38	2 (0.4%)
	Implant site haemorrhage	13 (3.8%); 16	-	13 (2.4%); 16	-
	Application site pain	7 (2.1%)	-	7 (1.3%)	-
	Implant site nerve injury	5 (1.5%)	-	5 (0.9%)	-
	Implant site erythema	4 (1.2%)	-	4 (0.7%)	-
	Post procedural infection	2 (0.6%)	-	2 (0.4%)	-
	Medical device site discomfort	1 (0.3%)	-	1 (0.2%)	-
General disorders and administration site conditions	Complication of device removal	8 (2.4%)	1 (0.5%)	9 (1.7%)	-
	Pyrexia	4 (1.2%); 5	-	4 (0.7%); 5	2 (0.4%)
	Device breakage	4 (1.2%)	-	4 (0.7%)	-
	Device deployment issue	3 (0.9%)	-	3 (0.6%)	-
	Device dislocation	2 (0.6%)	-	2 (0.4%)	-
Psychiatric disorders	Agitation	10 (2.9%)	5 (2.5%)	15 (2.8%)	-
	Anxiety	2 (0.6%)	1 (0.5%)	3 (0.6%)	-
	Restlessness	1 (0.3%)	-	1 (0.2%)	-
Gastrointestinal disorders	Vomiting	4 (1.2%)	-	4 (0.7%)	-
	Nausea	2 (0.6%)	1 (0.5%)	3 (0.6%)	-
	Oral fungal infection	1 (0.3%)	-	1 (0.2%)	-
	Pneumonia aspiration	2 (0.6%)	-	2 (0.4%)	-
	Sinusitis	1 (0.3%)	-	1 (0.2%)	1 (0.2%)

SOC	PT	Old Implant (N=339)	Modified Implant (N=197)	Total SPG (N=536)	Sham (N=519)
Respiratory, thoracic and mediastinal disorders	Pneumonia	1 (0.3%)	-	1 (0.2%)	-
	Respiratory failure	1 (0.3%)	-	1 (0.2%)	-
	Apnoea	1 (0.3%)	-	1 (0.2%)	-
	Bronchopneumonia	1 (0.3%)	-	1 (0.2%)	-
Nervous system disorders	Headache	4 (1.2%)	-	4 (0.7%)	-
	Depressed level of consciousness	1 (0.3%)	-	1 (0.2%)	-
Vascular disorders	Hypertension	-	3 (1.5%)	3 (0.6%)	-
	Hypotension	1 (0.3%)	-	1 (0.2%)	-
	Hypertensive crisis	1 (0.3%)	-	1 (0.2%)	-
Eye disorders	Lacrimation increased	-	2 (1.0%)	2 (0.4%)	-
Investigations	Oxygen saturation decreased	1 (0.3%)	-	1 (0.2%)	-
	C-reactive protein increased	1 (0.3%)	-	1 (0.2%)	-
Musculoskeletal and connective tissue disorders	Soft tissue injury	-	-	-	1 (0.2%)
	Back pain	1 (0.3%)	-	1 (0.2%)	-
Cardiac disorders	Tachycardia	1 (0.3%)	-	1 (0.2%)	-
Immune system disorders	Drug hypersensitivity	1 (0.3%)	-	1 (0.2%)	-
Infections and infestations	Infection	1 (0.3%)	-	1 (0.2%)	-
Total		**125 (36.9%); 133**	**15 (7.6%)**	**140 (26.1%); 148**	**6 (1.2%)**

Table 45 Non-Serious Implantation-Related Events

9.2.7.8.1.10 Stimulation-Related Events

No SAE was classified as definitely or probably related to the stimulation. Events in Table 46 were classified as possibly related to stimulation.

PT	SPG Stim. (N = 536)	Sham (N = 519)	P
Stroke in evolution	1 (0.2%)	1 (0.2%)	1.00
Hemorrhagic transformation stroke	1 (0.2%)	1 (0.2%)	1.00
Epilepsy	1 (0.2%)	-	1.00
Total	3 (0.6%)	2 (0.4%)	1.00

Table 46 Serious Adverse Events, Possibly Related to Stimulation

Table 47 includes non-serious stimulation-related events that occurred in at least 1% of the patients in either group:

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)	P
Injury, poisoning and procedural complications	Application site pain	84 (15.7%);110	4 (0.8%)	<0.001
	Implant site pain	34 (6.3%); 45	-	<0.001
Eye disorders	Lacrimation increased	71 (13.2%); 74	3 (0.6%)	<0.001
Nervous system disorders	Headache	19 (3.5%); 21	4 (0.8%); 6	0.004
General disorders and administration site conditions	Medical device discomfort	5 (0.9%); 6	6 (1.2%)	0.96

Table 47 Frequent Non-Serious Adverse Events Related to Stimulation

Lacrimation is a known surrogate of SPG activation and was not considered an adverse event by most investigators. Headache, which occurred in 3.5% of the patients, may be a side-effect of SPG activation. All headache cases resolved without sequelae.

9.2.7.8.2 Unrelated Events

The previous section provides the results of the pre-specified safety endpoints, including summary tables of adverse events that were classified as related or possibly related to the procedure or to the treatment. This section summarizes all other serious and non-serious adverse events (those that were classified as unrelated).

9.2.7.8.2.1 Unrelated Serious Adverse Events

The following table shows unrelated SAE's identified by the sponsor that occurred in at least 1% of the patients (in either group).

SOC	PT	SPG Stim. (N=536)	Sham (N=519)	p
Nervous system disorders	Cerebral infarction	25 (4.7%)	16 (3.1%)	0.24
	Stroke in evolution	18 (3.4%)	19 (3.7%)	0.92
	Haemorrhagic transformation stroke	7 (1.3%)	10 (1.9%)	0.58
Respiratory, thoracic and mediastinal disorders	Pneumonia	12 (2.2%)	12 (2.3%)	1.00
Cardiac disorders	Cardiac arrest	7 (1.3%)	5 (1.0%)	0.82
Gastrointestinal disorders	Clostridium colitis	1 (0.2%)	6 (1.2%)	0.12
General disorders and administration site conditions	Death	9 (1.7%)	8 (1.5%)	1.00
Infections and infestations	Sepsis	7 (1.3%)	3 (0.6%)	0.37

Table 48 Unrelated SAEs

In order to assess whether the slightly higher nominal rate of sepsis SAEs could be related to infections due to the implantation, the following table shows all the related and unrelated serious and non-serious events in the "Infections and Infestations" System Organ Class. Results are shown separately for both implant types.

PT	SPG Stim. (N=536)	Sham (N=519)	Old Implant (N=339)	New Implant (N=197)
Sepsis	7 (1.3%)	3 (0.6%)	5 (1.5%)	2 (1.0%)
Infection	3 (0.6%)	-	3 (0.9%)	-
Bacteraemia	3 (0.6%)	1 (0.2%)	2 (0.6%)	1 (0.5%)
Septic shock	1 (0.2%)	2 (0.4%)	1 (0.3%)	-
Staphylococcal sepsis	2 (0.4%)	-	2 (0.6%)	-
Localised infection	2 (0.4%)	-	2 (0.6%)	-
Tuberculosis	-	1 (0.2%)	-	-
Infections and infestations	-	1 (0.2%)	-	-
Staphylococcal infection	1 (0.2%)	-	1 (0.3%)	-
Total	19 (3.5%)	8 (1.5%)	16 (4.7%)	3 (1.5%)

Table 49 Infections and Infestations SOC - All Related and Unrelated Adverse Events

Infections were higher in the active group compared to the sham. The sponsor claimed that the nominally increased rate of infections might be related to the long implantation procedure of the old implant.

9.2.7.8.2.2 Unrelated Non-Serious Adverse Events

Table 50 shows unrelated non-serious adverse events that occurred in at least 1% of the patients in either group (highlighted events have $p<0.05$)[i]:

SOC	PT	SPG (N=536)	Sham (N=519)	p
Psychiatric disorders	Insomnia	39 (7.3%)	53 (10.2%)	0.11
	Depression	49 (9.1%)	36 (6.9%)	0.23
	Agitation	44 (8.2%)	34 (6.6%)	0.36
	Anxiety	24 (4.5%)	24 (4.6%)	1.00
	Post stroke depression	6 (1.1%)	9 (1.7%)	0.56
	Confusional state	7 (1.3%)	5 (1.0%)	0.82
Gastrointestinal disorders	Constipation	57 (10.6%)	61 (11.8%)	0.63
	Diarrhoea	23 (4.3%)	21 (4.0%)	0.96
	Nausea	15 (2.8%)	14 (2.7%)	1.00
	Vomiting	13 (2.4%)	12 (2.3%)	1.00
	Oral candidiasis	4 (0.7%)	7 (1.3%)	0.51
	Clostridium colitis	6 (1.1%)	7 (1.3%)	0.95
	Gastritis	7 (1.3%)	4 (0.8%)	0.58
Nervous system disorders	Headache	66 (12.3%)	70 (13.5%)	0.63
	Haemorrhagic transformation stroke	14 (2.6%)	19 (3.7%)	0.42
	Stroke in evolution	14 (2.6%)	6 (1.2%)	0.13
	Brain oedema	6 (1.1%)	9 (1.7%)	0.56
	Seizure	8 (1.5%)	7 (1.3%)	1.00
Renal and urinary disorders	Urinary tract infection	89 (16.6%)	96 (18.5%)	0.47
	Haematuria	8 (1.5%)	14 (2.7%)	0.25
	Renal failure	4 (0.7%)	12 (2.3%)	0.07
	Urinary retention	9 (1.7%)	9 (1.7%)	1.00
Metabolism and nutrition disorders	Hypokalaemia	46 (8.6%)	24 (4.6%)	0.01
	Vitamin b12 deficiency	15 (2.8%)	13 (2.5%)	0.92
	Hyperlipidaemia	8 (1.5%)	12 (2.3%)	0.45

SOC	PT	SPG (N=536)	Sham (N=519)	p
	Hypercholesterolaemia	10 (1.9%)	7 (1.3%)	0.67
	Hyperglycaemia	6 (1.1%)	3 (0.6%)	0.54
	Hypomagnesaemia	6 (1.1%)	2 (0.4%)	0.31
General disorders and administration site conditions	Pyrexia	63 (11.8%)	58 (11.2%)	0.84
	Pain	9 (1.7%)	9 (1.7%)	1.00
	Oedema peripheral	8 (1.5%)	5 (1.0%)	0.62
	Chest pain	4 (0.7%)	6 (1.2%)	0.71
Respiratory, thoracic and mediastinal disorders	Bronchitis	20 (3.7%)	9 (1.7%)	0.07
	Pneumonia	17 (3.2%)	15 (2.9%)	0.93
	Lower respiratory tract infection	5 (0.9%)	8 (1.5%)	0.54
	Epistaxis	4 (0.7%)	7 (1.3%)	0.51
	Nasopharyngitis	7 (1.3%)	2 (0.4%)	0.20
	Bronchopneumonia	6 (1.1%)	1 (0.2%)	0.14
Cardiac disorders	Atrial fibrillation	31 (5.8%)	25 (4.8%)	0.57
	Tachycardia	12 (2.2%)	8 (1.5%)	0.55
	Cardiac failure	8 (1.5%)	3 (0.6%)	0.25
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	18 (3.4%)	15 (2.9%)	0.80
	Back pain	5 (0.9%)	16 (3.1%)	0.02
	Pain in extremity	9 (1.7%)	6 (1.2%)	0.65
	Arthralgia	7 (1.3%)	7 (1.3%)	1.00
Vascular disorders	Hypertension	22 (4.1%)	18 (3.5%)	0.70
	Hypotension	12 (2.2%)	12 (2.3%)	1.00
	Carotid artery stenosis	10 (1.9%)	4 (0.8%)	0.20
Skin and subcutaneous tissue disorders	Rash	8 (1.5%)	5 (1.0%)	0.62
	Decubitus ulcer	8 (1.5%)	5 (1.0%)	0.62
Blood and lymphatic system disorders	Anaemia	21 (3.9%)	11 (2.1%)	0.13
Eye disorders	Conjunctivitis	12 (2.2%)	9 (1.7%)	0.71
Injury, poisoning and procedural complications	Fall	10 (1.9%)	8 (1.5%)	0.87
Endocrine disorders	Diabetes mellitus	6 (1.1%)	9 (1.7%)	0.56

Table 50 Unrelated Non-serious Adverse Events that Occurred in at Least 1% of the Patients in Either Group

[i] There are 54 comparisons, with no adjustment to multiplicity; hence, a few events with p<0.05 could be a play of chance.

9.2.7.8.3 Pooled Safety Results – ImpACT-24A & ImpACT-24B

Table 51 and Table 52 below show pooled safety results for all eligible patients and CCI patients, respectively.

	SPG Stim.	Sham	OR (95% CI)	p
SAE Rate	222/738 (30.1%)	182/620 (29.4%)	1.04 (0.82-1.31)	0.77
Mortality	102/738 (13.8%)	80/620 (12.9%)	1.08 (0.79-1.48)	0.62
Neurological Deterioration	61/738 (8.3%)	45/620 (7.3%)	1.15 (0.77-1.72)	0.49
Symptomatic ICH	5/738 (0.7%)	12/620 (1.9%)	0.35 (0.12-0.99)	0.04
Pneumonia SAE	35/738 (4.7%)	38/620 (6.1%)	0.76 (0.48-1.22)	0.26

Table 51 Pooled Safety Results – All Safety Analysis Set

	SPG Stim.	Sham	OR (95% CI)	p
SAE Rate	117/344 (34.0%)	119/313 (38.0%)	0.84 (0.61-1.16)	0.28
Mortality	63/344 (18.3%)	57/313 (18.2%)	1.01 (0.68-1.50)	0.97
Neurological Deterioration	27/344 (7.8%)	32/313 (10.2%)	0.75 (0.44-1.28)	0.29
Symptomatic ICH	2/344 (0.6%)	9/313 (2.9%)	0.20 (0.04-0.92)	0.02
Pneumonia SAE	20/344 (5.8%)	27/313 (8.6%)	0.65 (0.36-1.19)	0.16

Table 52 Pooled Safety Results – CCI Safety Analysis Set

The Panel will be asked to comment on questions about this study

9.3 ImpACT–24M

The ImpACT-24M study was a prospective, multi-center, single arm usability study to validate of the implantation procedure and demonstrate the ability to correctly identify a patient's stimulation level using physiological markers. Fifty patients were enrolled in 4 centers between May 2018 and final study visit in September 2018.

9.3.1 Study Objectives

The study had two main goals:

- Usability, focusing on simple and accurate implantation, and correct setting of the stimulation level.
- Signal of Effectiveness in patients with mild strokes.

9.3.2 Eligibility Criteria

Subject must sign the informed consent prior to any study activity as defined per this protocol. Subjects must meet all inclusion and exclusion criteria in order to be eligible for the study.

Compared with the eligibility criteria of ImpACT-24A and ImpACT-24B, the low NIHSS score, and hand-motor deficit requirements were designed in ImpACT-24M to select cooperative patients that will be able to

perform the motor function test and to undergo blood flow measurements using Common Carotid Doppler (CCD). The exclusion criteria were the same as in ImpACT-24B and ImpACT-24A, including no prior intervention with IV-tPA or mechanical thrombectomy.

The following are the key Inclusion/Exclusion criteria (see full list in Appendix C – Pivotal Study Inclusion/Exclusion Criteria):

9.3.2.1 Inclusion Criteria

1. Age: ≥ 18 years and ≤ 80 years.
2. Clinical diagnosis of anterior circulation stroke.
3. Baseline NIHSS ≥ 1 and ≤ 6 or lacunar stroke of any severity.
4. Ability to initiate treatment within 24 hours from stroke onset.
5. Signed informed consent from patient him/herself or legally authorized representative if applicable.

9.3.2.2 Exclusion Criteria

- No prior intervention with IV-tPA or mechanical thrombectomy

9.3.3 Effectiveness Endpoints

- Improvement in stroke symptoms (motor and/or sensory deficits) during stimulation
- Proportion of patients with unilateral lacrimation, nasal secretion, and/or facial redness (on the stimulation side).
- Increased blood flow in common carotid artery (non-Afib patients).
- Proportion of procedures with positive indication of reaching the sphenopalatine fossa.
- The difference in NIHSS between baseline and Day 7 vs. matched historical controls (patients in the control arm in the National Institute of Neurological Disorders and Stroke (NINDS) tPA Study).

9.3.4 Safety Endpoints

- Comparative 7-day safety data between the ISS500 stimulation group of this study and the ImpACT-24B study:
  - Incidence of Serious Adverse Events
  - Implantation Complications
  - Stimulation-related Adverse Events
- 7-day mortality
- Neurological deterioration
- Symptomatic intracranial hemorrhage (sICH)

9.3.5 Methods

9.3.5.1 Procedures

The study design included an implantation phase, a CTL validation phase, and a treatment phase. Patients received medical therapy according to the accepted clinical practice guidelines for AIS throughout their study participation.

Implantation was a bedside, minimally invasive procedure in which the INS was injected into greater palatine canal canal near the SPG.

After implantation, CT imaging was performed to assess the attained implant position, rated by a central positioning evaluator.

Active stimulation was then administered in daily 4-hour sessions, beginning immediately following the placement procedure and continuing for 5 consecutive days.

To ensure individual CTL in each treatment session, stimulation parameters started at a low level and were incrementally advanced until physiological evidence for SPG activation was observed: patient-reported tingling sensation over the nose bridge or ipsilateral cheek and/or unilateral lacrimation on the stimulation side.

On the second treatment day, the effectiveness of the stimulation at the CTL was validated by measuring peak systolic and end diastolic blood flow in the ipsilateral common carotid artery (CCA) before and during stimulation at the CTL. Up to 3 additional blood flow measurements were performed during the gradual stimulation ramp up. Blood flow was measured by common carotid duplex (CCD) readings of blood velocity and vessel diameter. Readings were performed 1cm proximal to the carotid bulb. CCD was performed in each center by a single experienced ultrasonographer. Blood flow measurements were not performed on patients with atrial fibrillation (due to high waveform variability which makes quantification less accurate in this situation).

Additionally, at the same treatment session, hand fine motor function was measured before and during stimulation (after 2 hours and 4 hours of stimulation) using quantitative measures of hand grasp and thumb pinch strength (Baseline Hydraulic Hand Dynamometers, Fabrication Enterprises Inc., White Plains NY, USA). Motor function reference measurements were performed on the non-affected hand.

Following the last treatment on day 5, the implant was removed with fine forceps. Follow up time was 7 days.

9.3.5.2 Sample Size

A sample size of 50 patients was judged sufficient to characterize implantation speed and accuracy. If a learning curve was noted with improving accuracy or accelerating speed during initial procedures, up to 50 additional patients would be recruited until stable performance on 50 consecutive patients was attained or a total of 100 patients was recruited.

In practice, no learning curve was noted, and the study was completed after 50 patients (see Results section below).

9.3.5.3 The Treatment and Treatment Allocation Schedule

All patients in this single-arm study received 5 daily SPG stimulation sessions of 4 hours per session.

Stimulation was delivered at the patient's CTL. To ensure individual CTL in each treatment session and avoid pain, stimulation parameters started at a low level and were incrementally advanced until physiological evidence for SPG activation was observed: patient-reported tingling sensation over the nose bridge or ipsilateral cheek and/or ipsilateral lacrimation.

