Sponsor's Executive Summary

Ischemic Stroke System (ISS)

PMA(b) (4)

Neurological Devices Panel

of the

Medical Devices Advisory Committee

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List of Abbreviations:

AE	Adverse Event
AFIB	Atrial Fibrillation
AIC	Akaike Information Criterion
AIS	Acute Ischemic Strokes
aPTT	Activated Partial Thromboplastic time
ARR	Absolute Risk Reduction
ASIC	Application Specific Integrated Circuit
ASPECTS	Alberta Stroke Program Early CT Score
BA	Blinded Assessor
BBB	Blood-Brain-Barrier
CA	Central Assessors
CBF	Cerebral Blood Flow
CCA	Common Carotid Artery
CCD	Common Carotid Doppler
CCI	Confirmed Cortical Involvement
CI	Confidence Interval
CONSORT	Consolidated Standards for the Reporting of Trials
CT	Computed Tomography
CTA	CT Angiography
CTL	Comfortable Tolerance Level
CTP	CT Perfusion
DSMB	Data & Safety Monitoring Board
DWI-MRI	Diffusion Weighted MRI
eCRF	Electronic Case Record Form
EDF	End-Diastolic absolute Blood Flow
EMA	European Medicines Agency
EP	End Point
EVT	Endovascular Thrombectomy
GPC	Greater Palatine Canal
GV CT	Implantation CT, used by the GuideView navigation system
IC	Informed Consent
ICH	International Harmonization
IDE	Investigational Device Exemptions
IFU	Indication For Use
Inc/Exc	Inclusion/Exclusion
INR	International Normalized Ratio
INS	Injectable Neurostimulator
iPRM	Integrated Patient Marker
IQR	Interquartile Range
ISS	Ischemic Stroke System
IA-tPA	Intra-arterial tissue plasminogen activator
IV-rtPA	Intravenous Recombinant Tissue Plasminogen Activator

LA	Local Assessors
LKW	Last-Known-Well
LOCF	Last Observation Carried Forward
LVO	Large Vessel Occlusion
MCA	Middle Cerebral Artery
MCID	Minimally Clinically Important Difference
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to Treat
MOA	Mechanism of Action
MRA	MR Angiography
MRI	Magnetic Resonance Imaging
MRP	MR Perfusion
mRS	Modified Rankin Scale
MTT	Mean Transit Time
MVO	Medium Vessel Occlusion
NCCT	Non-contrast Cranial CT
ND	Neurological Deterioration
NIHSS	The National Institutes of Health Stroke Scale
NNT	Number-Needed-to-Treat
NO	Nitric Oxide
OR	Odds Ratio
OUS	Out of US
PCB	Printed Circuit Board
PMA	Pre-Market Approval Application
PRM	Patient Reference Marker
PRO	Patient Reported Outcome
PSF	Peak-Systolic absolute Blood Flow
PT	Preferred Term
QoL	Quality of Life
RCS	Restricted Cubic Splines
RCT	Randomized Clinical Trial
RF	Radio Frequency
RFA	Rankin Focused Assessment
SAE	Serious Adverse Event
sICH	Symptomatic Intracerebral Hemorrhage
SIS-16	Stroke Impact Scale-16
SOC	System Organ Class
SPG	Sphenopalatine Ganglion
STAIR	The North American Stroke Therapy Academic Industry Roundtable
STK	Stroke
TFSO	Time From Stroke Onset
TJs	Tight Junctions

UADEs	Unanticipated Adverse Device Effects
Uw-mRS	Utility Weighted mRS
VIP	Vasoactive Intestinal Polypeptide
VISTA	Virtual International Stroke Trials Archive

1 Introduction

Acute ischemic strokes are devastating events that can result in lifetime of disability and reduced quality of life. Current guidelines recommend timely reperfusion with recanalization therapies, as it has been shown to effectively improve neurological outcomes. Unfortunately, its use is time dependent, and many patients are either ineligible or do not have access to treatment.

Sphenopalatine Ganglion (SPG) stimulation delivered by the Ischemic Stroke System (ISS500) is a first of its kind treatment option for 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.

SPG stimulation increases blood flow to the affected hemisphere of the brain by augmenting collateral blood flow. Stimulation is delivered via an acutely implanted neurostimulator. The implant is injected into the sphenopalatine fossa through the upper hard palate; this is intended to be done by a trained physician, during a simple procedure that utilizes a navigation system to facilitate appropriate placement. The neurostimulator is activated by an external system and delivers 4 hours of stimulation for 5 consecutive days in an in-patient setting, The implant is then removed after the completion of therapy on day 5. Because of its novel mechanism of action, the ISS500 can extend the time window for which patients can receive treatment, overcoming a treatment gap with IV-tPA and endovascular thrombectomy.

This Premarket Approval application (PMA(b)(4)) for the ISS500, concludes 20 years of development and clinical evaluation. This includes two randomized clinical trials, ImpACT-24A and ImpACT-24B, which were conducted under good clinical practice guidelines, meeting the highest data quality and trial design standards. These studies were conducted under FDA Investigational Device Exemptions (IDE) G070134 and G110090.

Data from these two trials consistently demonstrated that patients with confirmed cortical involvement (CCI) who received SPG Stimulation with the ISS500 achieved favorable disability outcomes, and improved quality of life compared to sham-controls. The ISS500 was also shown to have a favorable safety profile and a significantly reduced risk of symptomatic intracranial hemorrhages compared to the sham-control.

As with many first-of-a-kind devices, the ISS500 system components and implant technique has evolved over the years, with redesigns to simplify the implantation procedure. The final device has been thoroughly evaluated and data from the usability trial ImpACT-24M support that the final implant and procedure have significantly reduced procedural time and implant complications.

Based on the totality of the evidence from our pre-clinical and clinical development program, we are seeking approval of the ISS500 for the following indication:

"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)."

This document includes a summary of the unmet need, the clinical results, and an overview of the device, followed by a more detailed clinical background, study results and risk benefit assessment.

2 Executive Summary

2.1 Unmet Need

Stroke is a major public health burden in the US and around the world. It is the leading cause of acquired neurological disability and the 2nd leading cause of dementia, with 690,000 new ischemic stroke cases per year in the US (85% of all strokes).

Available therapies including pharmacologic IV-tPA[i] and devices for Endovascular Thrombectomy (EVT) effectively improve neurological outcomes, but their use is time dependent, and many patients are ineligible to receive treatment or do not have access to such specialized care.

When available, both treatments' aim is to restore blood flow to the ischemic region through direct reperfusion, by opening the occluded artery. These treatments work best when given as soon as possible, within 3-4.5h of stroke onset for IV-tPA, and within 6h or 24h for EVT – the benefits of EVT between 6 and 24 hours after stroke onset were limited to a highly selected population of patients – specifically those with small ischemic core and with large volume of salvageable tissue (penumbra).

Unfortunately, as the time from stroke onset (TFSO) increases, the ischemic core grows and the penumbra disappears, diminishing the potential benefit and increasing the risk of symptomatic intracranial hemorrhage associated with these therapies.

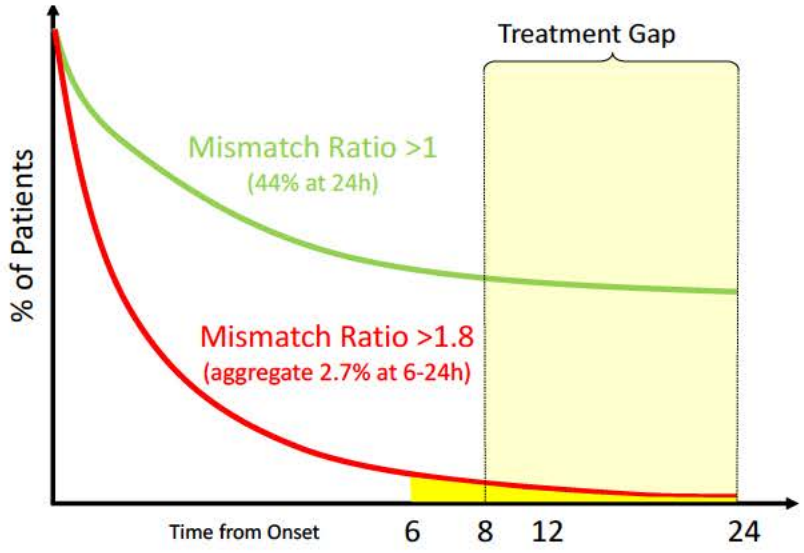

Figure 1 – Infarct Dynamics – the evolution of the penumbra and salvageable tissue [1, 2]

As a result, only 2%–3% of the patients who arrive at the hospital 8 to 24 hours after Last Known Well meet the criteria for EVT treatment beyond 6 hours after stroke, which are based on the DAWN and DEFUSE3 trials' criteria (red curve, Figure 1).[1] However, up

[i] IV-tPA - Intravenous recombinant tissue plasminogen activator

to 44% of patients have some salvageable tissue within 18–24 hours after stroke (green curve, Figure 1) and may benefit from treatment that is safe, even when the core is large and the penumbra is small.[2]

The collateral circulation plays an important role in maintaining blood flow to vulnerable ischemic tissue, and good collateral blood flow is associated with slower infarct expansion, and improved prognosis after stroke.[3, 4]

Another important effect of stroke is the disruption of intracellular tight junctions (TJs), resulting in compromised BBB integrity, increased permeability and poor regulation of transfer of molecules and ions across the BBB. [5]

BBB disruption after ischemia increases influx of fluid from the system circulation to the cerebral compartment, producing extracellular, vasogenic edema that adds to cytotoxic edema from ischemic cellular injury, increasing mass effect and herniation risk. [6]

Recent studies have shown that BBB opening is bi-phasic, and the second peak occurs between at 12–72 hours after stroke onset, as shown in Figure 2. [7]