All pulse parameters were identical to the pivotal ImpACT-24B study (b)(4)

As in ImpACT-24B, each 4-hour session was divided to 16 cycles of 15 minutes, (b)(4)

9.3.5.4 Concomitant Medications/Treatments

Similar to ImpACT-24B, during the study period, patients received concomitant treatment in accordance to the general management of ischemic stroke and secondary prevention, following the guidelines of the American Heart Association/American Stroke Association and of the European Stroke Organization (ESO), including the use of antiplatelet agents, management of secondary stroke, dyslipidemia, hypertension, diabetes and counselling regarding smoking cessation.

Prior to the enrollment of patients to the study, all therapies were allowed except thrombolysis or clot retrieval treatments.

The protocol did not restrict the use of concomitant medications, except as below:

1. Anticoagulation agents were not recommended immediately prior to implantation unless implantation was delayed, and anticoagulation therapy was indicated by accepted clinical practice guideliens. In such cases, bleeding propensity was re-assessed prior to implantation. Following completion of implantation, administration of anticoagulant agents was allowed.
2. The use of contraceptive hormones was prohibited during all study periods.
3. Scopolamine was not allowed to be used during the 5 treatment days. This restriction is related to the fact that a centrally acting anti-cholinergic drug may interfere with the hypothesized parasympathetic mechanism of action of SPG stimulation.
4. Investigational and off-label use of medication/therapy was prohibited during the study.

As part of the implantation procedure, the following drugs were applied:

5. Single dose of prophylactic antibiotics prior to the procedure
6. Local anesthesia
7. If the patient was agitated, intravenous anxiolytic agents were administered

All concomitant medications/therapies administered during the study were recorded in the appropriate CRF page.

9.3.5.5 Safety and Effectiveness Analysis Set

The Safety and Effectiveness Analysis Set included all patients who were enrolled to the trial. Blood flow analysis included only patients with valid CCD measurements.

9.3.5.6 Statistical Analysis

Patients with known atrial fibrillation did not undergo CCA measurements and were excluded from the blood flow analysis. Patients who were not able to cooperate with the dynamometer motor strength testing were excluded from the motor function analysis. Changes in CCA flow and in fine motor function were assessed as continuous variables (using paired t-test) and as dichotomized variables using a 20% change threshold for presence of moderate to substantial alteration (using $\chi 2$ analysis). The 20% threshold accords with that commonly used to guide induced hypertension in patients with vasospasm after subarachnoid hemorrhage, the most common cerebral blood flow augmentation clinical treatment setting.

The change in NIHSS between baseline and Day 7 was assessed by comparing enrolled patients with age- and deficit- matched historical controls from the NINDS rt-PA Study control group. Matching to NINDS-Study control patients was performed using 1:1 optimal inverse variance matching. Calipers were set for age at ±5 years and for NIHSS at ±1.

The NIHSS scores were matched for time from onset. ImpACT-24M patients 8-12h post-onset were matched to NINDS control patients based on NIHSS scores 2h after placebo drug (3.5-5h after onset); ImpACT-24M patients 12.1-24h post-onset were matched to NINDS control patients based on NIHSS scores 24h after onset.

Safety results are compared with ImpACT-24B.

9.3.6 Study Results

9.3.6.1 Patient Accountability, Demographics and Baseline Characteristics

Median age was 66 years (IQR 60-74), 44% were female, baseline deficit severity on the NIHSS was median 5 (IQR 4-5), and time from last known well (LKW) to first stimulation was median 18 hours (IQR 9-20).

All patients completed the 7-day NIHSS assessment and implant position assessment. CCD test was not performed in four patients (8%) who had a medical history of atrial fibrillation. Three patients were not cooperative in operating the motor-function assessment instruments.

9.3.6.2 Clinical Investigation Protocol (CIP) Compliance

No protocol deviations were reported.

9.3.6.3 Implantation Results

In 100% of the implantations (50/50) there was positive confirmation of correct implant position by CT scan.

Median skin-to-skin time was 4m 15s (IQR 3m 10s – 6m 48s) compared to 17.0m (IQR 12.5-24.0) in ImpACT-24B using the old registration technique (p<0.0001).

9.3.6.4 Stimulation Results

CTL was successfully determined based on physiological biomarkers of SPG activation in 96% of the patients (48/50), including 64% (32/50) who had ipsilateral lacrimation and tingling sensation, and 32% (16/50) who had tingling sensation only.

Figure 49 shows the distribution of the CTL levels using the physiologic method in ImpACT-24M. In 92% (46/50 patients) of the patients, the CTL (which was set using physiological surrogates) was below low to medium range. This is considered the "physiologically selected range".

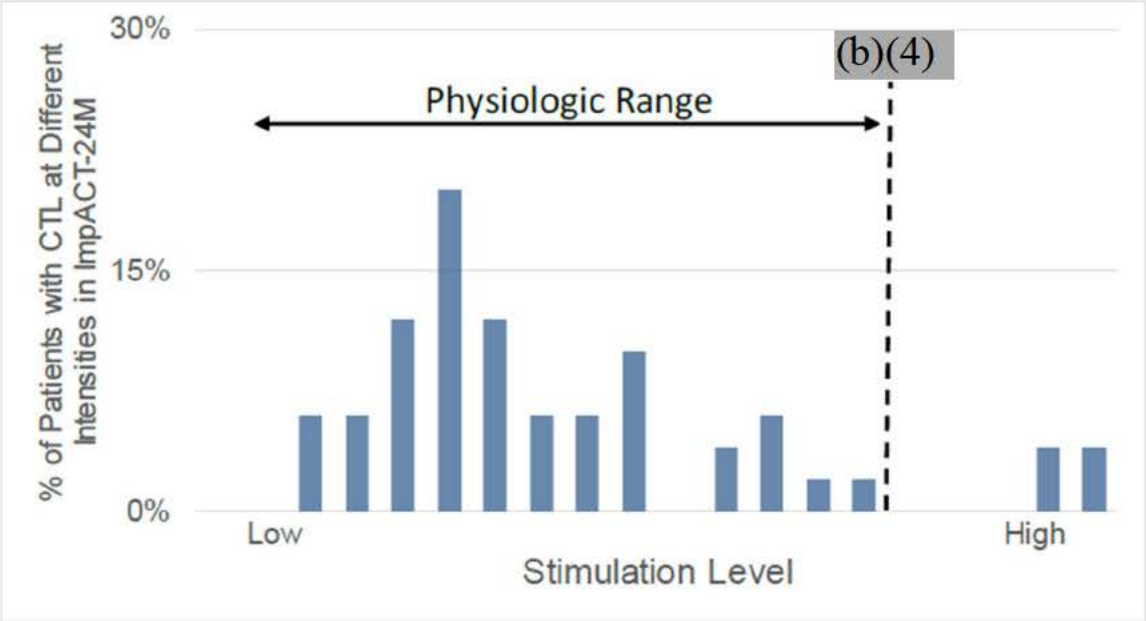

Figure 49 CTL Distribution in ImpACT-24M (% of patients at each level)

In 86% of the patients (43/50), the CTL fell within the intensity range associated in the ImpACT-24B trial with a 1.5-fold or greater increase in the odds ratio of a favorable outcome associated with SPG stimulation (b)(4) .

In 78% of the patients (39/50), the CTL fell within the intensity range associated with a statistically significant improvement in odds ratio (b)(4) In this range, the lower 95% confidence interval for the rate of favorable outcome in the SPG stimulation is higher than the upper 95% confidence interval for the rate of favorable outcome in the sham control group.

Forty-six (46) patients (92%) underwent CCD measurements and 45 (90%) had valid measurements before and during treatment at their CTL.

Stimulation was associated with increase in CCA vessel diameter and increase in flow velocity and flow volume in the CCA during both peak systole and end diastole (Figure 50, Table 53)

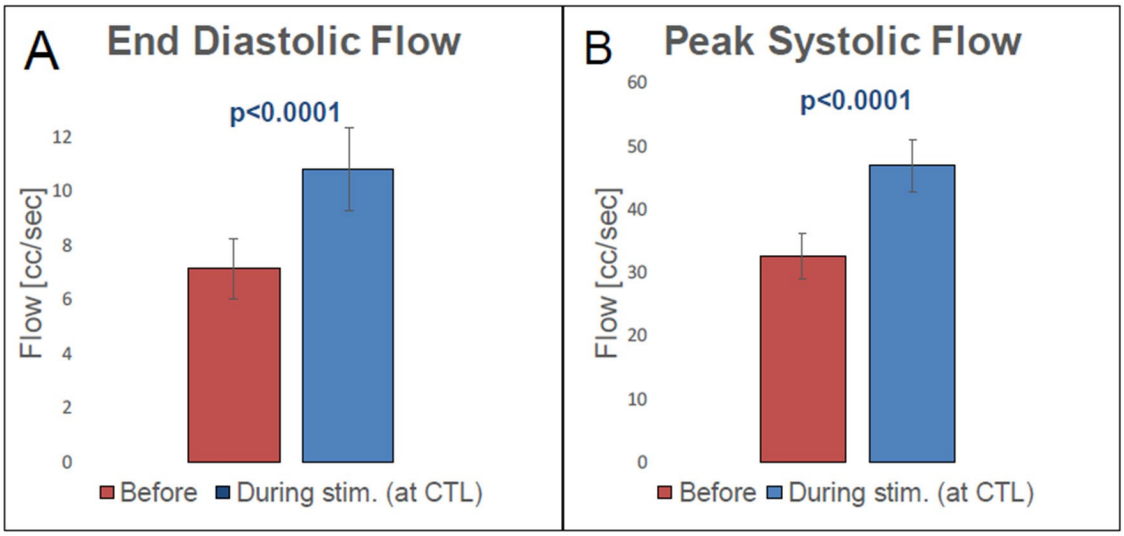

Figure 50 Peak Systolic (A) and End Diastolic Flow (B) Before and During Stimulation

	Baseline Mean (95% CI)	During Stimulation Mean (95% CI)	Increase Mean (95% CI); %	P value (for mean increase)
Diameter (mm)	8.0 (7.7-8.2)	8.9 (8.5-9.3)	0.9 (0.6-1.2); 11%	<0.0001
Peak systolic velocity (cm/sec)	65.6 (58.2-73.0)	76.8 (70.3-83.3)	11.2 (5.9-16.4); 17%	0.0001
Peak systolic flow (cc/sec)	32.5 (29.0-36.0)	46.9 (42.8-51.0)	14.4 (9.9-18.9); 44%	<0.0001
End diastolic velocity (cm/sec)	14.0 (12.1-15.9)	17.1 (15.7-18.5)	3.1 (1.5-4.7); 22%	0.0004
End diastolic flow (cc/sec)	7.1 (6.0-8.2)	10.8 (9.3-12.3)	3.7 (2.6-4.8); 52%	<0.0001

Table 53 Change in Ipsilateral Common Carotid Diameter and Flow with SPG Stimulation

Forty-seven (47) patients (94%) underwent grasp and pinch motor evaluation before stimulation, after two hours of stimulation, and after four hours of stimulation (Figure 51).

In 40/47 patients, improvement of 20% was measured in at least one of the fine motor parameters.

Mean pinch force in the affected hand increased by 1.3 (95% CI 0.9-1.7) lbs (30%) after 2h of stimulation and by 1.8 (95% CI 1.3-2.2) lbs (42%) after 4h of stimulation p<0.0001. Mean grasp force in the affected hand increased by 2.5 (95% CI 1.4-3.7) lbs (15%) after 2h of stimulation, and by 4.5 (95% CI 3.2-5.8) lbs (26%) after 4h of stimulation, p<0.0001). In contrast, in the unaffected hand, mean pinch force did not increase (changed by 0.2 and -0.1 lbs, p = 0.77) and mean grasp force did not increase (changed by -0.2 and 1.1 lbs, p=0.10).

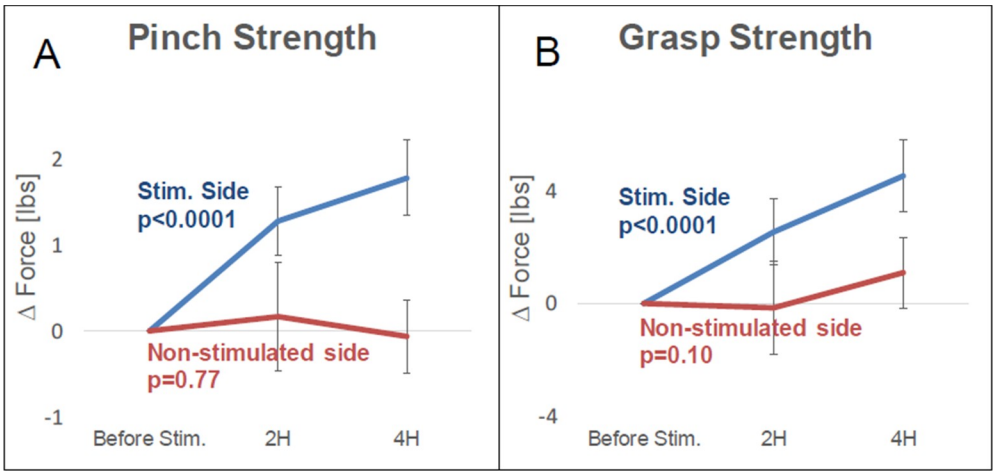

Figure 51 Fine Motor Function Improvement after 2 Hours and 4 Hours of Stimulation (A) Pinch and (B) Grasp

All p-values were computed using paired t-test.

A significant relation was observed between the degree of improvement in blood flow augmentation and the degree of improvement in hand strength (Figure 52).

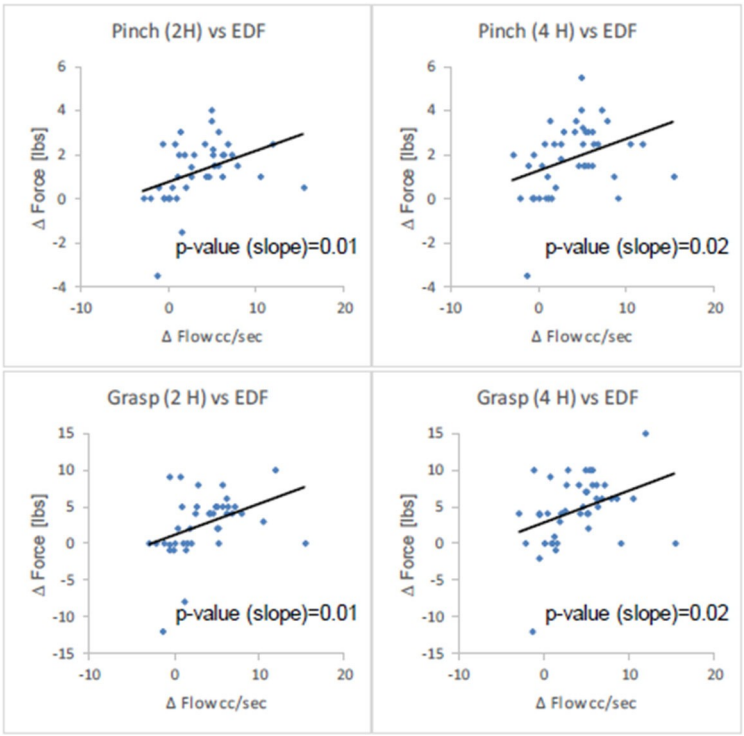

Figure 52 Change in Hand Strength vs. Change in Flow during Stimulation

All p-values in Figure 52 were calculated using t-test for significant slope. Sensitivity analyses were performed with negative changes truncated to zero and using F-test for the significance of correlation. [i]

[i] $P < 0.05$ for all parameter combinations, continuous and dichotomized except for continuous pinch vs PSF which showed a trend in the same direction that did not reach significance level at this sample size

Another sensitivity analysis was done with the dichotomized changes in flow and force. The results of this analysis are shown in Table 54 and are all significant.

	Pinch Strength at 4h			Grasp Strength at 4h		
	Substantially Improved (n=32)	Not substantially Improved (n=11)	P value[i]	Substantially Improved (n=27)	Not substantially Improved (n=16)	P value[vi]
EDF Change	84%	27%	0.0004	89%	38%	0.0004
PSF Change	88%	36%	0.0008	93%	44%	0.0004

Table 54 Relation between Hand Strength Improvement and Increased Blood Flow

Substantial improvement in strength or flow was defined as >20% increase.

Further post-hoc analysis showed that patients with ipsilateral lacrimation had significantly higher rate of improvement in flow (Table 55) and in strength (Table 56) compared to patients without lacrimation.

	Lacrimation		
	Yes (N = 30)	No (N = 15)	P value
EDF Change	83%	40%	0.003
PSF Change	83%	53%	0.03

Table 55 Relation between Lacrimation and Increased Blood Flow

	Lacrimation		
	Yes (N = 32)	No (N = 16)	P value
Pinch Strength at 4h	93%	40%	0.0001
Grasp Strength at 4h	80%	33%	0.002

Table 56 Relation between Lacrimation and Improved Hand Strength

9.3.6.5 Effectiveness Evaluation

In the NIHSS evolution analysis, matching yielded 98 patients, including 49/50 patients treated with SPG stimulation in the current trial, and 49/312 treated with supportive care in the NINDS rt-PA Study. The SPG stimulation and control patients were well balanced in age (mean 66.9 ± 8.4 vs 67.3 ± 8.7) and in day 1 NIHSS [median 5 (IQR 4-5) vs. 5 (IQR 4-6)]. Evolution of the NIHSS in the SPG stimulation patients was from median 5 (IQR 4-5) on day 1 to median 1 (IQR 1-2) on day 7; evolution of the NIHSS in the control patients was from median 5 (IQR 4-6) on day 1 to median 2 (IQR 2-4) on day 7. The normalized change in NIHSS from day 1 to day 7 was significantly more favorable in the SPG stimulation than control patients: median 75% (IQR 60%-80%) versus 50% (IQR 0%- 67%), p = 0.0003.

9.3.6.6 Safety Evaluation

9.3.6.6.1 Safety Endpoints

Within the 7-day follow-up period, no incidence occurred of mortality, neurological deterioration, sICH, or stimulation-related adverse events (including pain).

One patient had a SAE due to new stroke. The severity was medium, and it was adjudicated to be unrelated to the implantation or treatment. This SAE resulted in prolonged hospitalization and did not result in neurological deterioration (defined as increase of at least 4 NIHSS points).

One implantation-related non-serious adverse event was reported (mild nausea). This event was resolved in the same day.

Safety results were compared with ImpACT-24B.

	ImpACT-24M	ImpACT-24B
Mortality	0% (0/50)	5.4% (29/536)
SAE	2% (1/50)	14.0% (75/536)
Neurological Deterioration	0% (0/50)	7.6% (41/536)
Symptomatic ICH	0% (0/50)	0.6% (3/536)
Simulation-related AE	0% (0/50	33.4% (179/536)
Implantation-related AE	2% (1/50)	17.9% (96/536)

Table 57 Comparative Safety Data of ImpACT-24M and ImpACT-24B Stimulation Groups

9.3.6.7 Discussion

One of the major goals of the ImpACT-24M study is to validate a physiologic method for setting the stimulation level at the CTL using biomarkers of SPG activation. Using this method, the CTL was found successfully in 96% of the patients, leading to significant blood-flow augmentation which was correlated with improvement in motor function compared to baseline measurements before stimulation.

No pain or discomfort adverse events was reported in the study.

The ImpACT-24M study was also intended to validate a modified automatic registration algorithm that simplified the implantation procedure. The study achieved median skin-to-skin time of <5 minutes with zero misplacements. Figure 53 below shows the evolution of the implantation accuracy (represented by the misplacement rate) and simplicity (represented by skin-to-skin time) since the beginning of the pivotal study.

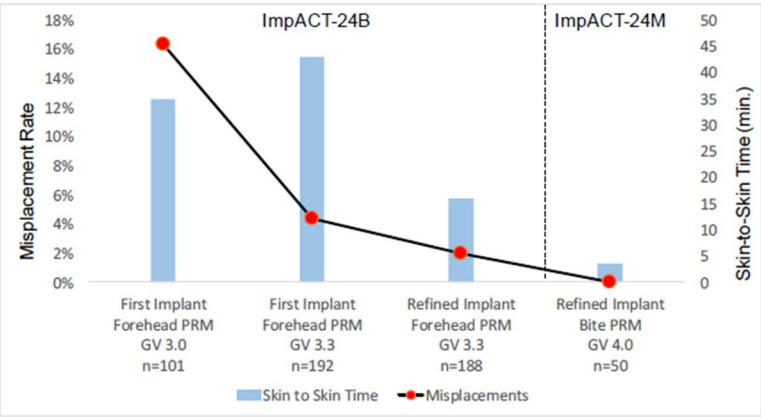

Figure 53 Misplacement Rate and Skin-to-skin Time

The ImpACT-24M study, as a single arm, non RCT study, was designed as a usability study and has a corresponding impact on the overall safety and effectiveness assessment of the ISS500. In this study, final functional outcome was measured 7 days after stroke using the NIHSS scale rather than disability at 90 days using the mRS as with most stroke studies, including the ImpACT-24B study. The lower rates of mortality, SAE, Neurological Deterioration and sICH in the current study were expected given the different study populations: mild strokes in ImpACT-24M (NIHSS 1-6) compared to moderate-severe strokes in ImpACT-24B (NIHSS 7-18).

10 Benefit-Risk Assessment

10.2 Summary of the Assessment of Benefit

There is considerable uncertainty in the extent of benefit resulting from a number of factors (described in detail further, below). The sources of uncertainty include the proposed use of a primary outcome measure (the sliding dichotomy mRS) that has not been used to support the approval of a stroke drug or device in the past. The extent to which this over- or under-estimates the benefit relative to more conventional analysis methodology is not known. In addition, relative to the mITT analysis, the larger difference between the groups for the intended use population analysis is driven by a smaller response in the sham group as can be seen above -- the treatment group response rate only changes by 1%.

FDA is uncertain whether the rates of favorable global disability outcome at 90 days in the ImpACT-24B study were clinically meaningful (using the sliding dichotomous mRS) in the mITT population; SPG stimulation 48.6% vs. sham at 45.5% (p=0.31). In the CCI population, SPG treatment vs. sham was 49.6% vs 39.9% (p=0.0258).

The sponsor claimed that the primary analysis result in the mITT population was not statistically significant; but claimed, the sliding dichotomous mRS at day 90 (also referred as the responder rate in this Summary) in the CCI population was close to the threshold for statistical significance with a p-value of 0.0258 (compared to the $p<0.025$ multiplicity-adjusted type I error-rate threshold) in favor of SPG stimulation, with SPG stimulation at 49.6% demonstrating a favorable 90-day disability outcome vs. sham at 39.9%.

FDA identified multiple points of uncertainty related to the design, implementation and interpretation of the results of the ImPACT-24B study in addition to the uncertainties mentioned earlier in this Executive Summary regarding the implantation procedure.

The Panel will be asked to comment on questions on the demonstration of the clinical benefit of the device.

The following are areas of uncertainty identified by the FDA:

10.2.1 Study Design - Sliding Dichotomy and the 90-day mRS, FDA Post-hoc Analysis

Uncertainty in model prediction and implications for effectiveness results

The primary effectiveness endpoint of the ImPACT-24B study was the sliding dichotomy mRS at the 90-day visit. Success in the primary outcome (sliding dichotomy) was defined as mRS better than the "win criterion" by one or more point, and failure was defined as the mRS being equal or worse than the "win criterion." The "win criterion" sliding dichotomy assessment was generated for each patient using a model created prior to trial initiation. The model was derived from analysis of 1,077 patients in control groups of 8 prior acute ischemic stroke trials that were entered into the Virtual International Stroke Trial Archive (VISTA). Refer to Appendix II for additional details on the VISTA Model.

Briefly, the primary effectiveness can be considered a responder analysis. That is, a patient would be considered as a responder if their actual 90-day mRS was better than the VISTA predicted outcome; otherwise, the patient would be considered a non-responder. More specifically, the "win criterion" was defined as the median (midpoint) of the VISTA outcome distribution. Success in the primary outcome was defined as an mRS that was better than the median by one or more point. Failure was defined as an mRS that was equal to or worse than the median. mRS of 5 and 6 were collapsed into a single worst outcome category, and an mRS score of 5 or 6 was considered as a failure in the primary effectiveness analysis.

FDA is uncertain about the interpretation of study results using the VISTA model in the ImpACT-24B effectiveness analysis. For one reason, a patient may be labeled as a responder by the model even if the treatment had no or very little effect. To assess the quality of the model, FDA compared the actual mRS and predicted mRS of the 519 patients in the sham group – which represent a sham surgery, without implantation of a device – of the mITT population from the ImPACT-24B study. Since no device was placed in the canal near the SPG, patients in the sham group should not experience any device effects. Therefore, if the model were ideal, there should not be any responders due to no device effects in this sham group: any responders would only be due to the non-specific effects of enrollment in the trial. However, FDA performed a post-hoc analysis that indicates that the VISTA model's accuracy to predict the observed mRS is only 22.2%. See Figure 54, below.

90-day Actual mRS vs. Predicted mRS in mITT Sham Group ImpACT-24B

Original VISTA Sliding Scale Model

Predicted mRS	0	1	2	3	4	5	6
6					1	1	
5					1	8	8
4	9	10	22	43	32	44	38
3	21	46	54	50	19	15	16
2	14	14	24	17	2	3	4
1	1	1	1				
0							

Actual mRS in Sham Group

The Y-axis of the table is the predicted mRS score using the Original VISTA model, and the X-axis is the actual mRS score. The numbers in orange represent correct predictions where the model prediction matches the actual mRS outcome. The numbers in blue and green are all erroneous predictions. From these data, the model demonstrates 22.2% accuracy (the sum of all orange numbers divided by the total of number of sham 519 patients or 115/519).

Figure 54 Accuracy of Original Vista Sliding Scale Model in Sham Group of ImpACT 24-B Trial

FDA is concerned that the low accuracy of the VISTA model adds significant uncertainty to the interpretation of the effectiveness results. Furthermore, the VISTA model was constructed using data from patients before significant changes to the care of stroke patients were widely adopted, including the use of endovascular thrombectomy.

FDA expressed this concern in FDA's Major Deficiency Letter to the sponsor on May 4, 2020. In response to FDA's uncertainty of the model, the sponsor conducted a sensitivity analysis using an updated model from 2015, a period after which endovascular thrombectomy was adopted. The figure below demonstrates our post-hoc analysis results using the updated VISTA model. The revised model showed 24.1% accuracy, which represents a slight improvement from the VISTA model originally adopted. However, this small improvement in the VISTA model's performance does not resolve FDA's concern that model inaccuracy creates significant uncertainty in the interpretation of the study results.

90-day Actual mRS vs. Predicted mRS in mITT Sham Group ImpACT-24B

Sponsor's Revised Sliding Scale Model

Predicted mRS	0	1	2	3	4	5	6
6							
5				1	6	19	14
4	8	10	21	45	30	36	32
3	20	31	47	44	16	13	16
2	15	29	31	20	3	3	3
1	2	1	2				1
0							

Actual mRS in Sham Group

The Y-axis of the table is the predicted mRS score using the Sponsor's Revised Sliding Scale model, and the X-axis is the actual mRS score. The numbers in orange represent correct predictions where the model prediction matches the actual mRS outcome. The numbers in blue and green are all erroneous predictions. From these data, the revised model demonstrates 24.1% accuracy.

Figure 55 Accuracy of Sponsor's Revised Sliding Scale Model in Sham Group of ImpACT 24-B Trial

Based on Figure 55 Accuracy of Sponsor's Revised Sliding Scale Model in Sham Group of ImpACT 24-B Trial, the new model showed 24.1% accuracy, which represents a slight improvement from the VISTA model originally adopted. However, this small improvement in the VISTA model's performance does not resolve FDA's concern that model inaccuracy creates high uncertainty in the interpretation of the study results.

In response to FDA Major Deficiency Letter dated May 4, 2020, the sponsor stated:

> *"Sliding Dichotomy may be criticized for inaccuracy of the model due to the following reasons:*
> *1. The use of historical data may not reflect [current accepted clinical practice guidelines]*
> *2. The model uses a few prognostic parameters and cannot predict outcome accurately*
>
> *These limitations may lead to an imperfect prognostic model. However, no bias is introduced by use of a less than perfect prognostic model - any imperfections in the model would apply just the same to the SPG stimulation and sham stimulation groups."*

FDA has remaining concerns. Randomization in clinical trials indeed can ensure a relative balance between the two arms. Some level of imbalance almost always exists, partly due to dropouts, and also because randomization only guarantees theoretical balance in terms of expectation. For example, 1,078 patients were randomized 1:1 into the two arms of the ImpACT-24B study, but the primary analysis set mITT had 481 patients in the active ISS500 group and 519 in the sham group. Moreover, the ISS500 group had 56.5% patients with stroke in left side of brain but the sham group had only 50.1%. While the uncertainty caused by such imbalance can usually be ignored for non-confounding factors, it is generally recommended to account for known strong confounding factors. Certain methods (e.g., stratified randomization, covariate adjusted analysis, etc.) may be used to further reduce the imbalance and the corresponding uncertainty.

FDA has concerns that the imperfect performance of the VISTA model may be a serious confounder of the sliding dichotomy responder analysis. It is not clear to FDA how much of the observed treatment difference between the two arms should be attributed to the imbalance of this factor which actually cannot be measured. This concern is greater for even smaller cohorts, for example, the US CCI group with only 19 SPG and 12 sham patients.

Post-hoc shift analysis

Due to the uncertainties identified above about the VISTA model, FDA conducted a post-hoc shift analysis using the van Elteren test as described in [Savitz, et al.] to directly compare the distributions of 90-day mRS of the two arms. The null hypothesis was that receiving the active or sham treatment was not associated with the 90-day mRS. Table 58 and Table 59 depict the results for the mITT and CCI groups from the direct comparison, which do not show a difference between the SPG and sham groups for both the mITT and CCI populations.

Frequency mRS score (row %)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**Total Subjects (row)**
ISS500	36 (7.5%)	81 (16.8%)	95 (19.8%)	113 (23.5%)	40 (8.3%)	50 (10.4%)	66 (13.7%)	481
Sham	45 (8.7%)	71 (13.7%)	101 (19.5%)	110 (21.2%)	55 (10.6%)	71 (13.7%)	66 (12.7%)	519
Total Subjects (column)	81	152	196	223	95	121	132	1000

Table 58 90-day mRS in the mITT Population (p-value = 0.3979) - Shift Analysis Using the van Elteren Test

Frequency mRS score (row %)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**Total Subjects (row)**
ISS500	9 (3.7%)	34 (13.9%)	42 (17.2%)	67 (27.5%)	20 (8.2%)	29 (11.9%)	43 (17.6%)	244
Sham	15 (5.4%)	23 (8.3%)	37 (13.4%)	66 (23.9%)	43 (15.6%)	45 (16.3%)	47 (17.0%)	276
Total Subjects (column)	24	57	79	133	63	74	90	520

Table 59 90-day mRS in the CCI Population (p-value = 0.0748) - Shift Analysis Using the van Elteren Test

The above post hoc analyses further highlight the significant uncertainty in the effectiveness data.

The Panel will be asked to comment on questions about this topic area.

10.2.2 Validity of Effectiveness Results – Uncertainty about the ITT Analysis

There were 554 randomized patients satisfying the definition of CCI (SPG: 278, sham 276). The final CCI analysis population included all 276 sham patients but excluded 34 (12%) SPG patients because they didn't receive SPG stimulation. This difference of exclusion rate (12% SPG vs. 0% sham) raises the concern whether the benefits of randomization still hold in the CCI analysis population. For exploratory purpose, FDA conducted an ITT-CCI analysis on the primary endpoint since usually an ITT is the recommended primary analysis set for superiority studies. FDA included all 554 randomized CCI patients. The result is SPG responder rate: 46.4%, sham responder rate: 39.9%, p-value: 0.12. The relatively large p-value (comparing with 0.0258 from mITT-CCI analysis) casts uncertainty on the effectiveness claim.

10.2.3 Validity of Effectiveness Results – Discussion on Device and Study Protocol Changes throughout ImpACT-24B

There have been several significant changes in the device, study protocol and SAP throughout the study that may introduce uncertainty in the study results.

As indicated in the regulatory history section, the device had been modified throughout ImpACT-24B, and the device design was not finalized until the usability study ImpACT-24M (Figure 56). Similarly, changes in protocol/SAP occurred throughout the conduct of the study. As indicated in Figure 57, major protocol changes included:

- Revising the SAP to define the mITT population as only the patients in which the implant was placed within 5mm from the SPG (instead of 15 mm),
- Adding patients with CCI as an additional primary endpoint,
- Adding additional analyses on:
    - Dichotomy mRS 0-2;
    - Dichotomy mRS 0-3;
    - Subgroup analyses by age, history of diabetes, history of atrial fibrillation; and
    - Covariates that were not stratified when performing the adjusted analysis (such as age, baseline NIHSS, baseline ASPECT score, and time from stroke onset).

Many of these changes were implemented in the last year of the study, though before unblinding as indicated by the sponsor. FDA is uncertain how these significant changes to the study protocol impacted the interpretation of the effectiveness study result, which demonstrated approximately a 10% benefit in the SPG group over the sham group in patients with CCI, who represented one of the primary analysis cohorts.

A change in design and clinical use may have an impact on effectiveness and safety. Studying the final device in a pivotal trial helps to reduce uncertainty, and it's important to use the device consistently throughout the trial unless it is found to raise safety concerns or present a danger to patients (in which case, changes to the device or study protocol would be appropriate and necessary). As the ImpACT-24B proceeded the device

changed, the implantation procedure and implant placement parameters also changed, and so did the study design and analyses (both during the study and after its completion). This was done rather than performing a second study with the final device in an appropriate sample of patients from the intended use population, which could reduce the uncertainty in interpreting the safety and effectiveness results.

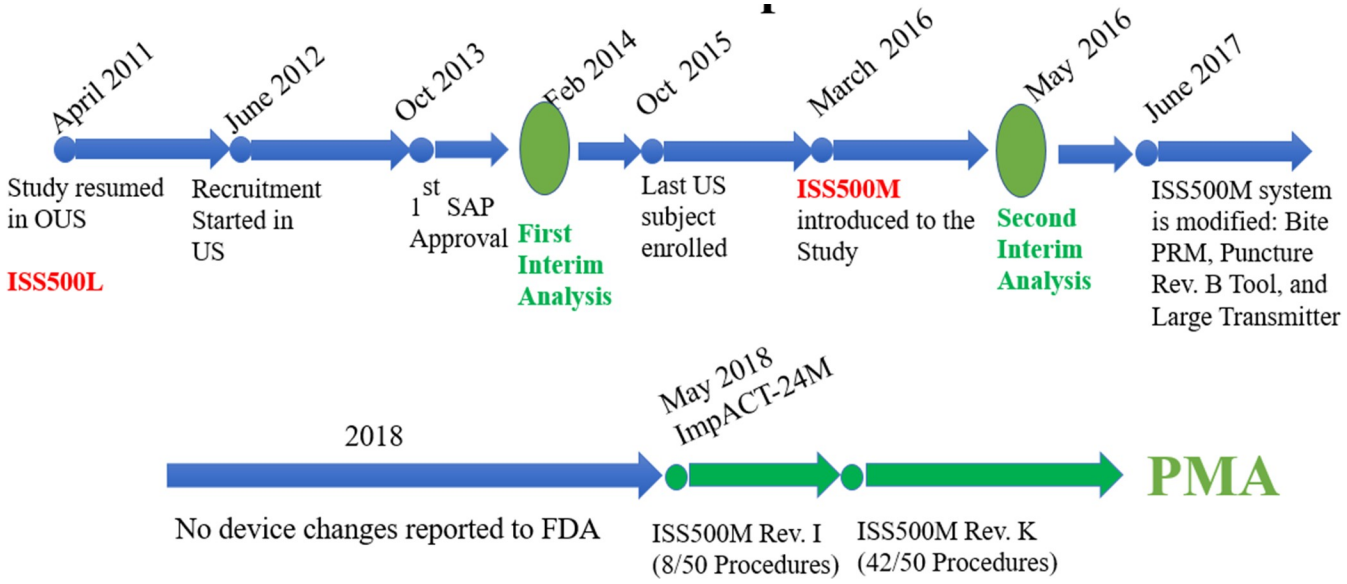

Figure 56 Major Device Changes Reported to FDA in ImpACT-24B and ImpACT-24M

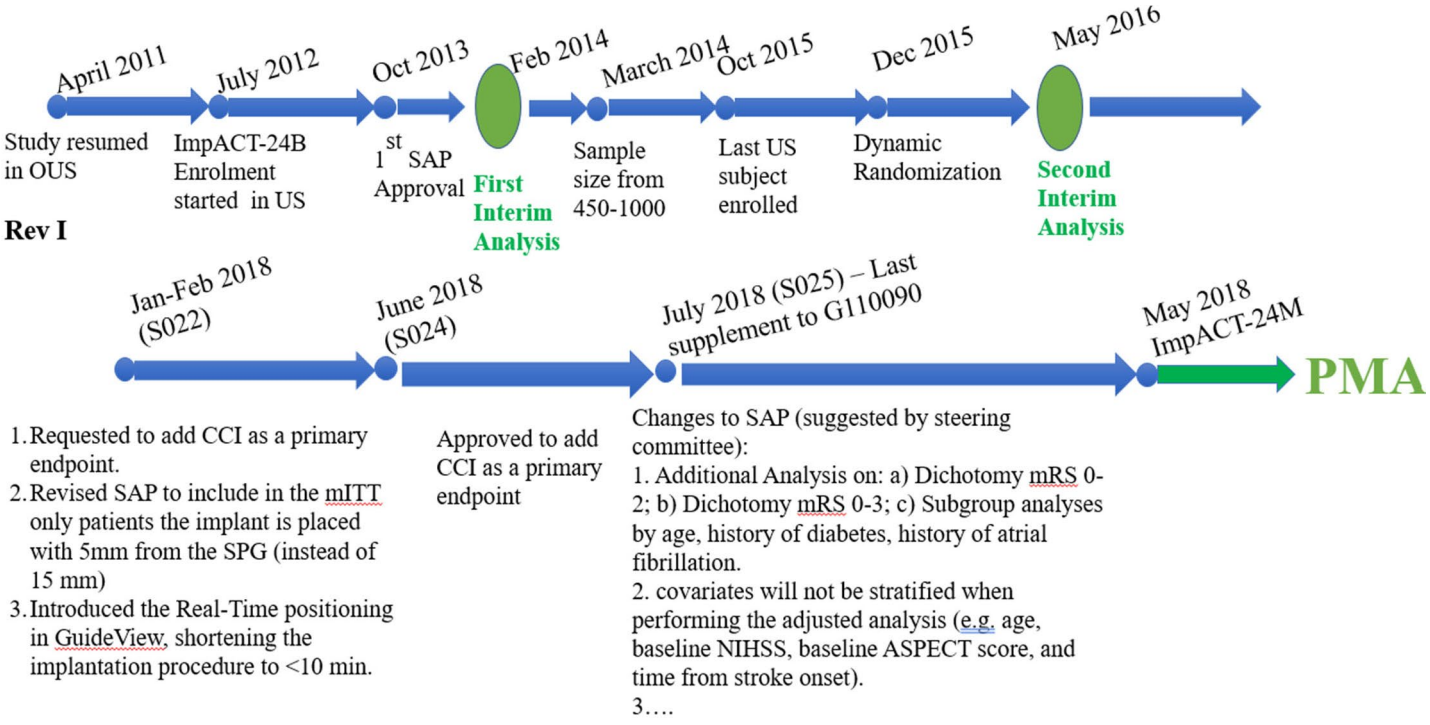

Figure 57 Major Protocol/SAP Changes in ImpACT-24B

10.2.4 Validity of Effectiveness Results – Discussion on Patient Selection

The studies presented (especially ImPACT 24B) did not use vessel imaging to identify the presence or absence of large vessel occlusion nor penumbral imaging to assess the impact of the treatment on the penumbra, which is the proposed mechanism of beneficial action. It is not clear whether the absence of this imaging increases the uncertainty of the effectiveness claim.