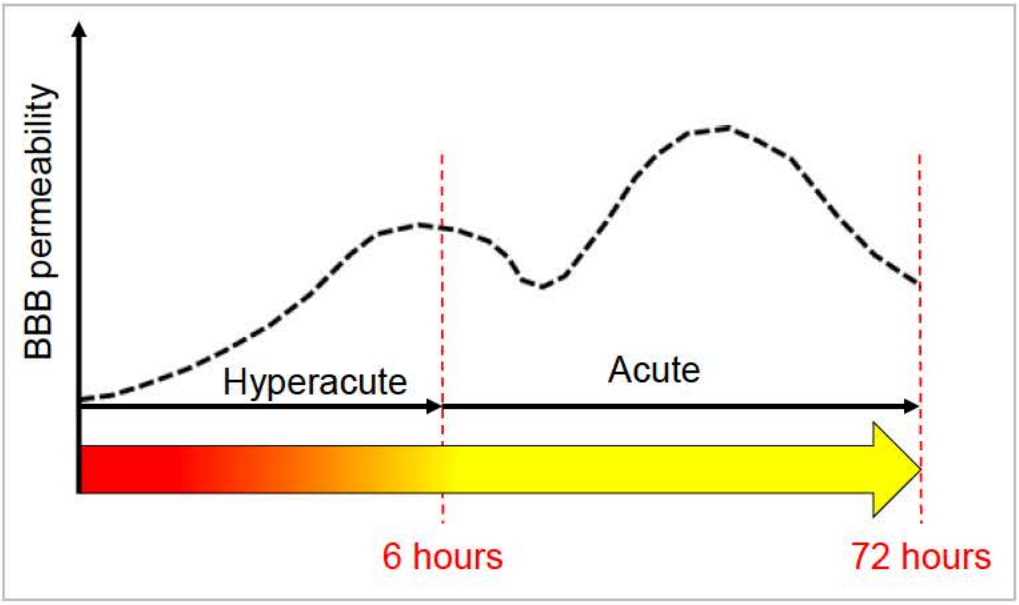

Figure 2 – BBB Disruption After Stroke [7]

Because of these effects (the penumbra turning into core and the BBB disruption), the use of direct reperfusion therapies beyond 6 hours is limited, presenting a gap with current therapies.

The unmet need for treatment in the late time window is amplified by the requirements for complex infrastructure and specific expertise required for EVT that are limited to a small number of large comprehensive stroke centers.

Therefore, there remains a significant unmet need for a safe and effective therapy for patients who arrive at the hospital 8 to 24 hours after their ischemic stroke and have no other treatment alternatives.

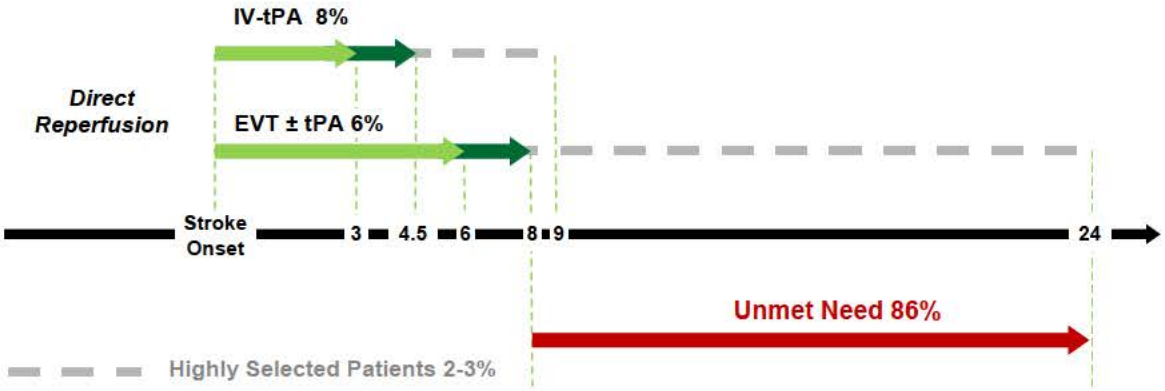

Figure 3 – Unmet Need

2.2 Device Overview

The Sphenopalatine Ganglion (SPG) is the source of parasympathetic vasodilatory innervation to the collateral network of the anterior cerebral circulation, and electrical stimulation of the SPG has been known to increase blood flow in the collateral arterial networks through vessel dilation and augmentation of collateral flow. [8]

The ISS500 is intended to treat stroke by SPG stimulation, under the following IFU:

"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 ISS500 is comprised of a device implant, an external treatment system, and an implantation system. The ISS500 requires that implantation and treatment be initiated between 8 and 24 hours from stroke onset.

The implant (Figure 4A) is injected into the sphenopalatine fossa through the upper hard palate (Figure 4B) and stimulates the sphenopalatine ganglion (Figure 4C). The implant is activated by an external system (Figure 4D) and delivers electrical pulses within a

predefined range to the SPG. Following implantation patients receive 4 hours of treatment per day, for 5 consecutive days in an inpatient setting (see details in sections 5.1 and 5.2).

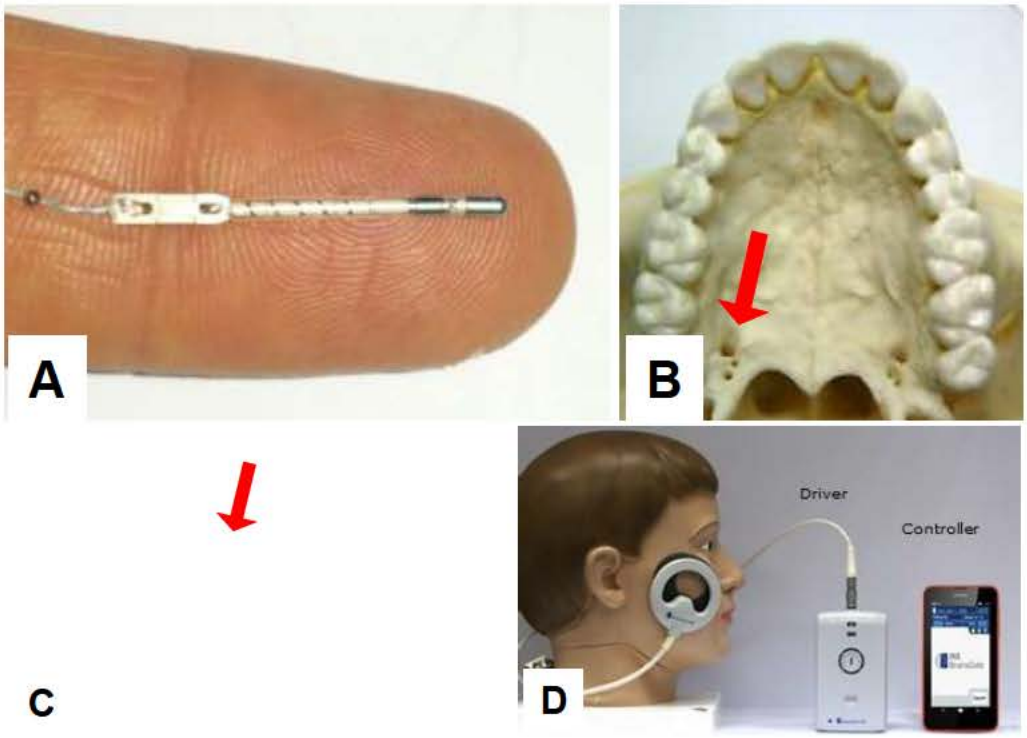

Figure 4 – The Implant (A), Implantation Site (B, C), and ISS System (D)

The stimulation level is set at each patient's comfortable tolerance level (CTL), within the "non-noxious physiologic range" (see discussion in section 7.6).

The implantation is a bed-side procedure performed under local anesthesia, aided by the GuideView optical navigation system (Figure 5). The implanted neurostimulator is removed with forceps following the last treatment session on day 5.

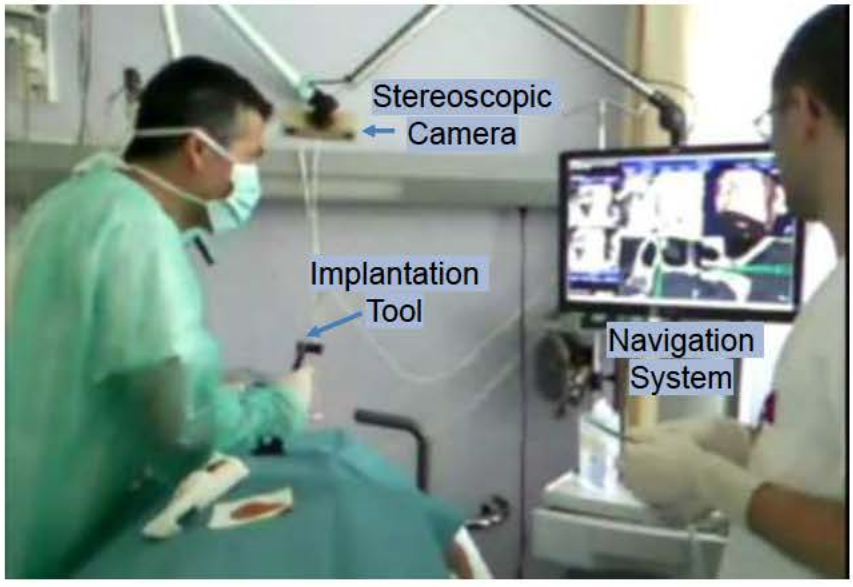

Figure 5 – The Implantation Procedure

2.3 Mechanism of Action

SPG stimulation is a novel mechanism of action that increases blood flow to the affected hemisphere of the brain by augmenting collateral blood-flow.[i] [6, 9] This is in contrast to direct reperfusion therapies, which rely on opening the occluded vessel (Figure 6).