The Panel will be asked to comment on a question about this topic area

10.2.5 Applicability of OUS Data to the US Patients - Few US Patients in the Studies

In the 1000-patient ImpACT-24B mITT population, there were 60 US subjects (6%) from 6 sites who enrolled in the trial between 2012 and 2015. Within the 520-patient confirmed cortical involvement (CCI) subpopulation, there were 31 US subjects (6%). Patients in ImpACT-24B continued enrollment and treatment until 2018. In the US CCI population, the success rates were 52.6% and 50.0% for treated versus sham patients (10 of 19 and 6 of 12, respectively). The 2.6% difference between groups is smaller than the 9.9% non-US rate (Table 60).

	US Subjects			OUS Subjects			Interaction P-value
	SPG stim (N=19)	Sham stim (N=12)	Odds ratio (95% CI)	SPG stim (N=225)	Sham stim (N=264)	Odds ratio (95% CI)	
Sliding Dichotomy	52.6% (10/19)	50.0% (6/12)	1.11 (0.26-4.72)	49.3% (111/225)	39.4% (104/264)	1.50 (1.05-2.15)	0.69

Table 60 Difference in Primary Effectiveness Between US and OUS CCI Patients

FDA expressed a concern about the lack of effectiveness in the US population to the sponsor in a Major Deficiency Letter dated May 4, 2020. In response, the sponsor noted that the lower responder/success rate in the US CCI population was likely due to imbalanced baseline characteristics between the two arms in the following 5 factors (Table 61):

			Intervention group	Sham-control group
ImpACT-24B	N		19	12
	Sex (% Female)	Female	9 (47.4%)	9 (75.0%)
	Diabetes	%	7 (36.8%)	2 (16.7%)
	Atrial Fibrillation	%	1 (5.3%)	2 (16.7%)
	Obesity	%	6 (31.6%)	2 (16.7%)
	Glucose, mg/dL	Mean (SD)	163.7 (96.8)	124.3 (21.1)

Table 61 Imbalanced Baseline Characteristics Between the SPG and Sham Group

To understand the lower success rate in the US, the sponsor performed an adjusted analysis that showed a treatment effect in the US at least as large as in the rest of the world. In particular, the sponsor conducted a post-hoc analysis by building a logistic regression model which included the five imbalanced factors and other "clinically important" ones:

> *Logit (responder probability) = Linear function of (US/OUS, ISS/Sham, US/OUS * ISS/Sham, Baseline NIHSS, ASPECT score, Age, Stroke side, Gender, Diabetes, Atrial Fibrillation, Time from last known well to first stimulation session, Glucose, Obesity, Predicted median-mean difference of 90-day mRS).*

The model was trained and analyzed on the 519 CCI (including both US and OUS) patients. The sponsor reported that the estimated odds ratios of treatment vs. sham and the corresponding 95% confidence intervals were 1.46 (0.98, 2.18) and 1.62 (0.30, 8.63) for OUS and US groups, respectively. They also conducted similar analyses for the pooled data (ImPACT-24A + ImPACT-24B) and for secondary endpoints mRS0-2, mRS0-3. The sponsor concluded that "*once the imbalance is accounted for, the effect in the US is as good as (or even slightly higher than) the effect in other countries*."

FDA has the following concerns about uncertainty regarding the sponsor's conclusion:

— US CCI SPG group (19 patients) and US CCI Sham group (12 patients) were both very small and baseline characteristics were imbalanced in several covariates. FDA is uncertain which (if any) baseline

characteristics, i.e., the SPG's or the sham's, can truthfully represent the indicated US population. Therefore, FDA is uncertain how results from this unbalanced and small sample size can be generalized to the entire indicated US patient population.

— Although the estimate of odds ratio of the US was 1.62 and greater than that of OUS (1.46), the lower limit of the confidence interval of the US was only 0.30 and much wider than that of OUS (0.98). Although we understand the very wide confidence interval of US was mainly due to the small sample size, the wide confidence interval casts uncertainty on the result.

— Finally, we emphasize again, all above analyses are post-hoc analyses. Any post-hoc analysis, including those conducted by FDA, naturally carries the uncertainty.

The Panel will be asked to comment on questions about this topic area.

10.2.6 Data Poolability

The ImPACT-24B study was conducted in many countries. The below table lists the performance by country in terms of the primary endpoint.

COUNTRY	ACTIVE GROUP SIZE	ACTIVE RESPONDER RATE	SHAM GROUP SIZE	SHAM RESPONDER RATE	(ACTIVE - SHAM) RESPONDER RATE
GEORGIA	76	55.26%	72	48.61%	6.65%
SERBIA	49	40.82%	67	40.30%	0.52%
SPAIN	36	50.00%	50	40.00%	10.00%
UNITED STATES	19	52.63%	12	50.00%	2.63%
CZECH REPUBLIC	11	27.27%	10	10.00%	17.27%
POLAND	9	55.56%	15	33.33%	22.22%
FRANCE	7	57.14%	6	50.00%	7.14%
ISRAEL	6	50.00%	8	12.50%	37.50%
GERMANY	5	100.00%	11	9.09%	90.91%
PORTUGAL	5	0.00%	5	80.00%	-80.00%
MACEDONIA, THE FORMER YUGOSLAV REPUBLIC OF	5	40.00%	2	50.00%	-10.00%
HONG KONG	5	20.00%	6	33.33%	-13.33%
ITALY	3	66.67%	1	0.00%	66.67%
CANADA	3	33.33%	3	66.67%	-33.33%
SLOVAKIA	2	100.00%	0	.	.
FINLAND	2	100.00%	6	16.67%	83.33%
DENMARK	1	100.00%	1	100.00%	0.00%
UKRAINE	0	.	1	0.00%	.

Table 62 ImPACT-24B CCI Primary Endpoint by Country

Table 62 indicates that ImPACT-24B had low CCI enrollment in many countries. The US, with 19 and 12 in the two arms, ranked at the 4th place. The sponsor conducted a country-poolability analysis by fitting a logistic regression model using Firth's method on the primary endpoint with covariates for treatment arm, country, and a treatment arm by country interaction. They reported that in both the mITT and CCI analyses, "*the interaction term joint test p-value was >0.15, a commonly used significance level for evaluating poolability of data (p-value = 0.74 and 0.52 for mITT and CCI, respectively)*". However, FDA is uncertain about the validity of such poolability analysis and the corresponding p-values because many countries have very low enrollment; for example Denmark only had 1 patient in SPG and 1 in sham group. FDA is concerned that these low-enrollment countries may introduce uncertainties to the effectiveness results.

To address this concern, FDA conducted an exploratory analysis by dividing the countries into two groups. The high-enrollment group consisted of the 4 countries with more or the same CCI enrollment as the US; the low-enrollment group included the remaining 14. The high-enrollment group had 381 total CCI patients, responder rates 50% (ISS500), 43.8% (Sham), and nominal p-value 0.244 (Chi-squared test). The low-enrollment group appeared to have much better results with 139 patients, responder rates 48.4% (ISS500), 29.3% (Sham), and nominal p-value 0.0208. Results indicated noticeable difference in the responder rate (i.e., the device effectiveness) between the high-enrollment group and the low-enrollment. This noticeable difference and the concern about the poolability by country increases the uncertainty of applying OUS data to US patients.

The Panel will be asked to comment on questions about this topic area.

10.3 Summary of the Assessment of Risk

There were a number of adverse events observed in the studies, some of which are attributable to the procedure, others attributable to the device itself. However, there is no data from large animals that would help to inform whether some of the observed events were related to the device, versus those that could be attributed to the nature of a subject's condition.

The following are areas of safety identified by the FDA:

10.3.1 Safety of the Device – Treatment

The sponsor proposed in the IFU that the device and related procedures (implantation and neurostimulation) are to be initiated in the acute ischemic stroke (AIS) patient with CCI 8 to 24 hours last known well. These patients are to be ineligible for or unable to obtain intravenous thrombolysis or neurothrombectomy. Treatment with the ISS500 is to be initiated during that 8-24 hour period with neurostimulation over 4 hours. The patients are to have the same treatment on the next 4 subsequent days.

There is concern regarding the unclear dose response in increased cerebral flow and other hemodynamic parameters that may result during this first neurostimulation treatment. The ischemic stroke patient is prone to cerebrovascular dysautoregulation. There is clinical concern regarding the next 4 days of treatment that occurs during a period when the ischemic core and the penumbra would be considered in a fragile state. Hemorrhagic transformation usually occurs during this timeframe and cerebral edema that occurs usually peaks at day 3-5 post stroke. While there is no requirement that a sponsor explain the mechanism of action of a medical device,

the proposed mechanism of action (MoA) for neurostimulation of the SPG is to increase cerebral blood flow (CBF) via collateral circulation to preserve as much cerebral tissue as possible. The device safety and effectiveness are not clear from the current results, particularly on the US CCI population and the totality of the data. The rationale is not clear about the use and safety of the device on 5 successive days in AIS patients. Those patients that receiving neurostimulation have not undergone attempted or confirmed revascularization during a period when ischemic cerebral tissues are vulnerable and may be at risk for reperfusion injury and edema. It is unclear if there is any or minimal benefit, and if it outweighs the risk of the full procedures of device use over 5 days (implantation and neurostimulation).

The proposed intended use of the device is in AIS patients >8<24 hours from last known well (LKW) with anterior circulation stroke with confirmed cortical involvement who are ineligible or at a facility that is unable to treat using IV thrombolysis or EVT. Cerebral blood flow was only measured in the usability ImpACT-24M, but not in ImpACT-24A and ImpACT-24B. FDA is uncertain whether data from the usability study ImpACT-24M are sufficient to demonstrate that ISS500 increases CBF to the ischemic region.

Per the ImpACT-24M investigational plan, the study was initiated to 'assess safety and signal of efficacy'. The patients were "Subjects with Mild Acute Ischemic Stroke in the anterior circulation within 24 hours from onset" with baseline NIHSS between 1 and 6. The patients were to be followed out to seven days post enrollment. The study objectives were to "1. Identify the personal stimulation level for each patient based on physiological biomarkers 2. Identify improvement in stroke symptoms during ISS500 treatment at the personal stimulation level". For the same investigation plan it stated, "A sample size of 50 patients was judged sufficient to characterize implantation speed and accuracy…" It is not clear that the sample size rationale is consistent with providing adequate CBF data itself or confirmation of data results reported from ImpACT-24B as far as functional outcome.

Additionally related to morbidity and outcome are cardiovascular and cerebrovascular risk factors. These risk factors include diabetes, obesity, and hypertension, which can increase the likelihood of such adverse events or less functional outcome improvement. Also, the burden may be greater in the US than in other areas or populations outside of the US. This may have some bearing or be related to the imbalances the sponsor suggests as a reason for the differences in the US CCI population outcome at 90 days. If that is the case, and if it were the only reason to have uncertainty regarding the data, it would still raise the concern regarding the validity and the applicability of the data and the device's use in the US population.

Cerebral reperfusion after a stroke has associated risks, including that of worsening stroke and hemorrhagic conversion. A device that increases CBF has the potential to impact cerebral perfusion pressure and systemic blood pressure in a population that is likely to have some measure of cerebral dysautoregulation at 8-24 hours post stroke. The data from ImpACT-24M does not appear to clarify or lessen the uncertainties related to the other studies, including ImpACT-24B. Part of this is that Imp-ACT24B and ImpACT-24M were done on different populations, objectives, outcomes measures and timeframes with different implantation devices and procedures. At best, it appears to support a randomized controlled trial using the proposed current device in the proposed AIS population in an adequate sample size with the appropriate functional outcome measures as primary and secondary endpoints to support the proposed IFU. FDA is uncertain whether safety data provided in ImpACT-24A, -24B and -24M adequately reflected the safety profile of the ISS500 device.

The Panel will be asked to comment on questions about this topic area.

10.3.2 Safety of Implantation and Stimulation Level

This section addresses the two usability issues that were identified during the clinical trials and have great importance on the generalizability of study results: one is correct implantation and the other is correct setting of stimulation intensity. Both issues were resolved, and the solutions were validated in a separate usability study (ImpACT-24M) which included 50 patients between May-September 2018[i].

10.3.2.1 Implantation Safety

Among the 481 mITT patients allocated to active SPG stimulation in ImpACT-24B, 306 (63.6%) of the implant procedures were performed by neurologists and 175 (36.4%) were performed by neuroradiologists, surgeons, and anesthesiologists. The number of neurostimulator placement procedures performed by implanters was mean 5.2 (±9.0).

Initial improvements in the navigation system reduced the misplacement rate but prolonged the procedure (Figure 59). With the introduction of the modified implant and additional improvements in navigation, misplacement rate dropped to 2%, and implantation time was reduced to 17 minutes (median skin-to-skin time). The main challenge in navigating the implant to the correct position was maintaining accurate registration between the patient and the pre-procedure guidance CT and accounting for patient motion during the procedure.

In ImpACT-24B, this was achieved using a patient-reference marker (PRM) that was attached to the patient's forehead (Forehead PRM, Figure 58 A), and much of the procedure time was dedicated to verification and fine-tuning of registration accuracy.

The ImpACT-24M usability study validated a new PRM, that is attached to the patient's upper maxilla using a dental impression (Bite PRM, Figure 58 B).

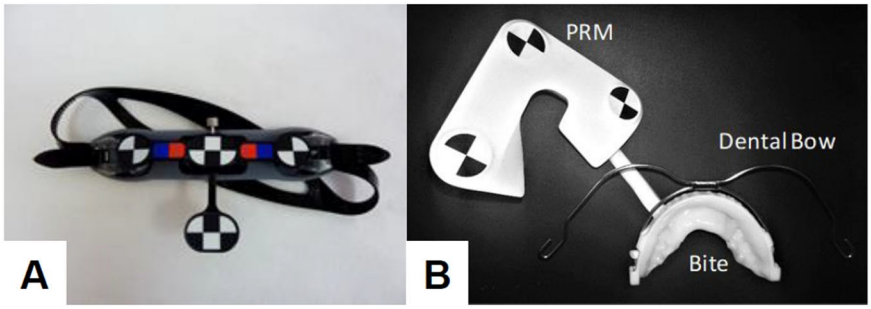

Figure 58 Forehead PRM (A) vs Bite PRM (B)

The following figure shows the rates of implant placement and procedure time in ImpACT-24B and ImpACT-24M.

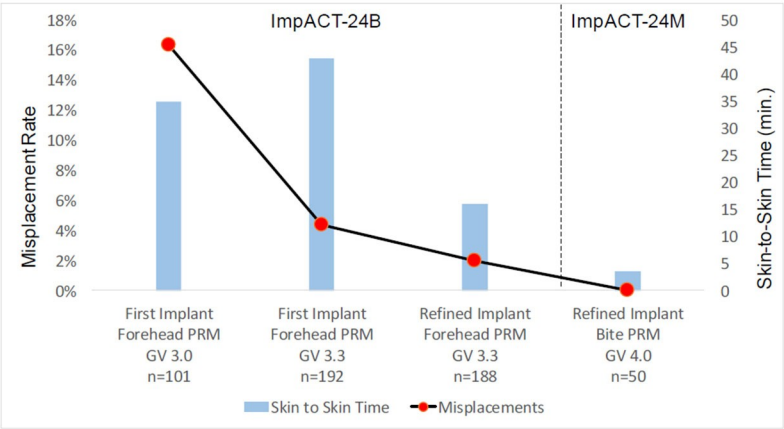

Figure 59 Misplacement Rate and Skin to Skin Time

Misplacement rate in ImpACT-24M was zero (0/50), and median skin-to-skin time was 4m 15s. (IQR 3m 10s – 6m 48s).

10.3.2.2 Stimulation Safety

In clinical practice, stimulation level is best set based on the unique physiological biomarkers of SPG activation, such as ipsilateral lacrimation and non-noxious tingling sensation over the cheek or nose bridge. When stimulation level begins to increase, the first biomarker to appear is the tingling sensation, then lacrimation, and if stimulation further increases, facial pain appears. Facial pain should be avoided as it indicates that treatment is applied at a "too high" level. Tingling sensation always precedes pain. The design of ImpACT-24B as a double-blind randomized trial precluded use of the unique physiologic biomarkers to guide stimulation intensity, for two reasons. First, only patients in the active SPG stimulation group would exhibit the physiologic biomarkers. Second, for blinding purposes, the transmitter (which was attached to the patient's cheek) had a built-in small vibrating engine, and all patients were exposed to vibration which mimicked the tingling sensation of SPG activation. Therefore, a different method for adjusting the stimulation to a level that would activate the SPG was used – stimulation was gradually increased until the patient reported mild facial discomfort or pain and then it was decreased to a comfortable level. However, this approach sometimes led to treatment above the comfortable level, in the sub-optimal range.

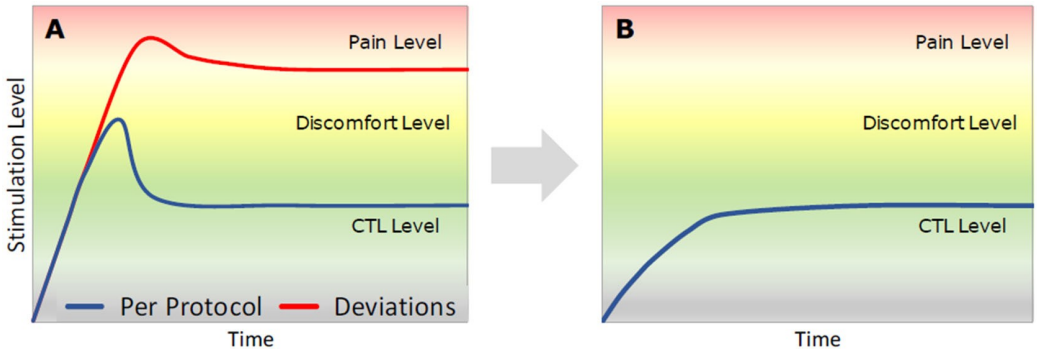

Figure 60 Setting the Stimulation Level based on Discomfort/Pain (A) vs. Physiological Signs (B)

The physiologic approach to stimulation intensity selection was validated in ImpACT-24M:

a. The CTL was found successfully based on physiological surrogates of SPG activation in 48/50 patients (96%).
b. Beneficial SPG activation was confirmed using measurements of cranially-directed blood flow through the common carotid artery. Peak Systolic Flow was increased by 44% ($p<0.0001$) and End Diastolic Flow was increased by 52% ($p<0.0001$) compared to baseline measurements before treatment initiation (Figure 61).

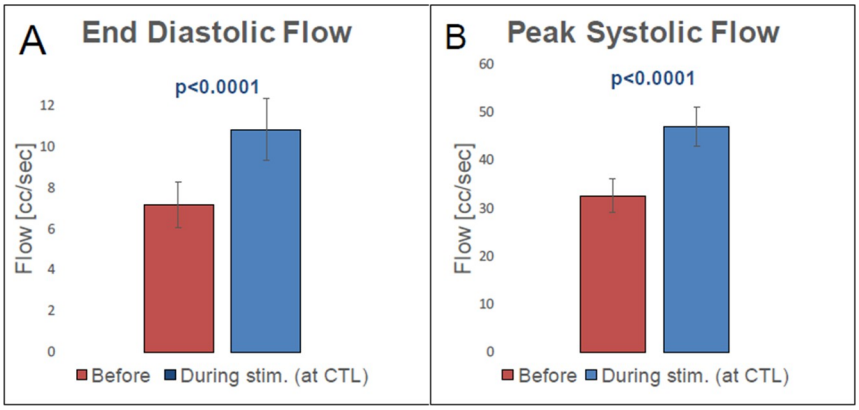

Figure 61 Blood Flow Increase - ImpACT-24M

Additionally, hand strength deficit on the affected side improved after 2 hours and 4 hours of SPG stimulation compared to baseline measurement before treatment (Figure 62).

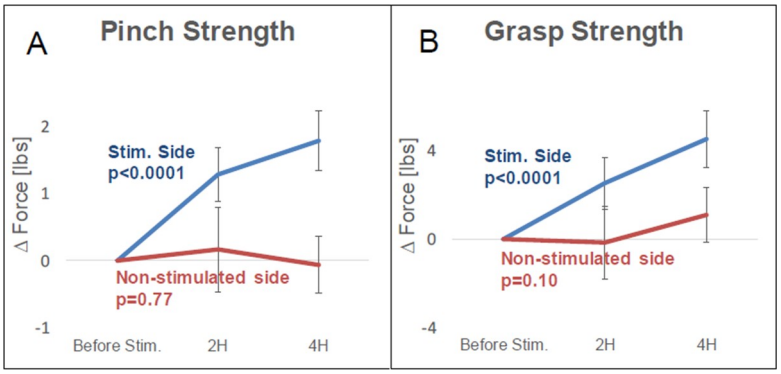

Figure 62 Hand-strength Improvement (A) Pinch; (B) Grasp

Figure 63 compares the distribution of CTL levels in ImpACT-24M (blue bars) with the dose-response curve in ImpACT-24B (green curve with grey 95% confidence interval).

In 92% of the patients in ImpACT-24M, the stimulation level was set (b)(4) using the physiologic

signs of SPG activation. This range is considered the "physiologically selected CTL Range", and it overlaps the range of stimulation levels that were found to be the most effective in the pivotal ImpACT-24B.

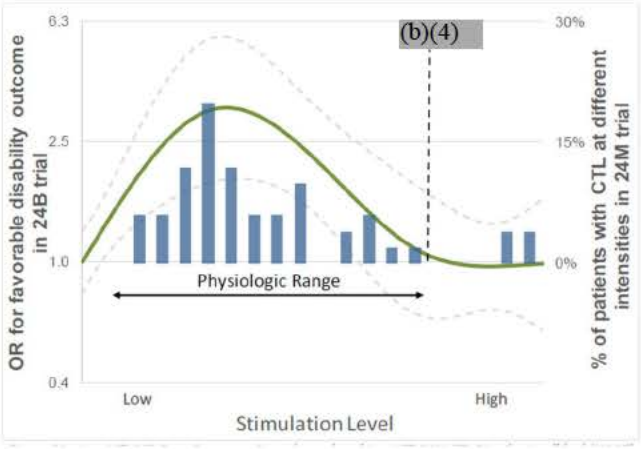

Figure 63 ImpACT-24B Dose Response Curve (green) and ImpACT-24M CTL Distribution (blue)

The sponsor concludes that ImpACT-24M confirmed that finding the CTL based on physiologic surrogates is practical and results at simulation levels at the low-medium range, which was shown to be the most effective stimulation range.

The Panel will be asked to comment on questions about this topic area.

11 Postmarket Approval Study

In general, post-market data collection is appropriate to investigate, among other issues, long-term considerations that might not be feasible to collect pre-market (for example, if it would take years to collect the relevant data). The device is not a long-term implant, and the sponsor has already conducted a large clinical trial to support approval. The sponsor provided a proposal for a post approval study study to collect data from multiple sources to capture implantation procedure safety information, clinical outcomes, device related complications, specific safety related incidents, and customer reports.

The Panel will be asked to comment on questions about this topic area.

12 Appendices

Appendix A Preclinical Information

All questions regarding the non-clinical testing have been addressed to FDA's satisfaction. The following sections describe the testing and evaluations completed by the company.

Sterilization/Shelf Life/Reuse

The INS Assembly

The INS Assembly was sterilized with a minimum sterility assurance level (SAL) of 10-6 using a validated ethylene oxide (EO) sterilization cycle. The EO sterilization cycle was validated in accordance with ISO 11135:2014 Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices. EO residual levels found on this product following EO sterilization process are below the maximum allowable limits of EO and Ethylene chlorohydrin (ECH) residual levels specified in ISO 10993-:2008(R)2012 Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals.

The bacterial endotoxin levels on the INS Assembly complied with the bacterial endotoxin limits specified in AAMI ST72 2011(R)2016 Bacterial endotoxins - Test methods routine monitoring and alternatives to batch testing.

Packaging performance and stability testing results demonstrated that the packaging system for the INS Assembly could withstand the environmental and mechanical stresses likely to be encountered during transportation and storage and maintain its sterile barrier up to two years.

The Puncture Tool and Tracer Tool

The Puncture Tool and Tracer Tool are reusable device and sold non-sterile. These tools require cleaning and steam sterilization by end-users at the US healthcare facilities prior to each clinical use. The recommended reprocessing instructions for these reusable devices were based on the cleaning and sterilization validation studies. These tools do not have stated shelf life.

Biocompatibility

Biocompatibility of all tissue-contacting components of the ISS500 device was evaluated in accordance with FDA's Biocompatibility Guidance: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process" (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf). The INS500I component of the ISS500 device is considered an implant device in prolonged (> 24 hours – 30 days) contact with neural tissue/bone. The Patient Sicker, Transmitter Cable, and the Nose Sticker are considered intact skin-contacting devices with limited (≤ 24 hours) contact. The Personal Bite Impression Tray, i.e., the iPRM, is considered a surface device in limited (≤ 24 hrs) contact with mucosal membrane. The tip of the Introducer is considered an external communicating device in limited (≤ 24 hrs) contact with tissue/bone and the handle of the Introducer is considered a surface device in limited (≤ 24 hrs) contact with a breached or compromised surface. The Puncture Tool is considered an external communicating device in limited (≤ 24 hrs) contact with tissue/bone. Biocompatibility testing was conducted on the tissue-contacting components of the ISS500 device in compliance with Good Laboratory Practices (GLP), 21 CFR Part 58 and is summarized in Table 1 below. All pre-specified test acceptance criteria were met and all tests passed.

Table1: Biocompatibility Test Data on the ISS500 Device

Biological Effect (Applicable Standard)	Test Method	Acceptance Criteria	Results
INS500I, Patient Sticker, Transmitter Cable, Introducer, Puncture Tool, iPRM			

Biological Effect (Applicable Standard)	Test Method	Acceptance Criteria	Results
Cytotoxicity (ISO 10993-5)	ISO MEM Elution Assay	Reactivity grade is not greater than mild reactivity (Grade 2)	PASS
INS500I, Nose Sticker, Introducer, Puncture Tool, iPRM, Nose Sticker			
Sensitization (ISO 10993-10)	ISO Guinea Pig Maximization Sensitization Test	Grades of <1 in the test group provided grades of < 1 are observed on the control animals. (If grades of ≥ 1 are noted on the control animals, then the reactions of the test animals which exceed most severe control reaction are presumed to be due to sensitization).	PASS
INS500I, Introducer, Puncture Tool, iPRM			
Irritation/Intracutaneous Reactivity (ISO 10993-10)	ISO Intracutaneous Reactivity Test	The difference between the test article and the control mean score is ≤ 1.0.	PASS
Patient Sticker, Transmitter Cable			
Sensitization (ISO 10993-10)	ISO Guinea Pig Closed Patch Sensitization Test	Grades of <1 in the test group provided grades of < 1 are observed on the control animals. (If grades of ≥ 1 are noted on the control animals, then the reactions of the test animals which exceed most severe control reaction are presumed to be due to sensitization).	PASS
Patient Sticker, Transmitter Cable, Nose Sticker			
Irritation/Intracutaneous Reactivity (ISO 10993-10)	ISO Skin Irritation Test in Rabbits	No acceptance criteria are specified in the standard. The irritation response is categorized from negligible to severe based on the Primary Irritation Index.	Acceptable Response
Nose Sticker, Patient Sticker			

Biological Effect (Applicable Standard)	Test Method	Acceptance Criteria	Results
Cytotoxicity (ISO 10993-5)	ISO Agarose Overlay Assay	Reactivity grade is not greater than mild reactivity (Grade 2)	PASS
INS500I, Introducer, Puncture Tool			
Systemic Toxicity (ISO 10993-11)	ISO Acute Systemic Toxicity Test	None of the test animals show a significantly greater biological reaction than the animals treated with vehicle control.	PASS
	Material-Mediated Rabbit Pyrogen Test	No rabbit shows an individual rise in temperature of 0.5°C or more above the baseline temperature.	PASS
INS500I			
Genotoxicity (ISO 10993-3)	Bacterial Reverse Mutation Assay (Ames Test)	There is less than 2-fold increase in the number of revertants when compared to the solvent controls in strains TA98, TA100, and WP2uvrA and less than 3-fold increase in the number of revertants when compared to the solvent control in strains TA1535 and TA1537.	PASS
	Mouse Lymphoma Assay	The test article induced mutant frequency (IMF) is lower than the Global Evaluation Factor (GEF) of 90 x 10^{-6}.	PASS
Combined Implantation/Neurotoxicity/Subacute Toxicity Study (ISO 10993-6 and ISO 10993-11)	A 4-week implantation study was conducted in rabbits to assess potential neurotoxicity, local tissue responses as well as systemic effects following implantation of the device near the sciatic nerve and femur. For each of the rabbits in the study, the test or control article was implanted adjacent to the sciatic nerve in one leg. In the same leg, another test or control article was implanted adjacent to the femur. There were no clinical or neurological observations that indicated toxicity caused by test or control article implantation. There were no statistically significant differences in mean body weight between the test and control groups. The hematology and clinical chemistry values showed no evidence of systemic toxicity and were similar between the test and		

Biological Effect (Applicable Standard)	Test Method	Acceptance Criteria	Results
	control article groups. Absolute organ weights, organ/body weight ratios and organ/brain weight ratios were similar between the test and control article groups. There was no microscopic or macroscopic evidence of systemic toxicity from the test article following implantation adjacent to the sciatic nerve and adjacent to the femur in the rabbit. Microscopically, the test article was classified as causing a minimal or no reaction following implantation at either site.		

Software Testing

The ISS500 system includes two subsystems, both containing hardware and software/firmware:

1) The implantation subsystem, which assists in placing the implant correctly
2) The treatment subsystem, which controls the treatment sessions

The **treatment software** is responsible for the following functions: (a) Adaptation Mode – adjusts the stimulation pulse parameters to the individual patient's Comfortable Tolerance Level (CTL), (b) Treatment Mode – delivers pulses of current to the patient. The treatment subsystem also includes driver firmware with a Lab Mode that is used internally for unit testing and integration testing. This Lab Mode is restricted to mitigate cybersecurity risks.

The **implantation software** runs the functions of the GuideView system, an optical stereotactic navigation system. These functions include: (a) Planning – identify target site for implantation in the CT imaging, as well as anatomical landmarks used for registration and verification, (b) Registration – matching (mapping) the CT images to the patient's anatomy, and (c) Navigation – assist in finding and confirming entry location and placing the implant.

As a system, the ISS500 software/firmware represents a Major level of concern based on the FDA Guidance Document, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" (U.S. Food and Drug Administration, 2005). The sponsor has provided the appropriate documentation and testing for this level of concern.

Electrical, Mechanical, and Thermal Safety

The ISS500 Device system has been tested for electrical safety according to EN 45502, ISO 14708-1, ISO 14708-3 – standards related to Implants for Surgery –Active Implantable Medicaid Devices –Implantable neurostimulators, and IEC 60601-1 Medical electrical equipment Part 1: General requirements for basic safety and essential performance for external electrical equipment.

Electromagnetic Compatibility (EMC) and Wireless Technology

The ISS500 device system has been tested for electromagnetic compatibility according to IEC 60601-1:2:2014. The EMC testing was performed for the test specified for the hospital environment. In addition, the ISS500 device system was also tested for the device system exposure to Radio-frequency identification (RFID) according to AIM 7351731, and the implantable INS was tested according to ISO 14708-3:2017. The EMC related safety and effectiveness of the device system was tested with wireless technologies actively turned on

and transmitting data. For certain EMC testing specified in the standards but were not performed, and device effects observed, the sponsor provided adequate justifications based on the device design and the risks associated with the device effects observed.

The ISS500 device system has been tested with Radiofrequency (RF) inductance for the communication between the Driver and the INS and Bluetooth for Controller and the Driver to program and monitor the treatment. Even if the Bluetooth communication is interrupted, the Driver continues to deliver treatment. The Controller also uses Wi-Fi connections and cellular network for temporary connections to transfer statistics from patient's treatment and service data to the server. In addition, the GuideView navigation system was tested using Wi-Fi connections for internet and for hospital network.

MRI Conditional Testing
MR Compatibility has been tested according to FDA Guidance for Industry and FDA Staff "Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment," issued May 20, 2021 (https://www.fda.gov/media/74201/download).

Cybersecurity
The Controller, Driver and GuideView systems incorporate software and external connectivity that may be subject to cyber threats. The following mitigations against cyber threats have been implemented:

1. Prevent tampering with data/information including stimulation parameters.
2. Prevent missed or incorrect implantation due to GuideView workstation tampering
3. Secure (private) patient data.
4. Prevent tampering with the software configuration and update process.

Software design requirements, configuration requirements and support processes were tested to mitigate the cyber threats

Animal Testing
Eighteen (18) rodent animal studies were performed to assess various aspects of tissue and animal response to SPG stimulation. The studies assessed blood flow, infarct size, neuronal survival, overall neurological function, and performance on specific motor and cognitive tasks using a variety of stimulation paradigms in both naïve and/or different AIS animal models. The studies demonstrated a general improvement in infarct size and various neurological assessment measures as a result of stimulation at various time points. There were some observations of significant animal mortality, which the sponsor attributed to the occlusion model. To fit the smaller anatomy of the rodent animal model, the devices used in the animal studies were modified device designs that have differences from the final device, which raises uncertainty regarding the applicability of the animal testing provided to demonstrate the safety of the final ISS500 device.

Design Verification and Validation Testing: The GuideView Navigation System

Bench Test Type	Applicable Standard or Guidance
Stereotactic Navigation Accuracy	ASTM, F2554-10 - Standard Practice for Measurement of Positional Accuracy of Computer Assisted Surgical Systems **Ground Truth Measurement:** Accuracy is assessed by comparison ground truth measurements taken with a verified calibrated system that are completely independent of the implantation system.
Registration and Calibration Accuracy	IEC62366-1:2005: Medical Devices - Part 1: Application of Usability Engineering to Medical Devices FDA Draft Guidance: Applying Human Factors and Usability Engineering to Optimize Medical Device Design

Key Design Verification and Validation Testing: the INS and the EDC Subsystem

INS500

Bench Test Type	Requirements of the Testing
INS Mechanical Forces	▪ The implant shall be flexible but shall withstand axial force of at least 600gr when at least 8 mm are in the canal and remaining implant is in the introducer. ▪ The INS shall withstand a pulling force of at least 2.5Kgf (actual extraction forces does not exceed 1Kgf) ▪ The INS body shall withstand a side force of at least 3Kgf. Upon failing, INS shall remain in one peace.
Seal	The INS shall be sealed to withstand humidity.
INS Functionality During Implantation	1) The INS shall keep its functionality after being handled by its dedicated introducer. 2) The INS functionality shall be verified as part of the implantation procedure immediately after implantation. 3) The INS shall keep its functionality for minimum of 10 days inside the human body after implantation procedure. 4) The INS shall be capable of keeping its original position once implanted in the GPC for a minimum duration of at least 5 days.
INS Functionality during Treatment	1) The data-exchange between the driver and the implant shall be digital and shall include date verification 2) (b)(4) 3) (b)(4) 4) (b)(4)

	5) Each treatment day shall have 16-24 pulse cycles that include a. 4x60 sec - on, b. 11 minutes – off 6) The pulse current shall be gradually increased during initial treatment stage 7) The electrode current shall not exceed pulse level of 2.5 mA peak for any incoming magnetic field from the transmitter (essential performance) 8) The INS shall provide indications to the system if data was received and verified and if the requested current was fully delivered to the patient. 9) Pulses used for positioning feedback shall not deliver current to the tissue.

Energy Delivery and Control system (EDC)

Bench Test Type	Requirements of the Testing
Electrical Parameters	a. (b)(4) b. The system shall keep its RF frequency through its life time to 6.78 MHZ±2%
Transmitter Device	**1)** The transmitter and implant shall be functional when their concentricity offset is up to 5mm **2)** Radiational power through the transmitter's coil area shall be less than 100 W/cm^2 to comply with IEEE C95.1. **3)** Charging time to enable full treatment session shall be 5 hours max.

INS 500 Introducer Assembly

The delivery of the INS into the canal is accomplished using the Introducer. The Introducer is designed to insert the INS all the way to the pterygopalatine fossa (near the canal's end, approximately 23mm) so that the tip of the INS is located next to the SPG. The Introducer incorporates the following features:

- Protecting the INS – during the initial insertion through the mucosa to the canal's entrance, the INS is protected inside the Introducer
- Tracked slider – the slider's 28mm range of travel is sufficient for all canal structures. The optical markers on the slider allow GuideView to track its advancement and the resulting position of the INS in the canal.
- Force limiter – during INS advancement in the canal the force limiter prevents the implanter from applying excessive force to the INS.
- Release mechanism – controlled release of the INS once it reaches its destination
- After the implant is released, excess thread is cut using scissors

Bench Test Type	Requirements of the Testing
Physical Characteristics	The force required to pull the INS from the Introducer before it is released shall be >200grf.

	In order to overcome the slider friction of the introducer, the user shall apply a maximum of 70grf. The implant-introducer mechanical connection shall allow for relative angles of 45 [deg] LAT\MED, 30 [deg] ANT/POST without losing functionality. The introducer shall include detectable markers, identified by the GuideView system to allow their navigation during the procedure.