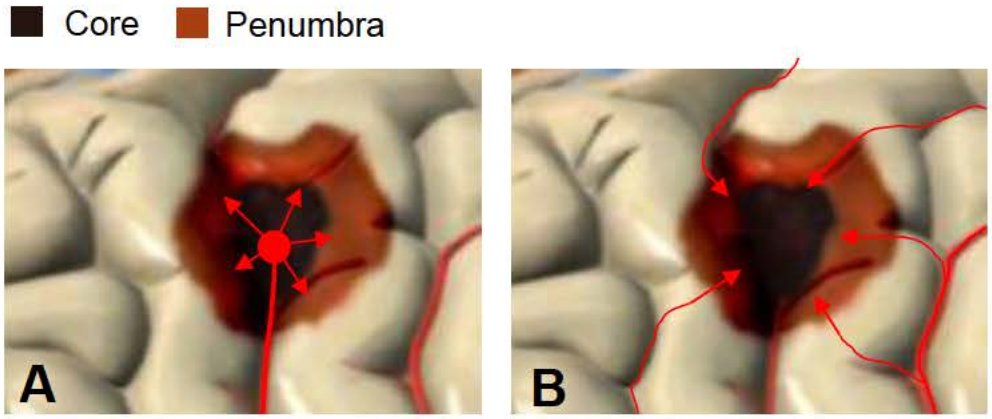

Figure 6 – Direct Reperfusion (A) vs Collateral Flow Augmentation (B)

Pre-clinical data have demonstrated that SPG Stimulation increases collateral blood flow to the ischemic field via collaterals. The white circle in Figure 7 marks the area of ischemic penumbra before stroke (A), after stroke, before stimulation (B), and during stimulation (C):

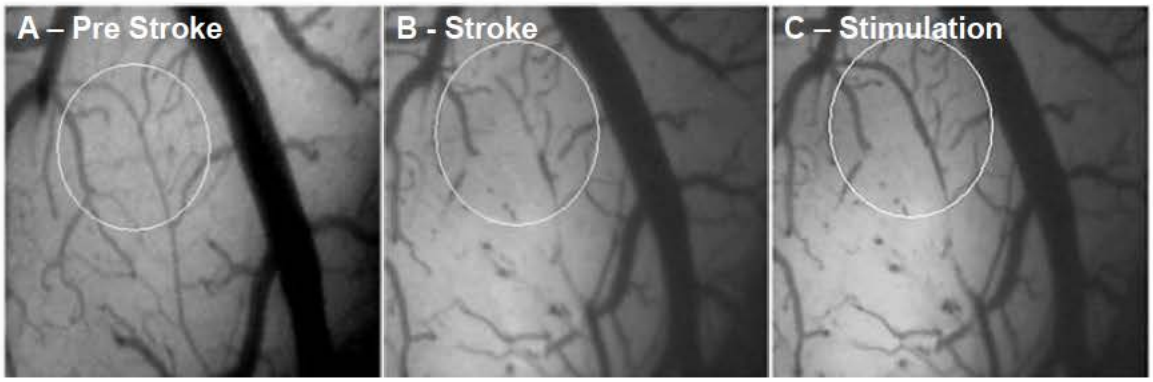

Figure 7 – Blood flow before stroke (A), during stroke (B) and during stimulation (C) in a rat model

By augmenting blood flow to the ischemic field, SPG stimulation aims to reduce the ischemic stress and preserve the BBB, allowing tissues to tolerate the reduction in direct perfusion through the initially occluded artery.

[i] A summary of the pre-clinical and clinical evidence is provided in Appendix K – Summary of MOA Evidence. For demonstration of blood flow in humans see section 7.5.3.4 (ImpACT-24M Results)

Pre-clinical stroke models have also demonstrated that SPG Stimulation can reduce the final infarct size and preserve the BBB, as demonstrated in Figure 8:

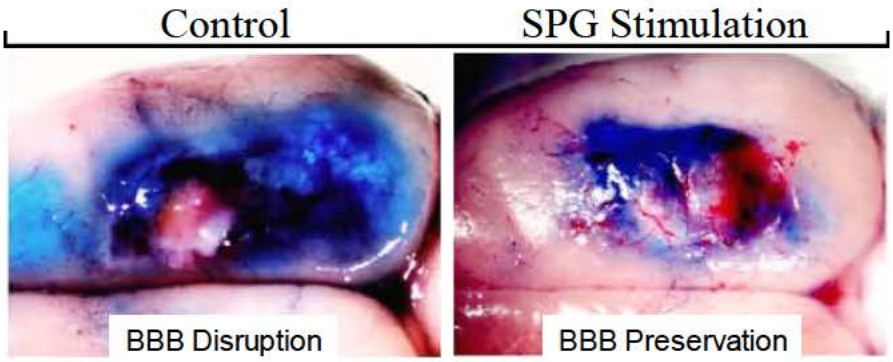

Figure 8 – BBB Protection by SPG Stimulation - Pre Clinical Stroke Model

The collateral arterial networks are most robust in the cerebral cortex.[3, 10, 11] Therefore, the increase in CBF is greatest in the brain's cortical regions, and the treatment effect is expected to be greatest in patients with Confirmed Cortical Involvement (CCI), the target population of this PMA.

An example of the stimulation effect in a CCI patient is shown in Figure 9 using CT Angiography. The occlusion (yellow circle on the left picture) reduced blood flow in the cortical region downstream. Repeated imaging after the first stimulation session shows that the vessel is still occluded (yellow circle on the right picture) but blood flow is increased in the ischemic cortical region through the collateral circulation.

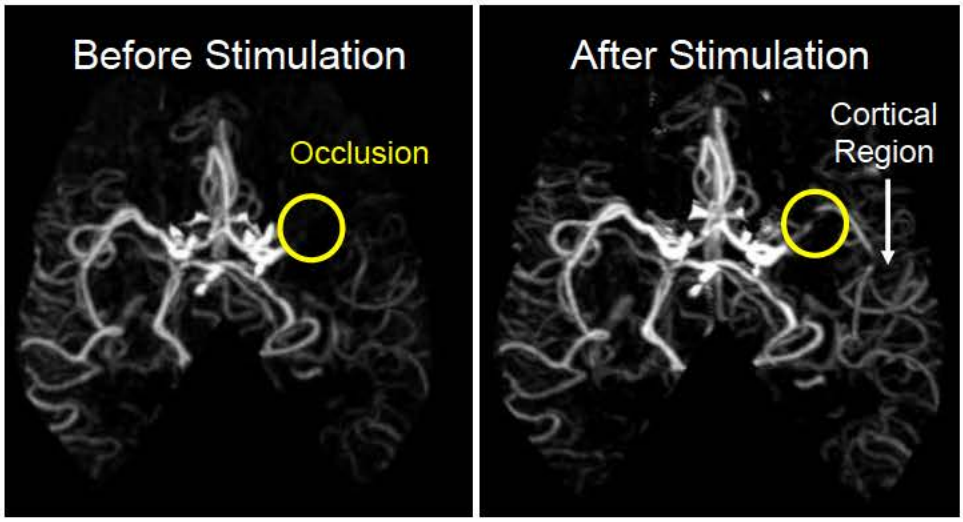

Figure 9 – CT Angiograpy of a CCI Patient Before and After SPG Stimulation

The effect is also evident in CT perfusion scans of the same patient, before and after stimulation. Substantial improvement in perfusion is demonstrated in the cortical region on the right image (after stimulation) compared to the baseline scan before stimulation (left).

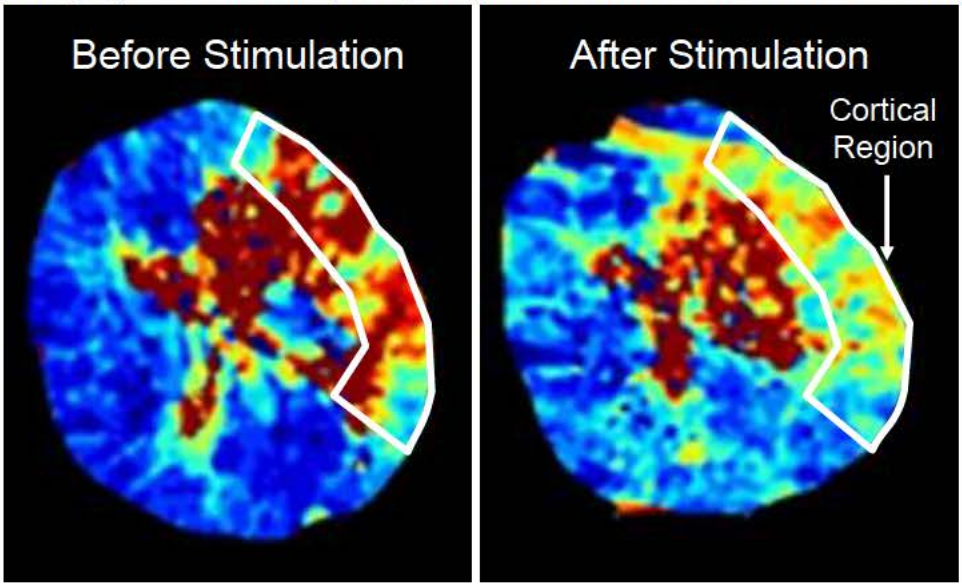

Figure 10 – CT Perfusion of a CCI Patient Before and After SPG Stimulation

The CCI population was a pre-specified primary analysis population in the pivotal study.

For more information about the mechanism of the device in acute ischemic stroke patients see Section 4.

2.4 Clinical Program Overview

The ISS500 has been clinically evaluated in more than 1400 patients in 4 global studies[i] in more than 70 centers (Table 1):

	ImpACT-1 (N=98)	ImpACT-24A (N=253)	ImpACT-24B (N=1,000)	ImpACT-24M (N=50)
RCT	No	2:1	1:1	No
Type	Feasibility	Pilot	Pivotal	Usability
Dates	2006-2008	2009-2011	2011-2018	2017-2018
IDE	OUS	G070134 + OUS	G110090 + OUS	OUS

Table 1 – ISS500 Clinical Evaluation Overview

2.5 Efficacy Results Summary

2.5.1 ImpACT-24B

The pivotal ImpACT-24B was a prospective, randomized double-blind[ii], sham-controlled, parallel-arm multicenter study. The primary objective was to assess the safety and effectiveness of SPG stimulation with the ISS as an adjunct to standard of care in subjects with acute ischemic stroke.