Appendix B The Sliding Dichotomy Model

The ImpACT-24B trial used the sliding dichotomy technique for analysis of disability outcome at 90 days, also known as baseline severity-adjusted analysis and as prognosis adjusted sliding dichotomy

In sliding dichotomy analysis, the "win criterion" for a patient (the disability threshold at which the patient will be considered to have a favorable outcome) is adjusted according to the outcome to be expected based on baseline prognostic variables.
If a patient has a mild deficit and other features indicating a good prognosis already at study entry, then only an excellent final outcome is considered a favorable result. If a patient has a moderate deficit and other features indicating an intermediate prognosis at study entry, then a good outcome or better is considered a favorable result. If a patient has a severe deficit and other features indicating a poor prognosis at entry, then a fair outcome or better is considered a favorable result.

The proportion of patients with prognosis-adjusted favorable results are compared across the two trial treatment groups.

For the ImpACT-24B trial, each patient's sliding dichotomy win criterion was generated using a model derived prior to trial launch from 1077 patients in control groups of 8 prior acute ischemic stroke trials entered into the Virtual International Stroke Trial Archive (VISTA). The derivation set patients were required to have age, NIHSS timing, and NIHSS score within the entry criteria range of the ImpACT-24B trial. Their mean age was 67.7 (±11.1), mean NIHSS 13.2 (±4.0), 46% were female, and 51% had left-brain stroke. The resulting prognostic model used to calibrate the sliding dichotomy in ImpACT-24B is described below.

Based on the patient's baseline NIH Stroke Scale (NIHSS) score, age, and stroke side, the predicted day 90 modified Rankin Scale (mRS) distribution is calculated using a multivariate logistic regression model, as follows:

$$Cumulative\ Prob(Day90\ mRS_j) = \frac{e^{L_j}}{1 + e^{L_j}}$$

Where:

$$L_j = \sum_{n=1}^{4} A_i * X_i + B_j$$

$X_{1,\ldots,4}$ are the patient's baseline parameters, A1,…,4 are their corresponding coefficients, and $B_{0,\ldots,5}$ are the mRS outcome intercepts, as defined in the table below:

	Variable	Parameter estimate
A_1	Baseline NIH Stroke Scale (NIHSS) score	-0·25393789
A_2	Age	-0·04509683
A_3	Left hemisphere stroke	0·31371044
A_4	Baseline NIHSS * Left hemisphere interaction	0·01440137
B_0	Intercept for mRS = 0	1·95456059
B_1	Intercept for mRS = 1	3·89845503
B_2	Intercept for mRS = 2	4·92602418
B_3	Intercept for mRS = 3	6·02778408
B_4	Intercept for mRS = 4	7·63046850
B_5	Intercept for mRS = 5	8·21967783

The median (midpoint) of this distribution is the expected outcome of the patient. Success in the primary outcome (sliding dichotomy) was defined as mRS better than the median by one or more point. Failure was defined as mRS equals or worse than the median. mRS 5 and 6 are collapsed into a single worst outcome category, and a mRS score of 5 as well as a mRS score of 6 is always considered a failure.

Appendix C Pivotal Study Inclusion/Exclusion Criteria

Inclusion Criteria

1. Age: ≥ 18 years and ≤ 85 years
2. Clinical diagnosis of an acute ischemic stroke in the Carotid, Middle or Anterior Cerebral Artery territories based on general physical examination and neurological examination
3. Baseline NIH Stroke Scale (NIHSS) ≥ 7 and ≤ 18 within 2 hours prior to device implantation
4. Ability to initiate treatment within 8-24 hours from stroke onset
5. Signed informed consent from patient him/herself or legally authorized representative if applicable

Exclusion Criteria

13 Neuro-imaging evidence of any intracranial hemorrhage or hemorrhagic transformation of brain infarct or other significant abnormality (e.g., tumor, abscess, suspect for subarachnoid hemorrhage).

14 Massive stroke, defined as acute parenchymal lesion with effacement of cerebral sulci in over 2/3 of the middle cerebral artery (MCA) territory.

15 Acute stroke due to lacunar infarct as defined by a clinical syndrome (pure motor hemiparesis, ataxic hemiparesis, sensorimotor stroke, dysarthriaclumsy hand syndrome), unless brain imaging demonstrates a

relevant lesion > 1.5 cm in size.

16 Clinical signs and symptoms or evidence for a relevant lesion by neuroimaging of an acute ischemic stroke in the posterior circulation (Vertebral, Basilar and/or Posterior Cerebral Artery territories), including but not limited to brain-stem findings and/or cerebellar findings and/or isolated homonymous hemianopia or cortical blindness.

17 Minor stroke with non-disabling deficit or rapidly improving neurological symptoms.

18 Treated with IV-tPA, intra-arterial (IA)-tPA, or neurothrombectomy devices for the current stroke.

19 NIHSS level of consciousness score ≥ 2.

20 Previous stroke in the last 6 months or previous stroke with existing sequelae

21 Pre-existing disability; Modified Rankin Score >1 upon screening

22 Patients with bleeding propensity and/or one of the following: international normalized ratio (INR) > 1.8, prolonged activated partial thromboplastin time (aPTT) ≥ 45 sec., platelets count < 75×109/L.

23 Known cerebral arteriovenous malformation, cerebral aneurysm.

24 Clinical suspicion of septic embolus.

25 Uncontrolled hypertension (systolic >185 mmHg and/or diastolic >110 mmHg), demonstrated on each of three repeated measurements taken within one hour regardless of whether or not the patient is taking antihypertensive medications.

26 Serious systemic infection.

27 Women known to be pregnant or having a positive or indeterminate pregnancy test.

28 Patients with other implanted neural stimulator/ electronic devices (pacemakers).

29 Any condition in the oral cavity that prevents implantation of the INS, such as patient is intubated, orthodontics or non-hygienic condition.

30 Life expectancy < 1 year from causes other than stroke.

31 Participating in any other therapeutic investigational trial within the last 30 days.

32 Known sensitivity to any medications to be used during study.

33 Subjects who have a clinically significant or unstable medical or surgical condition that may preclude safe and complete study participation. Conditions may include: cardiovascular, vascular, pulmonary, hepatic, renal or neurological (other than acute ischemic stroke), or neoplastic diseases, as determined by medical history, physical examination, laboratory tests, or ECG.

34 Subjects who, in the judgment of the investigator, are likely to be noncompliant or uncooperative during the study

Appendix D – ImpACT-24A Additional Information

D1 – Patient Accountibility

The study was conducted between first enrolment in February 2009 and final study visit in January 2011. Figure 64 is the consort chart. Of the 327 patients enrolled in the implantation phase, 6 exited before the implantation procedure started, 18 had incomplete implantations, and 303 had implantations completed and advanced to the randomized phase. Of the 6 patients who exited before the procedure, one was mistakenly randomized.

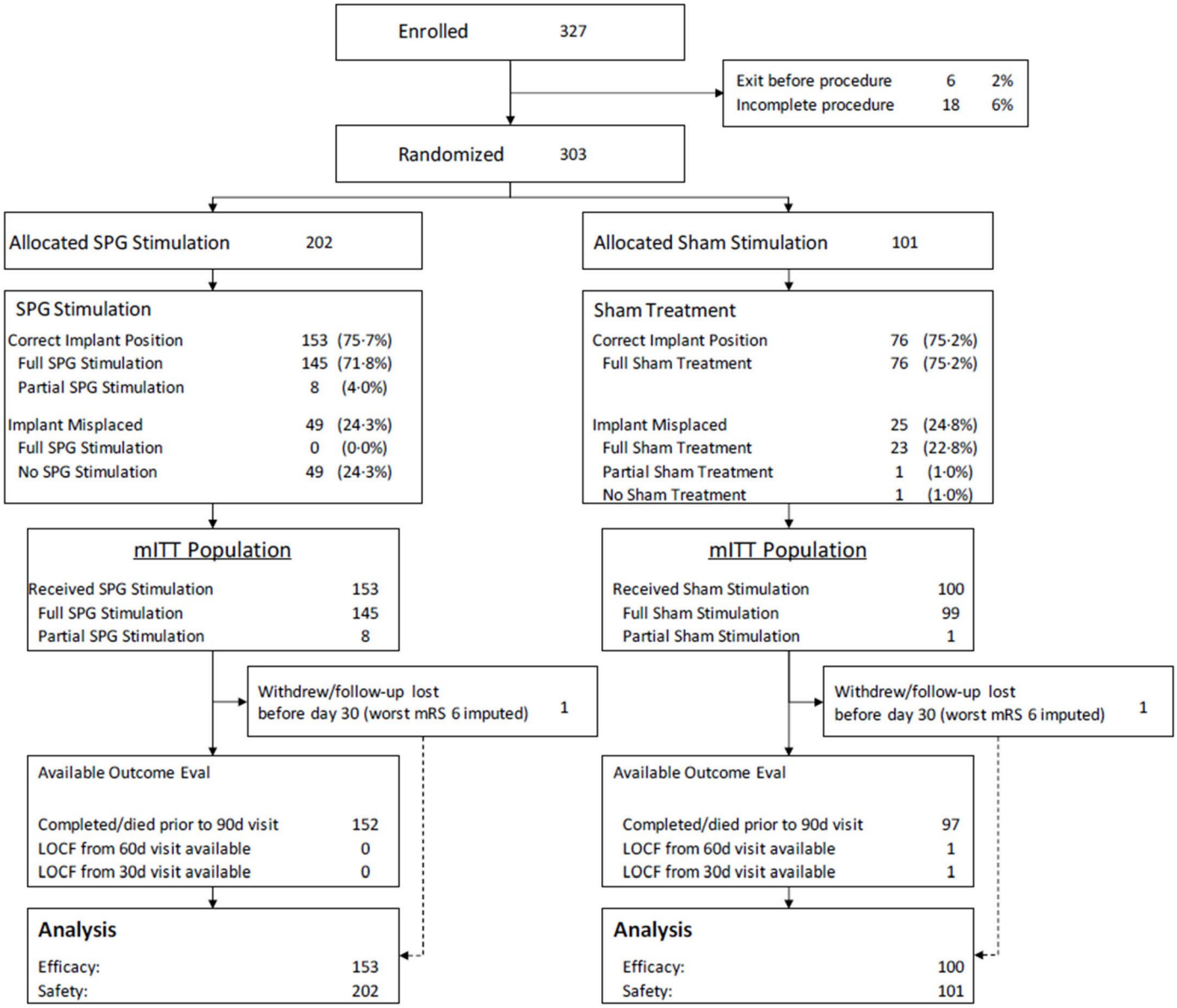

Figure 64 ImpACT-24A CONSORT Chart

In the SPG stimulation group, 153/202 (75.7%) of the patients received at least one active SPG stimulation session and were included in the mITT population, including 145 who completed at least 4 treatment sessions and 8 who completed less than 4, while 49 patients had off-target placements and consequently did not receive actual SPG stimulation. Sham treatment was considered to have been delivered regardless of implant position. Accordingly, in the sham stimulation group, 100/101 (99.0%) of patients received at least one sham stimulation session and were included in the mITT population, including 76 who had on-target placement and 24 who had off-target placements, while 1 patient did not receive any sham treatment. The resulting total number of patients in the mITT population was 253 (153 in the SPG stimulation group, 100 in the sham stimulation group).

Among the overall 303 randomized subjects, 298 completed the 90-day primary outcome follow-up assessment: 200/202 (99.0%) in the SPG stimulation group and 98/101 (97.0%) in the sham stimulation group. Among the 253 patients in the mITT population, in the SPG stimulation group, 152 (99.3%) of 153 completed the 90-day follow-up, and 1 (0.7%) had worst case mRS 6 imputed as no follow-up available; in the sham stimulation group, 97 (97.0%) of 100 patients completed the 90-day follow-up, 2 (2.0%) had last observation carried forward, and 1 (1.0%) had worst case mRS 6 imputed when no follow-up available (Figure 64). Rates of completion for the longer term, 6 and 12-month, assessments were lower (<75%), so the additional RIKS-Stroke endpoint was not formally analyzed.

D2 - Demographics and Baseline Characteristics in mITT Population

Table 63 provides the demographics and baseline C=characteristics in mITT Population. Day 5 imaging revealed that 12 mITT patients (4.7%) had posterior circulation infarcts (rather than anterior) and additional 12 (4.7%) had no final visualized infarct.

	mITT Population			
	SPG group (N = 153)	Sham-control group (N = 100)	All (N = 253)	p-value
Age, years	73 (64-79)	74 (64-79)	73 (64-79)	0.22
Sex (% Female)	82 (54%)	51 (51%)	133 (53%)	0.69
Median NIHSS (IQR)	11 (8 - 15)	11 (9 - 14)	11 (9 - 15)	0.50
Stroke side (left brain)	66 (43%)	52 (52%)	118 (47%)	0.17
Pre stroke mRS = 0	138 (90%)	85 (85%)	223 (88%)	0.21
Hypertension	115 (75%)	74 (74%)	189 (75%)	0.84
Diabetes	49 (32%)	36 (36%)	85 (34%)	0.51
Atrial Fibrillation	40 (26%)	39 (39%)	79 (31%)	0.03
Systolic blood pressure, mmHg	152.7 (20.8)	149.4 (26.2)	151.4 (23.1)	0.27
Median ASPECTS (IQR)	7 (5 - 10)	8 (7 - 10)	8 (5 - 10)	0.01
Time from last known well to first stimulation session, h	18.3 (14.7-22.4)	18.9 (14.4-22.5)	18.6 (14.6-22.4)	0.70

Table 63 Demographics and Baseline Characteristics in mITT Population

D3 - Primary Effectiveness Endpoint

Table 64 below shows the primary effectiveness endpoint of 90-day mRS analyzed using Sliding Dichotomy in the mITT population . There is no significant difference between the SPG stimulation and the sham groups in the primary effectiveness endpoint.

Outcome	SPG stim	Sham stim	Odds ratio (95% CI)	p-value
Sliding Dichotomy	76/153 (49.7%)	40/100 (40.0%)	1.48 (0.89-2.47)	0.13

Table 64 ImpACT-24 Primary Effectiveness Endpoint

D4- Effectiveness Analysis in Patients with Confirmed Cortical Involvement

Among the pre-specified baseline covariates, treatment interaction was observed only with stroke location, in patients with confirmed cortical involvement versus patients without confirmed cortical involvement. Therefore, a post-hoc analysis of the primary and secondary endpoint was performed in the CCI population (Table 65).

Outcome	SPG stim Favorable Outcome	Sham stim Favorable Outcome	Odds ratio (95% CI)	p-value
Sliding Dichotomy	25/50 (50.0%)	10/37 (27.0%)	2.70 (1.08-6.73)	0.03
Aphasia	16/25 (64.0%)	5/17 (29.4%)	4.27 (1.13-16.05)	0.03
Binary NIHSS	23/50 (46.0%)	9/36 (25.0%)	2.56 (1.00-6.52)	0.05
	SPG stim Mean (SD)	Sham stim Mean (SD)	Difference (95% CI)	p-value
SIS-16	43.6 (36.9)	31.9 (39.2)	11.7 (-4.6-28.0)	0.2

Table 65 Effectiveness in Patients with Confirmed Cortical Involvement

D5 – ImpACT-24A Stimulation-Related Non-Serious Adverse Events

The following table details the SOC and PT classification of all non-serious stimulation related events in ImpACT-24A. The table shows the number and percentage of patients having at least one event, followed by the number of events if it is different than the number of patients.

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
General disorders and administration site conditions	Pain	51 (25.2%); 72	8 (7.9%)
	Discomfort	3 (1.5%)	-
	Hyperthermia	1 (0.5%)	1 (1.0%)
	Lacrimation	1 (0.5%)	-
Nervous system disorders	Headache	8 (4.0%)	1 (1.0%)
	Paraesthesia	3 (1.5%)	-
	Subarachnoid haemorrhage	-	1 (1.0%)
	Neurological symptom	-	1 (1.0%)
	Localised numbness	1 (0.5%)	-
	Mastication disorder	1 (0.5%)	-
Injury, poisoning and procedural complications	Implant site pain	1 (0.5%)	1 (1.0%)
	Implant site numbness	-	1 (1.0%)
	Implant site reaction	1 (0.5%)	-
Vascular disorders	Epistaxis	-	1 (1.0%)
	Hypertensive crisis	1 (0.5%)	-
	Hypertension	1 (0.5%)	-
Psychiatric disorders	Agitation	1 (0.5%)	1 (1.0%)
Cardiac disorders	Bradycardia	1 (0.5%)	-
Gastrointestinal disorders	Salivary hypersecretion	1 (0.5%)	-
Musculoskeletal and connective tissue disorders	Muscle spasms	1 (0.5%)	-
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	-	1 (1.0%)

Table 66 Stimulation-Related Non-serious AEs by SOC/PT (ImpACT-24A)

D6 – ImpACT-24A Implantation-Related Frequent (>1%) Non-Serious Adverse Events

The following table details the SOC and PT classification of all non-serious implantation related or removal-related events in ImpACT-24A. Implantation was performed in ImpACT- 24A before randomization, therefore, the data are not divided by treatment arm.

SOC	PT	Events (%) N=303
Injury, poisoning and procedural complications	Implant site pain	14 (4.6%)
	Procedural pain	10 (3.3%)
	Complication of device removal	8 (2.6%)
	Implant site haemorrhage	7 (2.3%)
	Device migration	5 (1.7%)
	Implant site haematoma	1 (0.3%)
	Complication of device insertion	1 (0.3%)
	Implant site hemorrhage	2 (0.7%)
	Implant site nerve injury	1 (0.3%)
	Implant site reaction	1 (0.3%)
	Implant site bruising	1 (0.3%)
General disorders and administration site conditions	Pain	8 (2.6%)
	Hyperthermia	1 (0.3%)
	Discomfort	1 (0.3%)
	Wound secretion	1 (0.3%)
Gastrointestinal disorders	Mouth ulceration	1 (0.3%)
	Tooth fracture	1 (0.3%)
	Vomiting	1 (0.3%)
Psychiatric disorders	Agitation	2 (0.7%)
Respiratory, thoracic and mediastinal disorders	Hypoxia	1 (0.3%)
	Respiratory tract infection	1 (0.3%)
Vascular disorders	Melaena	1 (0.3%)
	Hypertension	1 (0.3%)
Cardiac disorders	Bradycardia	1 (0.3%)

Table 67 Implantation-Related Non-serious AEs by SOC/PT (ImpACT-24A)

D7 - ImpACT-24A Unrelated Serious Adverse Events

The following table details the SOC and PT classification of all SAEs in ImpACT-24A that were classified as

unrelated to the device or the procedure. The table shows the number and percentage of patients having at least one event, followed by the number of events if it is different than the number of patients.