The pre-specified primary endpoint was the modified Rankin Scale (mRS) at 90 days, analyzed using sliding dichotomy. Improvements in the mRS scale (even by one point) are directly related to lower disability or lower dependence in daily activities and are clinically meaningful (see details in Section 6.2.2).

The study had two pre-specified primary analysis populations, one including all patients who received at least one stimulation session (mITT), and one including only patients with confirmed cortical involvement (CCI), the target population of this PMA.

The pre-specified statistical analysis plan accounted for this multiplicity of endpoints, with a p-value of less than 0.025 needed to demonstrate statistical significance.

[i] Patients in all 4 trials were ineligible for or had no access to IV- tPA or EVT.

[ii] Patients and outcome assessors were blinded. See 7.2.1.6 Blinding Method, and 7.2.1.11 for blinding results

In the mITT population, the primary endpoint was not met, as demonstrated by both the 95% confidence interval and the p-value:

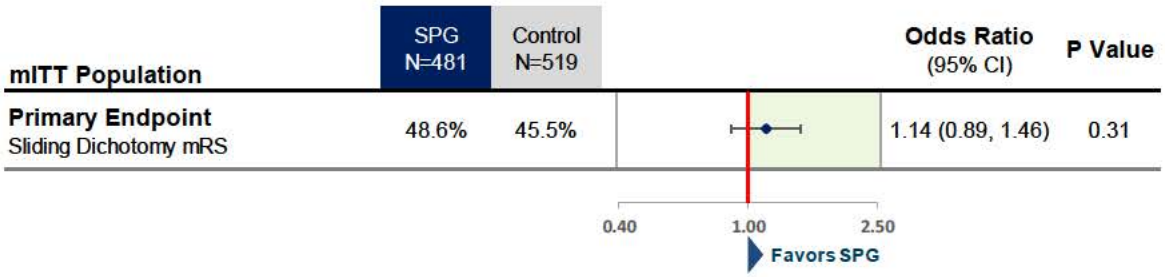

Figure 11 – Pivotal ImpACT-24B – mITT Population Primary Endpoint Results

Although the multiplicity-adjusted primary analysis did miss the formal significance level in the target CCI population (p=0.0258, compared to the p<0.025 multiplicity-adjusted threshold), the pre-specified primary endpoint did show a clinically meaningful reduction of disability levels in CCI patients treated with SPG stimulation compared to sham control (9.8% absolute risk reduction, OR = 1.48, 95% CI 1.05, 2.10).

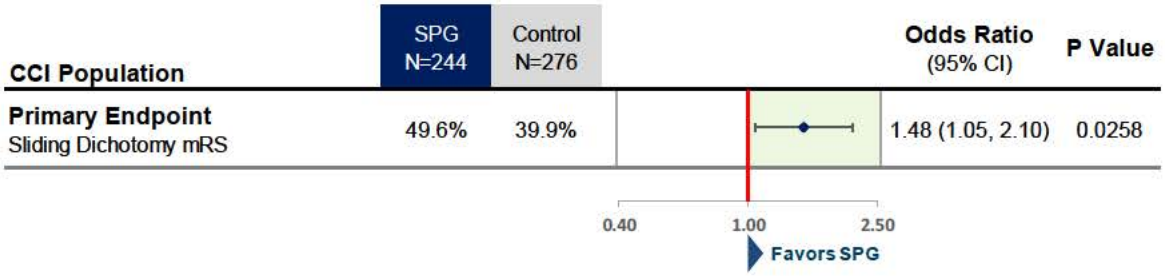

Figure 12 – Pivotal ImpACT-24B Study – CCI Population Primary Endpoint Results

This section focuses on the CCI population (the target of this PMA). Efficacy results in both populations (mITT and CCI) are provided in Section 7.

2.5.1.1 Interpretation of ImpACT-24B Primary Results

The ImpACT-24B pivotal trial was a prospective, multi-center, multinational, randomized, sham control, double-blind, adjunctive to standard of care, parallel arm study, and is, to our knowledge, the largest device trial in acute ischemic stroke patients.

The absolute risk reduction (ARR) of 9.8% in the primary CCI population is clinically meaningful, higher than the 1.5% Minimal Clinically Important Difference (MCID) in dichotomized endpoints in stroke [12], the 3% MCID for continuous utility-weighted endpoints [13] and higher than the 7% ARR that was pre-specified in the protocol as the minimum desirable non-diluted effect.

The CCI population was added to the statistical analysis plan in 2018, before unblinding the results. The change was triggered by an external event (the publication of the DAWN

study) and was not informed by the interim analyses in 2014 and 2016, which did not include any subgroup analysis.

The cumulative evidence, based on this finding as well as the relative consistency of benefit across a variety of other measures and definitions, as well as the clear mechanism of action, help mitigate the extent of uncertainty regarding the clinically significant benefits and risks, consistent with the FDA guidance on Consideration of Uncertainty in Making Benefit-Risk Determinations.

2.5.1.2 Secondary Outcomes

The uncertainty of treatment effectiveness in the CCI population is reduced by the consistent benefit across all secondary outcome measures in ImpACT-24B. These endpoints analyze the same day-90 mRS data in different ways, such as improvements in function independence (mRS 0-2), the ability to walk and perform body-self-care (mRS 0-3) and utility-weighted analysis. All these additional analyses, as well as the stroke-related quality of life analysis, support the results of the primary sliding dichotomy analysis and show that the benefit of SPG stimulation is independent of the choice of analysis method:

CCI Population	SPG N=244	Control N=276	Odds Ratio (95% CI)	P Value
Functional Independence Dichotomy mRS 0-2	34.8%	27.2%	1.43 (0.99, 2.08)	0.06
Able to Walk & Self Care Dichotomy mRS 0-3	62.3%	51.1%	1.58 (1.11, 2.25)	0.01
Stroke-Related Quality of Life SIS-16	52.2	43.9	1.48 (1.08, 2.02)	0.01
Global Disability Level Utility weighted mRS	50.0	43.9	1.37 (1.00, 1.87)	0.05

Figure 13 – Pivotal ImpACT-24B CCI Day 90 Secondary Efficacy Results

The uncertainty is also reduced by consistent and meaningful improvement in each of the categories of the SIS-16 assessment, which evaluate important aspects of post-stroke disability (Figure 14):[i]

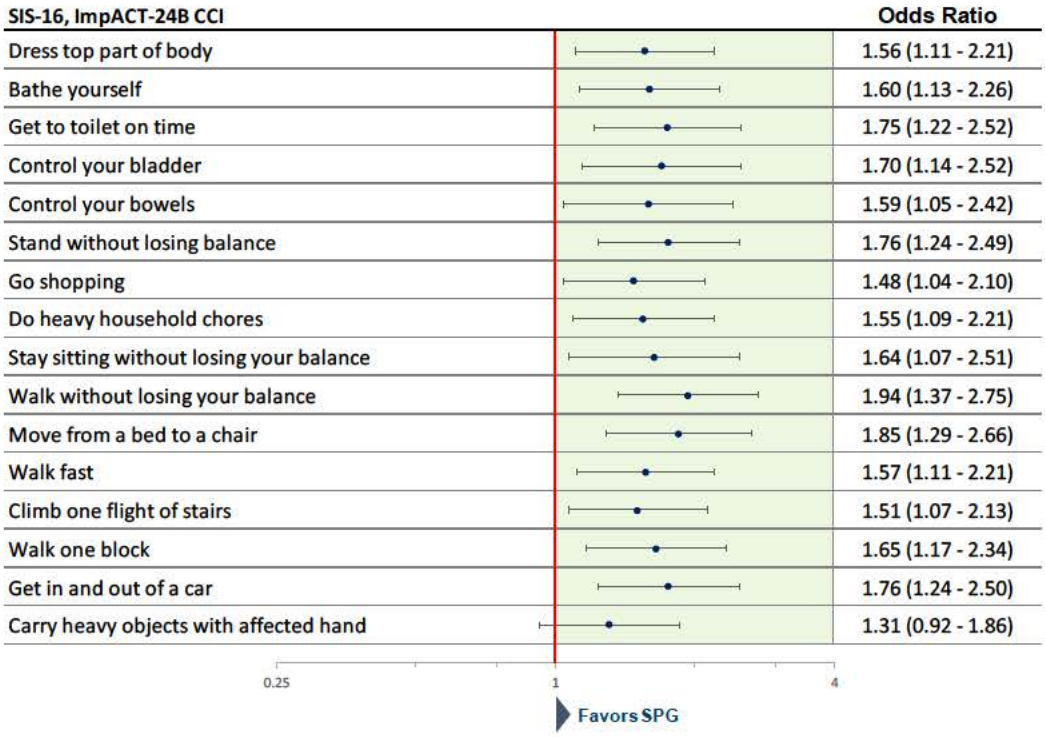

Figure 14 – SIS Results Breakdown - CCI

[i] Results in the mITT population are provided in Section 7

2.5.1.3 Long-term Effectiveness

The benefit of SPG Stimulation over sham persisted in long-term follow-up at 180 days and 1 year. The RIKS-Stroke is a patient-reported outcome measure that assesses disability, covering both instrumental and extended activities of daily living. Accordingly, it assesses from a patient reported-perspective the same outcome domain (disability) that the modified Rankin Scale assesses from a clinician reported-perspective. The RIKS-Stroke has been validated as having high correlation with concurrently assigned mRS scores (unweighted 0.82, weighted kappa 0.85). [14] The RIKS-Stroke therefore provides important information on the durability of benefit of SPG stimulation upon patient disability, showing that the benefits shown on the mRS at 3 months are maintained through 6 months and 1 year. See discussion of the limitations and advantages of the RIKS score in section 7.2.6.3.

Patients treated with SPG Stimulation reported greater improvements across all categories of the RIKS quality of life assessment (Figure 15).[i]

CCI Population RIKS - 180 Days	SPG N = 240	Control N = 273	Odds Ratio (95% CI)	P Value
Dependency			1.50 [1.09, 2.07]	0.01
Residence			1.39 [1.01, 1.92]	0.04
Mobility			1.49 [1.07, 2.06]	0.02
Toiletting			1.59 [1.12, 2.26]	0.01
Dressing			1.63 [1.15, 2.31]	0.01

CCI Population RIKS - 360 Days	SPG N = 241	Control N = 271	Odds Ratio (95% CI)	P Value
Dependency			1.37 [0.99, 1.88]	0.06
Residence			1.26 [0.91, 1.73]	0.16
Mobility			1.34 [0.97, 1.86]	0.07
Toiletting			1.37 [0.96, 1.94]	0.08
Dressing			1.58 [1.11, 2.23]	0.01

Figure 15 – Pivotal ImpACT-24B CCI RIKS Results at 180 and 360 days

[i] Results in the mITT population are provided in Section 7

2.5.1.4 Dose-response

A strong dose–response relationship was observed in ImpACT-24B, with an inverted U-shaped dose–effect curve (p=0.0006; see Section 7.2.6.4 and Figure 39).

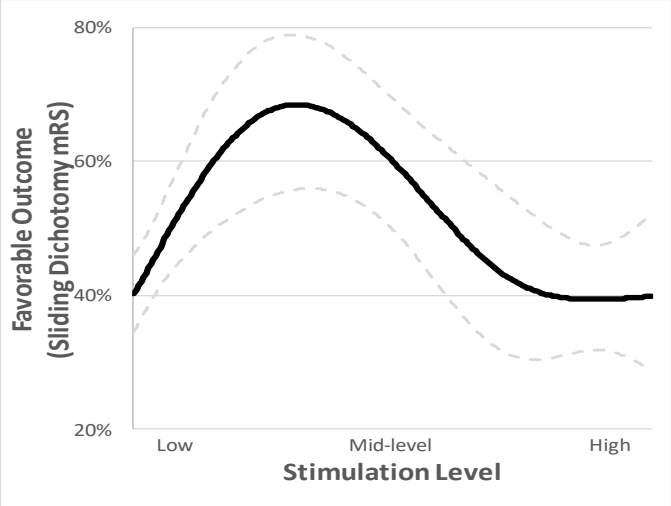

Figure 16. Study ImpACT-24B – Dose response in CCI population (rates of favorable outcome and associated 95% CI; cubic spline model, N=520)

U-shaped dose–responses for stimulation intensity are a common feature of electrical stimulation applied to neuronal systems, reflecting tuning of neurobiological systems to respond maximally at low–midrange levels. [15, 16]

2.5.2 Additional Supporting Data

2.5.2.1 ImpACT-24A

The results of the pivotal study (ImpACT-24B) are also consistent with the results of the previous pilot RCT (ImpACT-24A), which followed a similar protocol. Formal analysis showed no heterogeneity of treatment effect between the studies (p=0.88).

In addition to the formal statistical similarity, the results of both studies are also consistent with the mechanism of action which was demonstrated in pre-clinical data.

Both studies showed that the treatment effect was independent of the core size and the time from onset (within the 8- to 24-hour window):

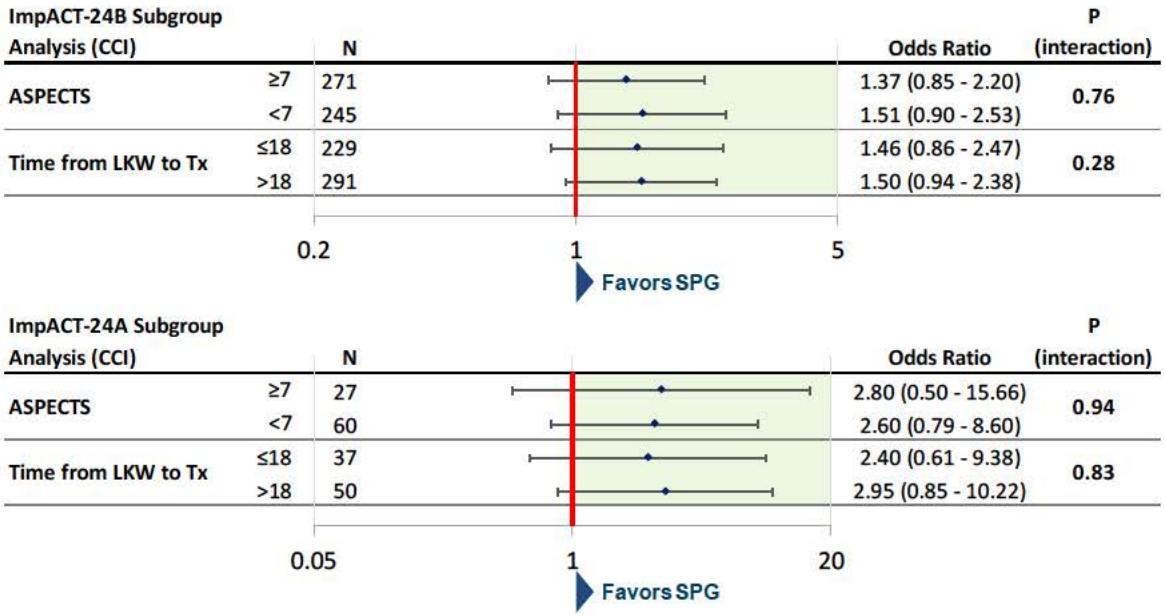

Figure 17 – Treatment Effect by Time from Onset and Core Size (ASPECTS) – ImpACT-24B and 24A CCI

Both studies also showed a lower rate of symptomatic intracranial hemorrhages in patients treated with SPG stimulation compared to sham control:

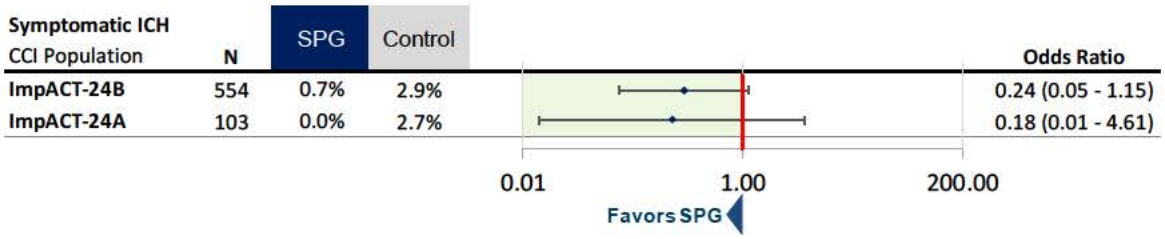

Figure 18 – Symptomatic Intracrantial Hemorrhages, ImpACT-24B vs. ImpACT-24A (CCI)

These unique effects of SPG stimulation, reproduced in both studies, are consistent with the pre-clinical results showing SPG stimulation increases blood flow to the ischemic region, stops the ischemic cascade and preserves the BBB which is most vulnerable 12–72 hours after stroke onset (see sections 2.1 and 2.3).

2.5.2.2 Pooled Post Hoc ImpACT-24A and ImpACT-24B

To assess the cumulative data from these two similar trials, an individual patient data meta-analysis was conducted on ImpACT-24A and ImpACT-24B (see details in section 7.4, including discussion of the poolability of the two studies).

The rate of favorable outcome in all endpoints in the meta-analysis was higher in the treated arm compared to the sham control:

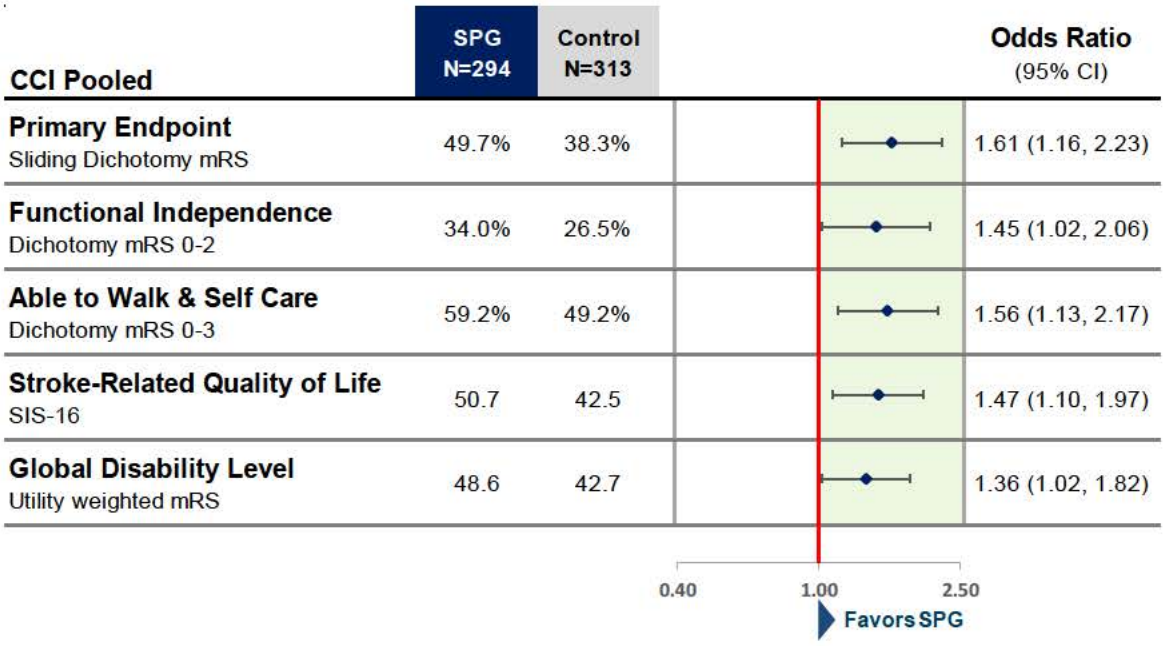

Figure 19 – Pooled CCI Efficacy Results in ImpACT-24B and 24A

2.6 Efficacy Conclusion

In summary, although the p-value in the CCI pre-specified primary analysis population was slightly higher than the multiplicity-adjusted threshold, the uncertainty of the clinically meaningful treatment benefit in the target CCI population is reduced by:

1. Consistent benefit in all other endpoints and follow up periods in the pivotal trial
2. A strong dose-response relationship
3. Consistent findings in the two RCT trials, the meta-analysis and pre-clinical studies

The totality of the evidence detailed above supports that SPG stimulation is effective in the target CCI population.