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
Respiratory, thoracic and mediastinal disorders	Respiratory failure	2 (1.0%)	5 (5.0%)
	Pneumonia	6 (3.0%); 8	4 (4.0%); 5
	Pneumonia aspiration	3 (1.5%)	1 (1.0%)
	Status asthmaticus	-	1 (1.0%)
	Respiratory arrest	-	1 (1.0%)
	Respiratory tract infection	1 (0.5%)	-
Nervous system disorders	Cerebral infarction	7 (3.5%)	1 (1.0%)
	Stroke in evolution	4 (2.0%)	2 (2.0%)
	Status epilepticus	-	1 (1.0%)
	Transient ischaemic attack	1 (0.5%)	1 (1.0%)
	Haemorrhagic transformation stroke	2 (1.0%)	-
	Neurological symptom	-	1 (1.0%)
	Intracranial pressure increased	2 (1.0%)	-
	Brain stem stroke	-	1 (1.0%)
	Brain oedema	1 (0.5%)	1 (1.0%)
	Cerebellar infarction	1 (0.5%)	-
Cardiac disorders	Acute myocardial infarction	5 (2.5%)	1 (1.0%)
	Bradyarrhythmia	1 (0.5%)	1 (1.0%)
	Bradycardia	-	1 (1.0%)
	Atrial fibrillation	-	1 (1.0%)
	Cardio-respiratory arrest	2 (1.0%)	-
	Endocarditis enterococcal	-	1 (1.0%)
	Left ventricular dysfunction	1 (0.5%)	-
	Acute coronary syndrome	1 (0.5%)	-
	Angina unstable	1 (0.5%)	-
	Pulmonary oedema	1 (0.5%)	-
	Cardiac arrest	1 (0.5%)	-
Vascular disorders	Pulmonary embolism	4 (2.0%)	3 (3.0%)
	Hypertensive crisis	-	1 (1.0%)
	Gastrointestinal haemorrhage	-	1 (1.0%)
	Cardiovascular insufficiency	-	1 (1.0%)
	Haematoma muscle	-	1 (1.0%)
	Haematemesis	1 (0.5%)	-

	Hypovolaemic shock	1 (0.5%)	-
Gastrointestinal disorders	Gastroenteritis	-	1 (1.0%)
	Gastrointestinal obstruction	-	1 (1.0%)
	Diarrhoea infectious	1 (0.5%)	-
	Gastric varices haemorrhage	1 (0.5%); 2	-
	Gastritis	1 (0.5%)	-
Infections and infestations	Catheter sepsis	-	1 (1.0%)
	Escherichia bacteraemia	-	1 (1.0%)
	Staphylococcal sepsis	1 (0.5%)	-
	Pulmonary tuberculosis	1 (0.5%)	-
	Sepsis	1 (0.5%)	-
Injury, poisoning and procedural complications	Feeding tube complication	1 (0.5%)	-
	Drug toxicity	1 (0.5%)	-
	Vascular procedure complication	1 (0.5%)	-
	Fall	1 (0.5%)	-
Renal and urinary disorders	Urinary tract infection	1 (0.5%)	1 (1.0%)
	Renal failure	-	1 (1.0%)
	Renal impairment	1 (0.5%)	-
Surgical and medical procedures	Carotid endarterectomy	1 (0.5%)	2 (2.0%)
	Cholecystectomy	-	1 (1.0%)
Hepatobiliary disorders	Perihepatic abscess	-	1 (1.0%)
	Hepatic failure	1 (0.5%)	-
	Cholelithiasis	1 (0.5%)	-
Investigations	International normalised ratio increased	-	1 (1.0%)
	Biopsy prostate	1 (0.5%)	-
	Hepatic enzyme abnormal	1 (0.5%)	-
Psychiatric disorders	Depression	-	1 (1.0%)
	Delirium	1 (0.5%)	-
	Confusional state	1 (0.5%)	-
General disorders and administration site conditions	Sudden death	1 (0.5%)	-
	Death	1 (0.5%)	-
Metabolism and nutrition disorders	Hypercalcaemia	1 (0.5%)	-
	Hypoglycemia	1 (0.5%)	-
Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain	-	1 (1.0%)
	Femur fracture	1 (0.5%)	-
Blood and lymphatic system disorders	Splenic infarction	1 (0.5%)	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastatic neoplasm	1 (0.5%)	-
Skin and subcutaneous tissue disorders	Skin ulcer	1 (0.5%)	-

Table 68 Unrelated Serious AEs by SOC/PT (ImpACT-24A)

D8 - ImpACT-24A Unrelated Non-Serious Adverse Events

The following table details the SOC and PT classification of all non-serious events in ImpACT-24A that were classified as unrelated to the device or the procedure. The table shows the number and percentage of patients having at least one event, followed by the number of events if it is different than the number of patients.

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
Gastrointestinal disorders	Constipation	38 (18.8%); 42	15 (14.9%)
	Vomiting	11 (5.4%)	2 (2.0%)
	Nausea	9 (4.5%)	4 (4.0%)
	Diarrhea	7 (3.5%)	2 (2.0%)
	Diarrhoea	3 (1.5%)	2 (2.0%)
	Dysphagia	-	2 (2.0%)
	Gastrointestinal infection	-	2 (2.0%)
	Gastroenteritis	2 (1.0%)	-
	Gastrooesophageal reflux disease	2 (1.0%)	-
	Anal fissure	-	1 (1.0%)
	Dyspepsia	2 (1.0%)	1 (1.0%)
	Clostridium difficile colitis	1 (0.5%); 2	1 (1.0%)
	Enteritis infectious	2 (1.0%)	-
	Oral disorder	-	1 (1.0%)
	Rectal haemorrhage	-	1 (1.0%)
	Abdominal distension	2 (1.0%)	-
	Hiccups	-	1 (1.0%); 3
	Faecaloma	2 (1.0%)	-
	Abdominal pain	-	1 (1.0%); 2
	Gastritis	1 (0.5%)	-
	Salivary hypersecretion	1 (0.5%)	-
	Enteritis	1 (0.5%)	-
	Clostridium colitis	1 (0.5%)	-
	Duodenal ulcer	1 (0.5%)	-
	Hiatus hernia	1 (0.5%)	-
	Ascites	1 (0.5%)	-
	Tooth fracture	1 (0.5%)	-
	Haematochezia	1 (0.5%)	-
	Gingival infection	1 (0.5%)	-
	Gingival ulceration	1 (0.5%)	-
	Mouth ulceration	1 (0.5%)	-
	Gastrointestinal haemorrhage	1 (0.5%)	-
	Gingival pain	1 (0.5%)	-
	Glossodynia	1 (0.5%)	-

Psychiatric disorders	Depression	32 (15.8%); 33	15 (14.9%)
	Agitation	13 (6.4%); 17	11 (10.9%)
	Insomnia	22 (10.9%); 23	9 (8.9%)
	Sleep disorder	8 (4.0%)	4 (4.0%)
	Delirium	2 (1.0%)	2 (2.0%)
	Mental disorder due to a general medical condition	2 (1.0%)	-
	Anxiety	2 (1.0%)	1 (1.0%)
	Vascular dementia	2 (1.0%)	1 (1.0%)
	Hallucination	2 (1.0%)	-
	Panic attack	-	1 (1.0%)
	Disorientation	1 (0.5%)	-
	Dementia alzheimer's type	1 (0.5%)	-
	Adjustment disorder	1 (0.5%)	-
	Lethargy	1 (0.5%)	-
	Confusional state	1 (0.5%)	-
Metabolism and nutrition disorders	Hypokalaemia	26 (12.9%); 30	10 (9.9%); 11
	Diabetes mellitus	3 (1.5%)	4 (4.0%)
	Hyponatraemia	4 (2.0%); 5	3 (3.0%)
	Hyperglycaemia	6 (3.0%); 7	-
	Hypercholesterolaemia	2 (1.0%)	3 (3.0%)
	Gouty arthritis	5 (2.5%)	-
	Hypokalemia	4 (2.0%)	-
	Hyperlipidaemia	4 (2.0%)	1 (1.0%)
	Glucose tolerance impaired	2 (1.0%)	2 (2.0%)
	Hyperhomocysteinaemia	1 (0.5%)	2 (2.0%)
	Hypomagnesaemia	2 (1.0%)	2 (2.0%)
	Hyperuricaemia	2 (1.0%)	-
	Hyperlipidemia	2 (1.0%)	1 (1.0%)
	Underweight	-	1 (1.0%)
	Gout	1 (0.5%)	1 (1.0%)
	Hypervolaemia	-	1 (1.0%)
	Vitamin b12 deficiency	2 (1.0%)	-
	Dehydration	1 (0.5%)	1 (1.0%)
	Hyperglycemia	2 (1.0%)	-
	Hypertriglyceridaemia	-	1 (1.0%)
	Hypoglycaemia	1 (0.5%)	1 (1.0%)
	Hypomagnesemia	1 (0.5%)	1 (1.0%)
	Hypocalcaemia	-	1 (1.0%)
	Hypoalbuminaemia	-	1 (1.0%)
	Hyperkalaemia	1 (0.5%)	-
	Dyslipidaemia	1 (0.5%)	-

	Hypernatraemia	1 (0.5%)	-
	Hypophosphataemia	1 (0.5%)	-
Nervous system disorders	Headache	14 (6.9%)	11 (10.9%); 12
	Asymptomatic hemorrhagic transformation stroke	1 (0.5%)	3 (3.0%)
	Stroke in evolution	5 (2.5%)	1 (1.0%)
	Muscle spasticity	5 (2.5%)	1 (1.0%)
	Neurological symptom	5 (2.5%)	2 (2.0%); 3
	Neuralgia	4 (2.0%)	1 (1.0%)
	Partial seizures	4 (2.0%)	1 (1.0%)
	Somnolence	2 (1.0%); 4	2 (2.0%)
	Epilepsy	3 (1.5%)	1 (1.0%)
	Cerebral infarction	2 (1.0%)	1 (1.0%)
	Syncope	2 (1.0%)	-
	Dysphonia	-	1 (1.0%)
	Central pain syndrome	2 (1.0%)	-
	Myoclonus	-	1 (1.0%)
	Convulsion	2 (1.0%)	-
	Brain oedema	2 (1.0%)	-
	Sedation	-	1 (1.0%)
	Dizziness	2 (1.0%)	-
	Allodynia	1 (0.5%)	1 (1.0%)
	Status epilepticus	1 (0.5%)	-
	Carpal tunnel syndrome	1 (0.5%)	-
	Sleep apnoea syndrome	1 (0.5%)	-
	Ependymitis	1 (0.5%)	-
	Basal ganglia infarction	1 (0.5%)	-
	Parkinsonism	1 (0.5%)	-
	Polyneuropathy	1 (0.5%)	-
	Tremor	1 (0.5%)	-
	Haemorrhagic transformation stroke	1 (0.5%)	-
	Partial seizure	1 (0.5%)	-
	Complex partial seizures	1 (0.5%)	-
	Trigeminal neuralgia	1 (0.5%)	-
	Confusional state	1 (0.5%)	-
	Hypoaesthesia	1 (0.5%); 2	-
Renal and urinary disorders	Urinary tract infection	30 (14.9%); 36	20 (19.8%); 24
	Urinary retention	6 (3.0%)	4 (4.0%)

	Haematuria	3 (1.5%)	3 (3.0%)
	Urinary incontinence	2 (1.0%)	2 (2.0%)
	Renal impairment	3 (1.5%); 4	-
	Oliguria	2 (1.0%)	-
	Incontinence	2 (1.0%)	-
	Bladder pain	-	1 (1.0%)
	Renal failure acute	2 (1.0%)	-
	Renal failure	1 (0.5%)	-
	Proteinuria	1 (0.5%)	-
General disorders and administration site conditions	Hyperthermia	29 (14.4%); 33	13 (12.9%); 14
	Pain	8 (4.0%); 9	3 (3.0%); 4
	Chest pain	2 (1.0%)	2 (2.0%)
	Oedema peripheral	3 (1.5%)	-
	Limb pain	2 (1.0%)	1 (1.0%)
	Fatigue	2 (1.0%)	-
	Pyrexia	-	1 (1.0%); 2
	Pain localised	1 (0.5%)	-
	Gait disturbance	1 (0.5%)	-
	Hyperpyrexia	1 (0.5%)	-
	Chest discomfort	1 (0.5%)	-
	Inflammation	1 (0.5%)	-
Respiratory, thoracic and mediastinal disorders	Pneumonia	11 (5.4%); 12	7 (6.9%)
	Respiratory tract infection	5 (2.5%)	7 (6.9%)
	Pneumonia aspiration	4 (2.0%)	3 (3.0%)
	Dyspnoea	4 (2.0%)	3 (3.0%)
	Upper respiratory tract infection	1 (0.5%)	1 (1.0%)
	Pleural effusion	2 (1.0%)	-
	Aspiration	-	1 (1.0%)
	Hypoxia	-	1 (1.0%)
	Cough	2 (1.0%)	1 (1.0%)
	Chronic obstructive pulmonary disease	1 (0.5%)	-
	Throat pain	1 (0.5%)	-
	Lung infiltration	1 (0.5%)	-
	Bronchospasm	1 (0.5%)	-
	Upper respiratory infection	1 (0.5%)	-
	Rhinorrhoea	1 (0.5%)	-
	Pharyngolaryngeal pain	1 (0.5%)	-
	Throat irritation	1 (0.5%)	-
	Bronchitis	1 (0.5%)	-
	Wheezing	1 (0.5%)	-

Vascular disorders	Hypertension	13 (6.4%); 15	9 (8.9%); 10
	Hypotension	7 (3.5%)	2 (2.0%)
	Hypertensive crisis	1 (0.5%)	3 (3.0%)
	Deep vein thrombosis	3 (1.5%)	1 (1.0%)
	Carotid artery stenosis	2 (1.0%)	-
	Peripheral arterial occlusive disease	2 (1.0%)	-
	Hypovolaemic shock	-	1 (1.0%)
	Haematoma	-	1 (1.0%)
	Thrombophlebitis superficial	1 (0.5%)	-
	Portal hypertension	1 (0.5%)	-
	Venous thrombosis	1 (0.5%)	-
	Myocardial ischaemia	1 (0.5%)	-
	Peripheral embolism	1 (0.5%)	-
	Gastrointestinal haemorrhage	1 (0.5%)	-
	Contusion	1 (0.5%)	-
	Haemorrhoids	1 (0.5%)	-
	Orthostatic hypotension	1 (0.5%); 2	-
	Pulmonary embolism	1 (0.5%)	-
Cardiac disorders	Atrial fibrillation	16 (7.9%)	5 (5.0%); 7
	Tachycardia	2 (1.0%)	3 (3.0%)
	Oedema peripheral	5 (2.5%)	-
	Bradycardia	3 (1.5%); 5	2 (2.0%)
	Aortic valve calcification	-	1 (1.0%)
	Cardiac failure	2 (1.0%)	1 (1.0%)
	Chest pain	2 (1.0%); 3	-
	Acute myocardial infarction	-	1 (1.0%)
	Supraventricular tachyarrhythmia	-	1 (1.0%)
	Ventricular extrasystoles	-	1 (1.0%)
	Left ventricular hypertrophy	1 (0.5%)	-
	Angina pectoris	1 (0.5%)	-
	Atrial tachycardia	1 (0.5%)	-
	Acute coronary syndrome	1 (0.5%)	-
	Atrial septal defect	1 (0.5%)	-
	Atrioventricular block	1 (0.5%)	-
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	9 (4.5%)	5 (5.0%)
	Back pain	3 (1.5%)	3 (3.0%)
	Myalgia	3 (1.5%)	-
	Arthralgia	2 (1.0%)	-
	Arthritis	2 (1.0%)	-
	Pain in extremity	2 (1.0%)	-
	Muscular weakness	-	1 (1.0%)

	Muscle spasms	1 (0.5%)	1 (1.0%)
	Contusion	1 (0.5%)	-
	Joint dislocation	1 (0.5%)	-
	Soft tissue necrosis	1 (0.5%)	-
	Joint swelling	1 (0.5%)	-
	Musculoskeletal chest pain	1 (0.5%)	-
Infections and infestations	Staphylococcal infection	-	2 (2.0%)
	Candidiasis	3 (1.5%)	1 (1.0%)
	Oral candidiasis	3 (1.5%)	1 (1.0%)
	Influenza	3 (1.5%)	-
	Infection	-	1 (1.0%)
	Skin candida	-	1 (1.0%)
	Candiduria	-	1 (1.0%)
	Oral fungal infection	2 (1.0%)	-
	Viral infection	1 (0.5%)	-
	Peritonitis bacterial	1 (0.5%)	-
	Urinary tract infection enterococcal	1 (0.5%)	-
	Tonsillitis	1 (0.5%)	-
	Oropharyngeal candidiasis	1 (0.5%)	-
	Skin structures and soft tissue infections	1 (0.5%)	-
	Catheter related infection	1 (0.5%)	-
	Post herpetic neuralgia	1 (0.5%)	-
	Herpes zoster	1 (0.5%)	-
	Fungal infection	1 (0.5%)	-
Skin and subcutaneous tissue disorders	Rash	-	3 (3.0%)
	Pruritus	1 (0.5%)	3 (3.0%)
	Dermatitis	-	1 (1.0%)
	Rash erythematous	1 (0.5%)	1 (1.0%)
	Decubitus ulcer	1 (0.5%)	1 (1.0%)
	Cellulitis	-	1 (1.0%)
	Dermatitis allergic	-	1 (1.0%)
	Itching	2 (1.0%)	-
	Skin laceration	1 (0.5%)	-
	Vitiligo	1 (0.5%)	-
	Erythema	1 (0.5%)	-
	Penile ulceration	1 (0.5%)	-
	Purpura	1 (0.5%)	-
	Eczema	1 (0.5%)	-
Investigations	Echocardiogram abnormal	1 (0.5%)	1 (1.0%)
	Methicillin-resistant staphylococcal aureus test	-	1 (1.0%)

	C-reactive protein increased	1 (0.5%)	1 (1.0%)
	Cardioactive drug level increased	-	1 (1.0%)
	Angiogram	1 (0.5%)	-
	Hepatic enzyme abnormal	1 (0.5%)	-
	Endoscopy gastrointestinal abnormal	1 (0.5%)	-
	Blood creatine phosphokinase increased	1 (0.5%)	-
	Prostatic specific antigen increased	1 (0.5%)	-
	Liver function test abnormal	1 (0.5%)	-
	White blood cell count increased	1 (0.5%)	-
Injury, poisoning and procedural complications	Fall	1 (0.5%)	1 (1.0%)
	Skin laceration	-	1 (1.0%)
	Soft tissue injury	2 (1.0%)	-
	Skin injury	1 (0.5%)	1 (1.0%)
	Vascular procedure complication	1 (0.5%)	-
	Drug toxicity	1 (0.5%)	-
Blood and lymphatic system disorders	Anaemia	1 (0.5%)	2 (2.0%)
	Anaemia macrocytic	-	1 (1.0%)
	Leukocytosis	-	1 (1.0%)
	Lymphoma	1 (0.5%)	-
Endocrine disorders	Hypoglycaemia	2 (1.0%)	-
	Hypothyroidism	2 (1.0%)	-
	Diabetic ketoacidosis	-	1 (1.0%)
	Hyperthyroidism	1 (0.5%)	-
Eye disorders	Conjunctivitis	-	2 (2.0%)
	Glaucoma	1 (0.5%)	-
	Dry eye	1 (0.5%)	-
	Vision blurred	1 (0.5%)	-
Immune system disorders	Drug hypersensitivity	2 (1.0%)	1 (1.0%)
	Allergy to chemicals	1 (0.5%)	-
	Rhinitis allergic	1 (0.5%)	-
Reproductive system and breast disorders	Benign prostatic hyperplasia	-	1 (1.0%)
	Vaginal infection	-	1 (1.0%)
	Prostatomegaly	1 (0.5%)	-
	Scrotal infection	1 (0.5%)	-
Surgical and medical procedures	Gastrointestinal tube insertion	-	2 (2.0%)
Hepatobiliary disorders	Hepatic infarction	1 (0.5%)	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to bone	1 (0.5%)	-

Table 69 Unrelated Non-serious AEs by SOC/PT (ImpACT-24A)

Appendix E – ImpACT-24B Additional Methods

E1- Blinding Principles

The study was designed to maintain blinding, based on the following principles:

1) Regardless of actual allocation, all patients received active/sham stimulation sessions, including or mimicking active treatment.
2) The primary endpoint assessment was done by dedicated on-site (local) outcome assessors, masked to treatment group assignment, who were not involved in the implantation.
3) The assessment done by the Local Assessor was recorded on video. This video was reviewed by an off-site blinded Central Assessor, who made an independent mRS assessment.
4) Questionnaires asked the patient and the Local Assessor whether they believed that the patient was treated. Answers to these questionnaires are used to estimate the blinding quality of the trial.