2.7 Safety Results Summary

The safety of the device was well characterized in more than 1400 patients, including more than 650 CCI patients.

2.7.1 Serious Adverse Events

The following figures summarize the safety results in all patients and in the CCI population:

All Pooled	SPG N=738	Control N=620	Odds Ratio (95% CI)	P Value
Mortality	13.8%	12.9%	1.08 (0.79, 1.48)	0.62
Serious Adverse Events	30.1%	29.4%	1.04 (0.82, 1.31)	0.77
Neurological Deterioration	8.3%	7.3%	1.15 (0.77, 1.72)	0.49
Pneumonia SAE	4.7%	6.1%	0.76 (0.48, 1.22)	0.26
Symptomatic ICH	0.7%	1.9%	0.35 (0.12, 0.99)	0.04

CCI Pooled	SPG N=344	Control N=313	Odds Ratio (95% CI)	P Value
Mortality	18.3%	18.2%	1.01 (0.68, 1.50)	0.97
Serious Adverse Events	34.0%	38.0%	0.84 (0.61, 1.16)	0.28
Neurological Deterioration	7.8%	10.2%	0.75 (0.44, 1.28)	0.29
Pneumonia SAE	5.8%	8.6%	0.65 (0.36, 1.19)	0.16
Symptomatic ICH	0.6%	2.9%	0.20 (0.04, 0.92)	0.02

Figure 20 – Pooled Safety Results in the Full and CCI safety analysis sets

The following figure shows the % Patients without SAE by Time from stroke onset in the full population:

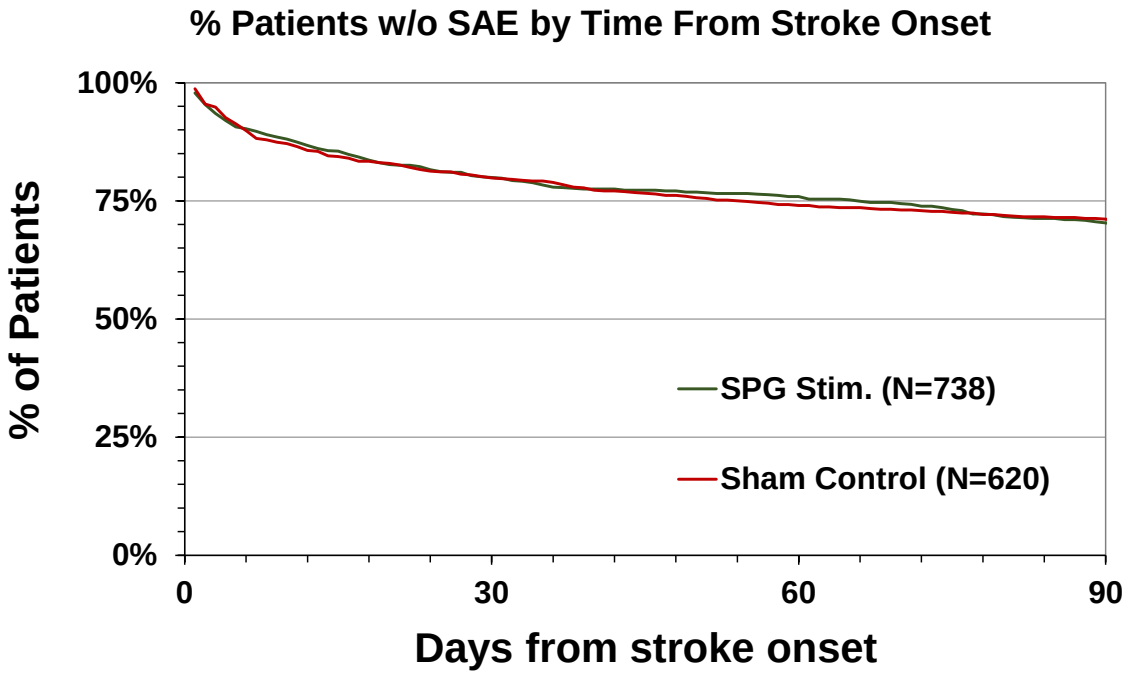

Figure 21 – % Patients without SAE by Time from stroke onset - All Patients (Pooled)

Safety results of the two studies are provided in sections 7.2.5 and 7.3.5 below.

2.7.2 Implantation Safety

Implantation is a bed-side procedure performed under local anesthesia. The final device was implanted in 247 patients, including the last 197 in ImpACT-24B using an older version of the implantation system, and all 50 patients in ImpACT-24M using the final implantation system.[i] The following figures show the implantation site immediately after injecting the implant (left) and after the implant is removed by pulling the extraction thread (right). Prophylactic antibiotic is administered to prevent infection.

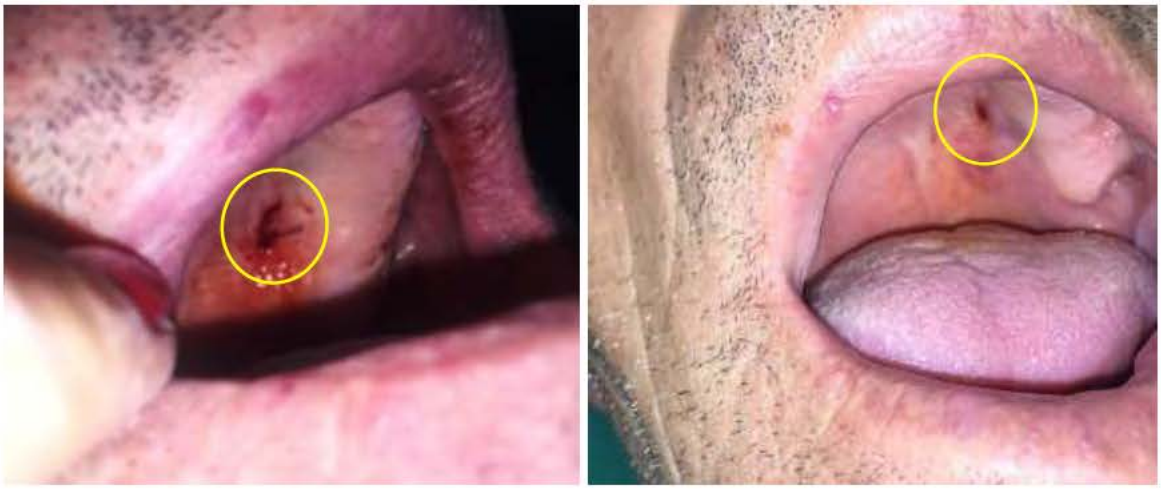

Figure 22 – Implantation site after implant injection (left) and after implant removal on day 5 (right)

The following table summarizes the implantation safety. Median implantation duration of the final device was less than 5 minutes, with no adverse events and no implantation failures.

	Final Device (N=50)	Final Implant / Old PRM (N=197)	Old Implant / Old PRM (N-339)
Clinical Study	ImpACT-24M	ImpACT-24B	
Skin to skin time, Median (IQR) [min.]	4 (3-7)	17 (12-23)	35 (25-52)
SAE	-	0.5%	0.6%
AE	-	8%	37%
Misplacements, %(n)	-	2%	8%
Incomplete Procedures, %(n)	-	2%	5%

Table 2 – Implantation Safety Overview

In summary, the implantation is safe and simple.

[i] The treatment is identical in both implants. For more information about the changes in the device during the study, see section 6.1

2.8 Clinical Perspective

ImpACT-24B and ImpACT-24A demonstrated the safety and effectiveness of SPG stimulation for CCI patients. However, when considering the generalizability of these results to clinical use, two areas for improvement have been identified, implemented, and validated in ImpACT-24M.

2.8.1 Implantation Simplicity

As shown in Table 2, the final implantation procedure was validated in ImpACT-24M. There were no misplacements and no SAEs in 50 implantations, and the median skin-to-skin time was 4 minutes (IQR 3-7), compared to 17 minutes (IQR 12-23) at the end of ImpACT-24B.

Therefore, the implantation safety data from ImpACT-24B represents a worst-case scenario compared to what is expected in clinical use.

2.8.2 Setting the Dose Correctly at the Patient's CTL

A practical method to set the stimulation level correctly in clinical routine was validated in ImpACT-24M. This method sets the CTL based on non-noxious physiologic signs of SPG activation (lacrimation and tingling sensation, without reaching the level of discomfort or pain). This approach could not be used in the randomized clinical trials because the blinding mechanism (transmitter vibration for both arms) mimicked the tingling sensation. Figure 23 compares the clinical approach (validated ImpACT-24M) to the method used in the randomized trials (ImpACT-24A and ImpACT-24B), which sometimes led to stimulation at levels exceeding the CTL.

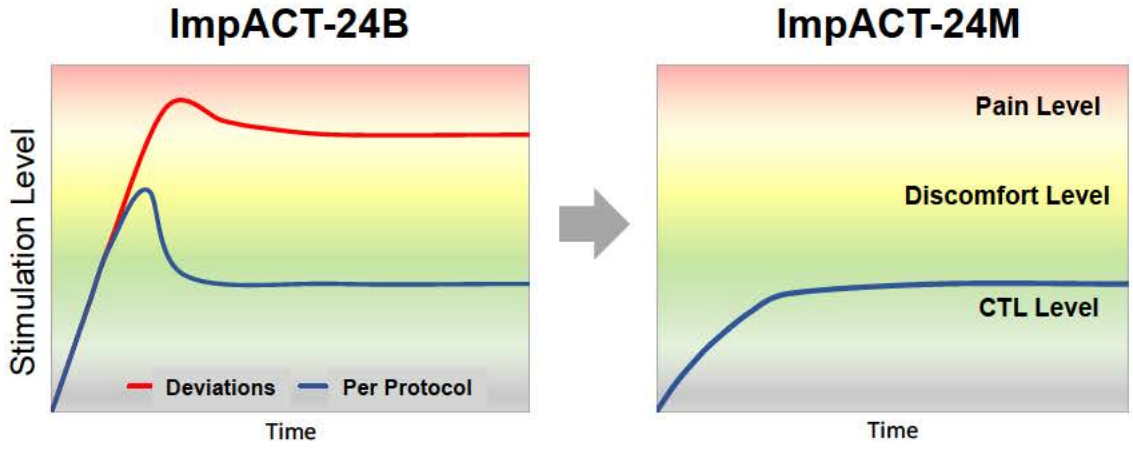

Figure 23 – Patient's Comfortable Tolerance Level (CTL) – ImpACT-24M vs ImpACT-24B

The above figure shows that using the clinical method (in ImpACT-24M), stimulation levels were far from the painful level and no pain was reported in this study.

The study showed that stimulation at the CTL improved motor function during stimulation compared to baseline measurements before stimulation (Figure 24). At the same time, stimulation at the CTL also increased blood flow in the common carotid artery.

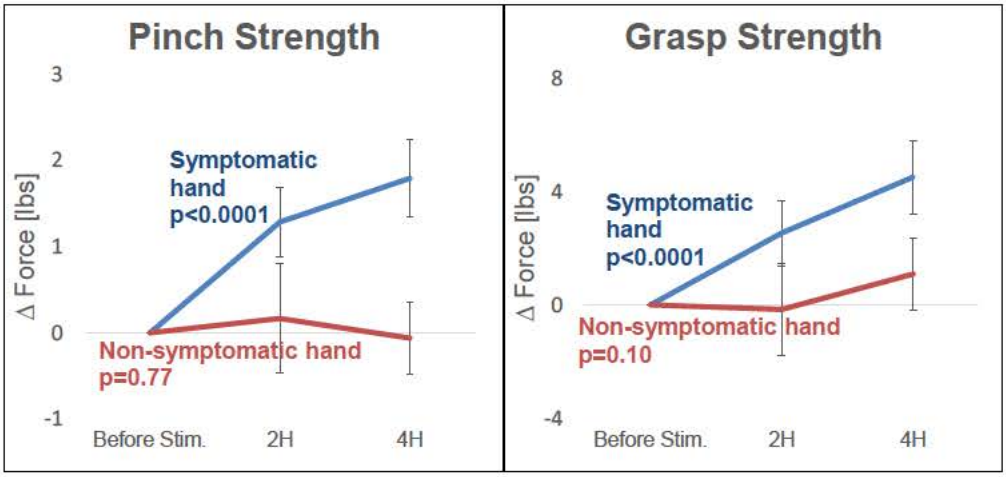

Figure 24 – ImpACT-24M – SPG Stimulation Improved Pinch Strengh (left) and Grasp Strength (right)

When using the physiologic approach, the CTL was found in 92% of the patients within the medium range (where the highest benefit was observed in ImpACT-24B), compared to only 50% in ImpACT-24B. Discomfort and pain adverse events did not occur in any patient (0/50).

In light of these findings, the final device limits the stimulation level to ensure that all patients in clinical practice will be treated within this range (see Figure 25) and avoid pain. The blue bars in Figure 25 show the distribution of stimulation levels in ImpACT-24M and the green curve is the ImpACT-24B dose response curve.

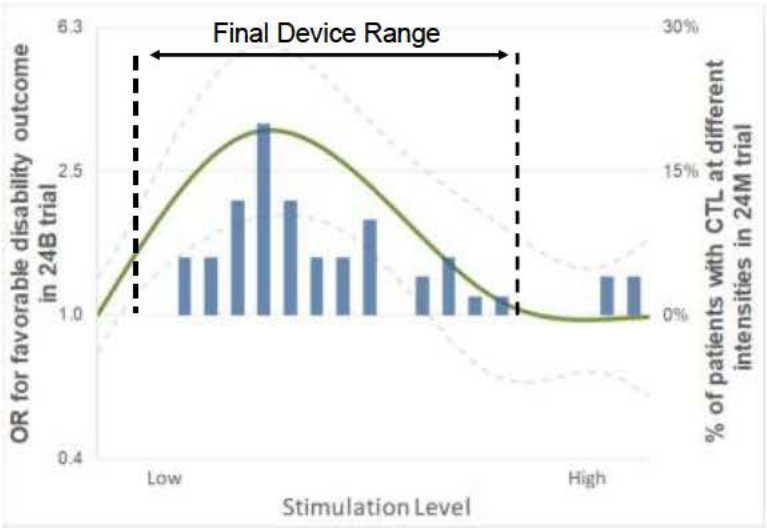

Figure 25 – Dose Response in ImpACT-24B (green, N=520) and Distribution of CTL Levels in ImpACT-24M (blue, N=50)

The clinical impact of limiting the dose range in routine clinical use to the range of maximal benefit (based on the dose-response curve) is demonstrated in Figure 26. The figure shows

the effect in CCI patients treated within the final device dose range compared to sham control in ImpACT-24B. The results show that the expected benefits of SPG stimulation in clinical use (as estimated by this subgroup) are markedly higher than the primary and secondary outcomes in ImpACT-24B (where 50% of the patients were outside this range):

CCI Final Device Dose Range	SPG N=117	Control N=276	Odds Ratio (95% CI)	P Value
Primary Endpoint Sliding Dichotomy mRS	59.0%	39.9%	2.17 (1.40, 3.37)	0.0005
Functional Independence Dichotomy mRS 0-2	44.4%	27.2%	2.14 (1.37, 3.37)	0.0008
Able to Walk & Self Care Dichotomy mRS 0-3	73.5%	51.1%	2.66 (1.65, 4.27)	<.0001
Stroke-Related Quality of Life SIS-16	60.1	43.9	2.19 (1.47, 3.26)	0.0001
Global Disability Level Utility weighted mRS	58.3	43.9	2.11 (1.41, 3.12)	0.0002

Figure 26 – ImpACT-24B CCI – Efficacy Results in the Final Device Dose Range

In summary, the two challenges in the transition of SPG stimulation from clinical studies to routine clinical use were addressed, and the improvements were validated in the ImpACT-24M usability study. The study results support that implantation simplicity, and the magnitude of benefit will be better than in the pivotal study.

2.9 Benefit-Risk Summary

If approved, SPG stimulation will fulfill an unmet need by expanding the treatment window for CCI patients who do not meet the strict criteria for late EVT. Figure 27 illustrates the current treatment gap, with the blue arrow demonstrating where SPG stimulation fits into the stroke treatment paradigm; it is estimated that ~10% of US ischemic stroke patients will be eligible for SPG stimulation (see Appendix L – Estimated Number of Eligible US Patients for additional details).

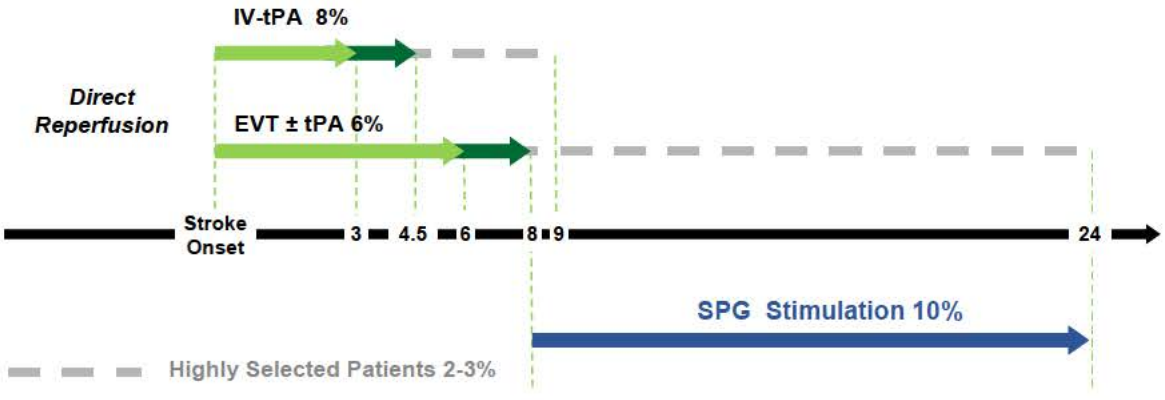

Figure 27 – The extended therapeutic window

Effectiveness results demonstrate a clinically meaningful treatment benefit (Figure 28), even though the p-value for the primary endpoint in the CCI population was slightly above the multiplicity-adjusted threshold.