E2 - Analysis of Patient Blinding

The sponsor stated that the patient blinding questionnaire, administered on day 5, asked the patient if he/she believed he/she received active treatment. Patients who were unable to answer (for example, patients in coma or patients with global aphasia) are excluded from this analysis. Patients able to respond could choose one of 3 answers:

- "I think the treatment I received was an actual treatment" (in short, “treated”)
- "I think the treatment I received was a sham treatment" (in short, “sham”)
- "I don't know" (in short, “Don't know”)

$$Pt\_Blinding(i) = \begin{cases} 1, Incorrect\ \boldsymbol{OR} \\ Don't\ Know\ \boldsymbol{OR} \\ Treated \\ \\ 0,\ Otherwise \end{cases}$$

At the study level, the blinding of patients is adequate if:

$$l_p < \frac{100}{N} \sum_{i=1}^{N} Pt\_Blinding(i)$$

Where: lp = 90% (success threshold) and N is the number of patients who answered the questionnaire.

E3 - Analysis of Assessor Blinding

Patient outcome was assessed by blinded Local Assessors (LA) and by blinded Central Assessors (CA).

The Local Assessor's questionnaire, administered at the last follow-up visit (at day 90), asked the Local Assessor if he/she believed the patient had received the treatment. Local Assessors could choose one of 3 answers:

1. "I think that this patient received actual treatment" (in short, “treated”)
2. "I think that this patient received sham treatment" (in short, “sham”)
3. "I don't know" (in short, “Don't know”)

$$Assessor\_Blinding(i) = \begin{cases} 1, & Incorrect\ \boldsymbol{OR} \\ & Don't\ Know\ \boldsymbol{OR} \\ & mRS(LA) = mRS(CA) \\ 0, & Otherwise \end{cases}$$

Where mRS(LA) and mRS(CA) are the mRS scores estimated by the Local Assessor and Central Assessor, respectively.

At the study level, the blinding of the local assessors is adequate if:

$$l_{LA} < \frac{100}{M} \sum_{i=1}^{M} LA\_Blinding(i)$$

Where: lLA = 90% (success threshold) and M is the number of patients for which both a local assessment and a central assessment are available.

E4- Interim Analyses – Blinding

Interim Analyses were performed by an External Statistician. The conclusions (futility and/or sample size recommendations) were communicated to the Sponsor and DSMB, in accordance with the SAP. Additional Effectiveness results per DSMB request were sent directly from the External Statistician to the DSMB, maintaining Sponsor blinding. The DSMB documented its review in two separate letters, an open letter which contained recommendations with regards to continuation of the study, and a closed letter which contained their risk-benefit assessment. The sponsor, investigators, and steering committee were not exposed to the closed letter.

E5 - Blood Flow Measurements During Stimulation Sessions

The protocol restricted blood flow measurements such as Common Carotid Artery Doppler (CCAD) or Trans Cranial Doppler (TCD)) during SPG stimulation because it could result in un-blinding of the patients’ treatment allocation. Therefore, these examinations should not be performed during stimulation sessions.

The protocol allowed the tests in cases where such measurements are urgently called for as part of a patient's' assessment and care according to accepted clinical practice guidelines. In this case, the protocol states that stimulation should be stopped before the examination and resumed subsequently.

E6 - Treatment of Acute Ischemic Stroke

The protocol required that during all study periods, investigators treat AIS in accordance with the general management of ischemic stroke and secondary prevention, following the guidelines of the Stroke Association or the European Stroke Organization (ESO), including the use of antiplatelets, management of secondary stroke, dyslipidemia, hypertension, diabetes and counseling regarding smoking cessation. The protocol forbid off-label uses of drugs and devices.

E7 - Concomitant Treatment

All concomitant medications/therapies administered during the study are to be recorded in the appropriate CRF page.

With the exception of the listed medications below, the protocol did not restrict the use of concomitant medications. In the protocol,

d. Anticoagulation agents are not recommended prior to implantation unless implantation is delayed and anticoagulation therapy is indicated by accepted clinical practice guidelines. In such cases, bleeding propensity should be re-assessed prior to implantation. Patients could not be enrolled if INR was > 1.8 or PTT ≥ 45 sec. Following completion of implantation, administration of anticoagulant agents was allowed.
e. In case mechanical thrombectomy was indicated for the patient's well-being, SPG stimulation treatment was to be stopped and not resumed.
f. The use of contraceptive hormones was prohibited during all study periods.
g. Scopolamine was not allowed to be used during the five (5) treatment days because a centrally acting anti-cholinergic drug may interfere with the hypothesized parasympathetic mechanism of action of SPG stimulation.
h. Investigational and off-label use of medication/therapy was prohibited during the study.

As part of the implantation procedure, the following drugs were applied:

i. Single dose of prophylactic antibiotics prior to the procedure
j. Local anesthesia
k. If the patient was agitated, intravenous anxiolytic agents were administrated

These drugs are not expected to affect the clinical outcome of the patient as they were administered in small doses during the first few hours after enrolment and the clinical outcome was measured 90 days afterwards.

Appendix F - ImpACT-24B Additional Results

F1 - Overall Baseline Characteristics

Table below shows the overall baseline characertics of the SPG and Sham groups in the mITT and CCI populations.

	mITT Population			CCI Population		
	SPG Group	Sham Group	p-value	SPG Group	Sham Group	p-value
N	481	519		244	276	
Median age, years (IQR)	70 (62, 77)	71 (63, 77)	0.34	70 (63, 77)	72 (64, 77)	0.22
Sex (female)	49.5%	52.2%	0.42	48.4%	48.9%	0.97
Median NIHSS (IQR)	12 (9, 14)	12 (9, 14)	0.73	13 (12, 15)	13 (11, 15)	0.65
Stroke side (left brain)	56.5%	50.1%	0.05	57.4%	52.2%	0.27
Pre-stroke mRS = 0*	91.5%	94.4%	0.09	91.4%	93.8%	0.37
Hypertension**	87.1%	84.4%	0.26	87.3%	85.1%	0.56
Diabetes**	23.7%	27.4%	0.21	22.1%	23.9%	0.71
Atrial Fibrillation**	24.7%	26.0%	0.70	33.6%	30.8%	0.56
Smoking**	10.2%	8.7%	0.48	9.0%	9.4%	0.99
Alcohol**	2.3%	3.9%	0.21	2.9%	4.3%	0.51
Obesity**	5.6%	4.6%	0.57	6.1%	3.6%	0.26
Systolic Blood Pressure, mean (SD)	148.1 (18.6)	148.7 (18.3)	0.60	148.2 (18.0)	148.9 (18.5)	0.66
Diastolic Blood Pressure, mean (SD)	82.7 (11.3)	82.9 (11.9)	0.78	83.2 (11.6)	83.3 (11.3)	0.97
Heart Rate, mean (SD)	77.7 (13.5)	78.2 (13.5)	0.52	78.0 (15.1)	79.2 (14.2)	0.36
INR, mean (SD)	1.1 (0.2)	1.0 (0.1)	0.14	1.1 (0.2)	1.0 (0.1)	0.05
aPTT, mean (SD)	29.0 (6.8)	28.6 (6.9)	0.45	29.2 (6.7)	27.8 (6.4)	0.03
Glucose, mean (SD)	135.3 (49.7)	134.3 (46.7)	0.74	135.2 (51.2)	134.5 (42.7)	0.87
Pre-Stroke Residence (home without assistance)	97.7%	98.8%	0.25	97.5%	98.6%	0.60
Median ASPECTS (IQR)	7 (6, 9)	7 (6, 9)	0.98	7 (5, 8)	7 (5, 8)	0.49
Median time from LKW to 1st stim, hrs (IQR)	19.9 (16.0, 22.6)	18.7 (15.7, 21.8)	0.003	19.7 (15.8, 22.5)	18.5 (15.5, 21.1)	0.04
Median time from LKW to rand., hrs (IQR)	16.7 (13.4, 20.2)	16.6 (13.7, 19.9)	0.66	16.3 (13.2, 19.5)	16.4 (13.6, 19.2)	1.00

*All other patients had pre-stroke mRS =1, except one patient recruited with a pre-stroke mRS = 2 (protocol deviation)
** Medical history data are based on automatic parsing a free-text medical history field in the eCRF
***P-values for continuous variables obtained via t-tests for comparison of means and a median test for comparison of medians. Categorical data compared via Chi-square tests (continuity corrected).

Table 70 Demographics and Baseline Characteristics

F2 - Baseline Characteristics – mITT VS. non-mITT

Table 71 shows the baseline patient characteristics among patients allocated to active SPG Stimulation who: A) received stimulation and entered the mITT Population, vs. B) did not receive stimulation and did not enter

the mITT population, constituting the non-mITT population. Among patients allocated to sham stimulation, there were too few (4/523) who did not enter the mITT population for informative statistical comparison of mITT vs. non-mITT patients.

Patients in both groups had similar baseline characteristics.

	All Patients Allocated to SPG Stimulation			CCI Patients Allocated to SPG Stimulation		
	mITT	Non-mITT	All	mITT	Non-mITT	All
N	481	74	555	244	34	278
Median age, years (IQR)	70 (62, 77)	73 (62, 79)	70 (62, 77)	70 (63, 77)	74 (66, 79)	71 (64, 78)
Sex (female)	49.5%	49.3%	49.5%	48.4%	50.0%	48.6%
Median NIHSS (IQR)	12 (9, 14)	12 (10, 15)	12 (9, 14)	13 (12, 15)	14 (12, 16)	13 (12, 15)
Stroke side (left brain)	56.5%	46.6%	55.2%	57.4%	47.1%	56.1%
Pre-stroke mRS = 0*	91.5%	91.7%	91.5%	91.4%	94.1%	91.7%
Hypertension**	87.1%	62.2%	83.8%	87.3%	64.7%	84.5%
Diabetes**	23.7%	18.9%	23.1%	22.1%	17.6%	21.6%
Atrial Fibrillation**	24.7%	31.1%	25.6%	33.6%	38.2%	34.2%
Smoking**	10.2%	13.5%	10.6%	9.0%	14.7%	9.7%
Alcohol**	2.3%	5.4%	2.7%	2.9%	2.9%	2.9%
Obesity**	5.6%	6.8%	5.8%	6.1%	5.9%	6.1%
Systolic Blood Pressure, mean (SD)	148.1 (18.6)	153.2 (19.1)	148.7 (18.7)	148.2 (18.0)	152.8 (22.8)	148.7 (18.7)
Diastolic Blood Pressure, mean (SD)	82.7 (11.3)	85.6 (10.5)	83.1 (11.2)	83.2 (11.6)	84.0 (11.4)	83.3 (11.6)
Heart Rate, mean (SD)	77.7 (13.5)	79.7 (12.5)	77.9 (13.4)	78.0 (15.1)	81.0 (12.6)	78.4 (14.8)
INR, mean (SD)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
aPTT, mean (SD)	29.0 (6.8)	27.8 (7.0)	28.9 (6.8)	29.2 (6.7)	28.2 (5.5)	29.1 (6.6)
Glucose, mean (SD)	135.3 (49.7)	133.8 (44.2)	135.1 (49.0)	135.2 (51.2)	137.7 (46.7)	135.5 (50.6)
Pre-Stroke Residence (home without assistance)	97.7%	95.9%	97.5%	97.5%	97.1%	97.5%
Median ASPECTS (IQR)	7 (6, 9)	7 (5, 8)	7 (6, 9)	7 (5, 8)	7 (5, 7)	7 (5, 8)
Median time from LKW to rand., hrs (IQR)	16.7 (13.4, 20.2)	14.9 (11.9, 18.8)	16.4 (13.3, 20.0)	16.3 (13.2, 19.5)	15.4 (13.3, 18.3)	16.2 (13.3, 19.3)
*All other patients had pre-stroke mRS =1, except one patient recruited with a pre-stroke mRS = 2 (protocol deviation) **Medical history data are based on automatic parsing a free-text medical history field in the eCRF						

Table 72 mITT vs. non-mITT Demographics and Baseline

F3 - Baseline Characteristics in the CCI and the non-CCI mITT Populations

Table 73 CCI and non-CCI populations Demographics and Baselineshows the baseline patient characteristics in the CCI and the non-CCI mITT populations.

	CCI Population			non-CCI Population		
	SPG Group	Sham Group	All	SPG Group	Sham Group	All
N	244	276	520	237	243	480
Median age, years (IQR)	70 (63, 77)	72 (64, 77)	71 (64, 77)	70 (61, 77)	69 (62, 76)	69 (62, 76)
Sex (female)	48.4%	48.9%	48.7%	50.6%	56.0%	53.3%
Median NIHSS (IQR)	13 (12, 15)	13 (11, 15)	13 (11, 15)	9 (8, 12)	9 (8, 12)	9 (8, 12)
Stroke side (left brain)	57.4%	52.2%	54.6%	55.7%	47.7%	51.7%
Pre-stroke mRS = 0*	91.4%	93.8%	92.7%	91.6%	95.1%	93.3%
Hypertension**	87.3%	85.1%	86.2%	86.9%	83.5%	85.2%
Diabetes**	22.1%	23.9%	23.1%	25.3%	31.3%	28.3%
Atrial Fibrillation**	33.6%	30.8%	32.1%	15.6%	20.6%	18.1%
Smoking**	9.0%	9.4%	9.2%	11.4%	7.8%	9.6%
Alcohol**	2.9%	4.3%	3.7%	1.7%	3.3%	2.5%
Obesity**	6.1%	3.6%	4.8%	5.1%	5.8%	5.4%
Systolic Blood Pressure, mean (SD)	148.2 (18.0)	148.9 (18.5)	148.6 (18.3)	147.9 (19.2)	148.4 (18.0)	148.2 (18.6)
Diastolic Blood Pressure, mean (SD)	83.2 (11.6)	83.3 (11.3)	83.2 (11.5)	82.2 (10.9)	82.6 (12.6)	82.4 (11.7)
Heart Rate, mean (SD)	78.0 (15.1)	79.2 (14.2)	78.7 (14.6)	77.3 (11.7)	77.1 (12.7)	77.2 (12.2)
INR, mean (SD)	1.1 (0.2)	1.0 (0.1)	1.1 (0.1)	1.1 (0.1)	1.1 (0.2)	1.1 (0.2)
aPTT, mean (SD)	29.2 (6.7)	27.8 (6.4)	28.5 (6.6)	28.8 (6.9)	29.5 (7.3)	29.1 (7.1)
Glucose, mean (SD)	135.2 (51.2)	134.5 (42.7)	134.8 (46.9)	135.4 (48.3)	134.1 (51.0)	134.7 (49.6)
Pre-Stroke Residence (home without assistance)	97.5%	98.6%	98.1%	97.9%	99.2%	98.5%
Median ASPECTS (IQR)	7 (5, 8)	7 (5, 8)	7 (5, 8)	8 (7, 9)	9 (7, 9)	8 (7, 9)
Median time from LKW to 1st stim, hrs (IQR)	19.7 (15.8, 22.5)	18.5 (15.5, 21.1)	19.2 (15.6, 21.7)	20.5 (16.2, 22.9)	19.1 (16.0, 22.3)	19.5 (16.1, 22.5)
Median time from LKW to rand., hrs (IQR)	16.3 (13.2, 19.5)	16.4 (13.6, 19.2)	16.3 (13.5, 19.4)	17.3 (13.5, 20.6)	16.8 (13.8, 20.5)	17.0 (13.7, 20.5)

*All other patients had pre-stroke mRS =1, except one patient recruited with a pre-stroke mRS = 2 (protocol deviation)
**Medical history data are based on automatic parsing a free-text medical history field in the eCRF

Table 73 CCI and non-CCI populations Demographics and Baseline

F4 - Baseline Characteristics – Per Protocol and Safety Analysis populations

Table below shows per protocol and safety populations demographics and baseline

	Per Protocol (PP) Population			Safety Population		
	SPG Group	Sham Group	All	SPG Group	Sham Group	All
N	417	481	898	536	519	1055
Median age, years (IQR)	70 (62, 77)	71 (63, 77)	70 (63, 77)	70 (62, 77)	71 (63, 77)	71 (63, 77)
Sex (female)	50.4%	51.1%	50.8%	49.6%	52.2%	50.9%
Median NIHSS (IQR)	11 (9, 14)	12 (9, 14)	11 (9, 14)	12 (9, 14)	12 (9, 14)	12 (9, 14)
Stroke side (left brain)	56.4%	50.3%	53.1%	55.4%	50.1%	52.8%
Pre-stroke mRS = 0*	90.9%	94.6%	92.9%	91.8%	94.4%	93.1%
Hypertension**	85.6%	84.2%	84.9%	85.3%	84.4%	84.8%
Diabetes**	24.2%	28.3%	26.4%	22.9%	27.4%	25.1%
Atrial Fibrillation**	24.7%	25.8%	25.3%	25.6%	26.0%	25.8%
Smoking**	10.8%	8.9%	9.8%	10.6%	8.7%	9.7%
Alcohol**	2.2%	4.2%	3.2%	2.8%	3.9%	3.3%
Obesity**	6.2%	4.8%	5.5%	5.6%	4.6%	5.1%
Systolic Blood Pressure, mean (SD)	148.3 (18.5)	148.6 (18.0)	148.5 (18.2)	148.7 (18.9)	148.7 (18.3)	148.7 (18.6)
Diastolic Blood Pressure, mean (SD)	82.7 (11.3)	83.1 (11.8)	82.9 (11.6)	83.1 (11.2)	82.9 (11.9)	83.0 (11.6)
Heart Rate, mean (SD)	77.9 (13.5)	78.3 (13.5)	78.1 (13.5)	78.0 (13.4)	78.2 (13.5)	78.1 (13.4)
INR, mean (SD)	1.1 (0.2)	1.0 (0.1)	1.1 (0.2)	1.1 (0.2)	1.0 (0.1)	1.1 (0.2)
aPTT, mean (SD)	28.6 (6.5)	28.4 (6.8)	28.5 (6.7)	28.9 (6.9)	28.6 (6.9)	28.7 (6.9)
Glucose, mean (SD)	135.4 (49.9)	134.9 (47.9)	135.1 (48.8)	135.1 (48.9)	134.3 (46.7)	134.7 (47.8)
Pre-Stroke Residence (home without assistance)	97.4%	98.8%	98.1%	97.6%	98.8%	98.2%
Median ASPECTS (IQR)	8 (6, 9)	8 (6, 9)	8 (6, 9)	7 (6, 9)	7 (6, 9)	7 (6, 9)
Median time from LKW to 1st stim, hrs (IQR)	20.0 (16.2, 22.7)	18.5 (15.5, 21.8)	19.3 (15.8, 22.3)	19.9 (16.0, 22.6)	18.7 (15.7, 21.8)	19.3 (15.9, 22.2)
Median time from LKW to rand., hrs (IQR)	16.8 (13.5, 20.4)	16.5 (13.6, 19.9)	16.6 (13.5, 20.1)	16.4 (13.4, 19.9)	16.6 (13.7, 19.9)	16.5 (13.5, 19.9)
*All other patients had pre-stroke mRS =1, except one patient recruited with a pre-stroke mRS = 2 (protocol deviation) **Medical history data are based on automatic parsing a free-text medical history field in the eCRF						

Table 74 Per Protocol and Safety Populations Demographics and Baseline

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