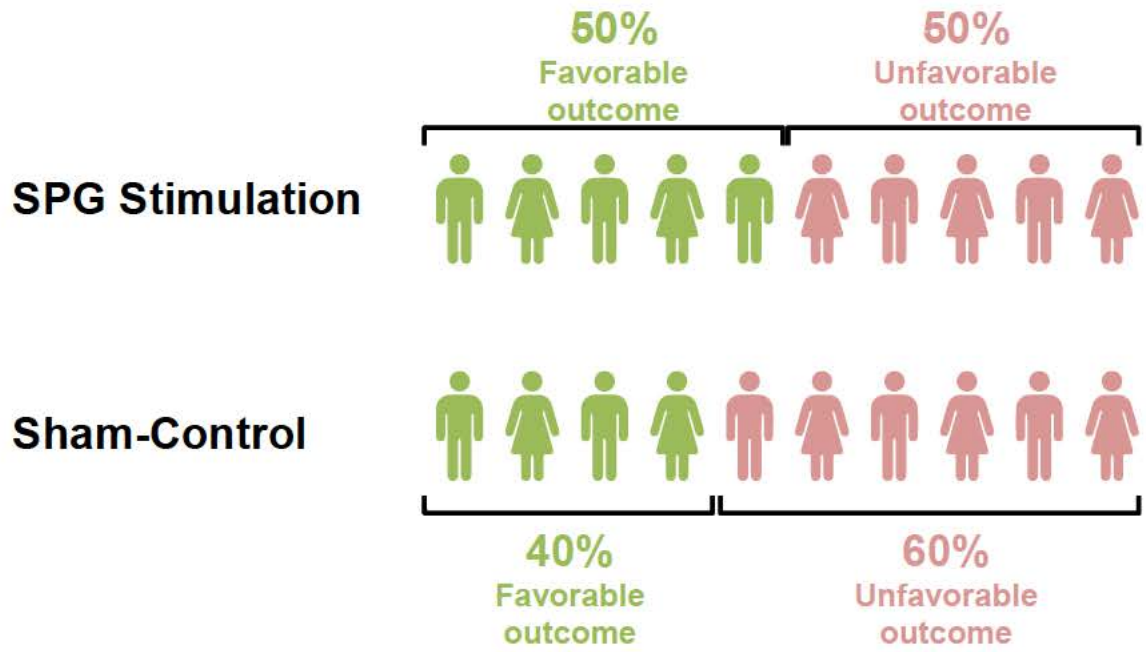

Figure 28 – Clnically Meaningful Outcomes (ImpACT-24B CCI)

The uncertainty of the effectiveness conclusions is reduced by:

- Consistent benefit in all secondary endpoints demonstrating lower disability and improved quality of life,
- Persistence of benefit in long-term follow up at 180, 360 days
- Strong dose response relationship in ImpACT-24B and same optimal dose range in ImpACT-24M (the final device dose range)
- Robust treatment effect in the pivotal study in patients stimulated within the final device dose range
- Homogeneity of treatment effect between ImpACT-24B and ImpACT-24A, as demonstrated by formal statistical analysis
- Findings from the two randomized controlled trials and the pooled analysis are similar and consistent with pre-clinical data

SAE and mortality rates were nominally higher in the treated group in ImpACT-24B and lower in ImpACT-24A and the pooled safety data show that SPG stimulation does not increase the risks of mortality, serious adverse events, and common stroke complications.

A lower rate of symptomatic intracranial hemorrhages (sICH) in the treated arm was observed in both studies. Patients in the sham-control arm had 5 times higher odds of experiencing an adverse symptomatic intracranial hemorrhage compared to treated patients (bottom of Figure 20).

The implantation procedure evolved during the clinical trials and study learnings were implemented to simplify the procedure. The final procedure was validated in 50 patients with no misplacements or complications and median skin-to-skin time of 4 minutes. Therefore, the implantation safety data from ImpACT-24A and ImpACT-24B, which showed no significant complications, represent a worst-case scenario (longer procedures).

Considering the totality of evidence, the probable benefits of the ISS500 outweigh the low risks and support its use in patients with CCI who have no other treatment options. This treatment provides a clinically meaningful benefit of reduced post-stroke disability and improved quality of life.

This innovative first of a kind technology addresses the unmet need for a treatment that is simple to administer and is safe and effective in an 8 to 24-hour window in patients who are ineligible for, or have no access to, alternative therapies.

See Appendix J – Benefit-Risk Assessment for complete evaluation in accordance with FDA guidance on factors to consider when making benefit-risk determinations in medical device premarket approval.

3 Ischemic Stroke Background

Summary:

- Stroke is a leading cause of disability
- The sudden lack of blood supply in stroke triggers a cascade of events that elaborate tissue injury
- Reperfusion therapies are effective, but efficacy diminishes, and the risk of hemorrhage risk increases over time
- Only 2–3% of all stroke patients are currently eligible for treatment in the late window due to penumbra size
- Clear unmet need for safe and effective treatment in an 8- to 24-hour window

3.1 Acute Ischemic Stroke

Stroke is a leading cause of disability worldwide. In the US alone, approximately 800,000 people suffer a stroke every year, with 690,000 of these events diagnosed as ischemic strokes.

3.1.1 Physiology of Stroke

Ischemic damage in stroke results from a cascade of cellular and molecular events triggered by sudden lack of blood supply. Neurons are more vulnerable than glia and vascular cells and become quickly dysfunctional or die when exposed to hypoxia-ischemia.[17] Ischemic damage is more rapid and severe in the center of the ischemic territory (ischemic core), where flow is lowest.[18] At the periphery of the ischemic region, the so-called ischemic penumbra, neuronal damage develops more slowly because blood flow arising from adjacent vascular territories (collateral flow) keeps cerebral perfusion above the threshold for immediate cell death.[18] In the ischemic penumbra, cells can survive the ischemic stress for minutes to hours, but not indefinitely. There is a clear relationship between the status of collateral blood flow and the rate of penumbral deterioration. [18]

Additional ischemic cascades occurring in the infarct core and penumbra lead to the breakdown of the blood-brain-barrier (BBB). The BBB failure leads to leakage of fluids and serum metabolites, which are toxic to brain cells. This further causes brain edema, alteration of local homeostasis, exacerbation of brain damage, and herniation.

If untreated, the penumbra progressively evolves into irreversibly damaged tissue until it has vanished entirely.[19, 20]

3.1.2 Stroke Diagnosis

Screening for stroke is done by combining neurological and imaging examinations.

Stroke symptoms are typically visible, especially in moderate-severe stroke. The neurological deficits related to stroke are usually quantified using The National Institutes of Health Stroke Scale (NIHSS) score. The score can range from 0 to 42 points as a summation of criterion-based integer scores in 11 different domains of neurological function.

Imaging is used to determine the appropriate treatment. Cranial Non-contrast CT (NCCT) has near-perfect sensitivity to detect fresh intracranial hemorrhage and exclude patients from reperfusion therapies, but its sensitivity for diagnosis of ischemic stroke is poor if ischemia is recent, small, or in the posterior fossa. However, early ischemic changes on NCCT in large anterior circulation regions (indexed by the ASPECTS[i] scale) are an indication of an established core and are often used to identify patients who may not benefit from direct reperfusion.[21] The sensitivity of NCCT increases within hours from the onset of stroke. Diffusion weighted MRI (DWI-MRI) is more sensitive than NCCT in the acute setting and can detect acute brain ischemia in about 90% of patients with ischemic stroke.

Candidates for Endovascular Thrombectomy (EVT) are identified using CT Angiography (CTA) or MR Angiography (MRA), which visualize the location of vessel occlusion.

CT Perfusion (CTP) and MR Perfusion (MRP) enable the differentiation of salvageable ischemic brain tissue (the penumbra) from the irrevocably damaged infarcted brain (the infarct core) and are used in late time windows to select candidates for late-window thrombectomy.

The penumbra volume is typically defined as the volume of tissue in which the time to maximum in perfusion imaging is greater than 6 seconds (in short, the Tmax6 volume) and the core volume is typically defined as the volume of tissue in which the time to maximum is greater than 10 seconds.

A target mismatch ratio (the ratio between these two volumes) of 1.8 is often used as the threshold for eligibility for thrombectomy beyond 6 hours from onset.

[i] ASPECTS: The Alberta Stroke Program Early CT Score is a 10-point quantitative topographic CT scan score used for patients with middle cerebral artery (MCA) stroke

3.1.3 Stroke Outcomes Assessment – the mRS Scale

The modified Rankin Scale (mRS, see Figure 29) rates global disability after stroke and is the most comprehensive and widely employed primary outcome measure in acute stroke trials. [22]

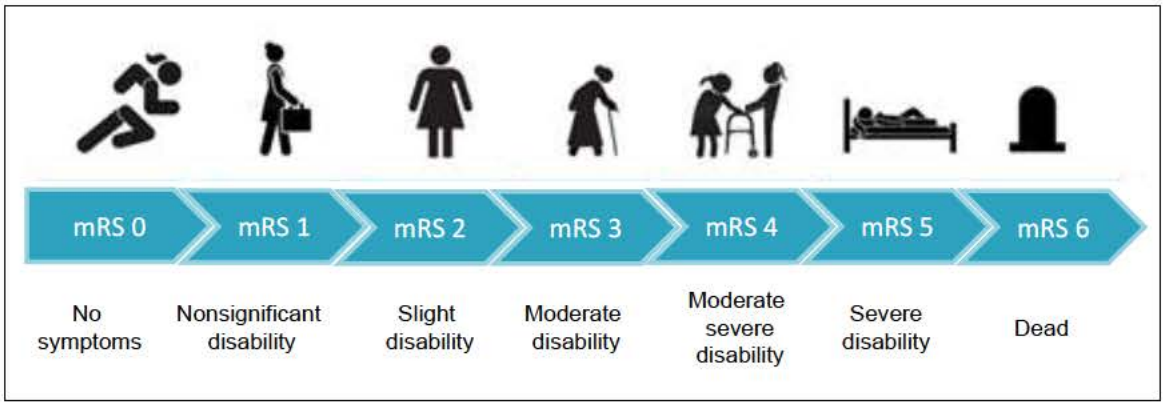

Figure 29 – The mRS Global Disability Scale

A study quantifying the patient-centered value of the benefit of each transition between mRS disability levels showed that all one-step transitions in the mRS disability scale are valued by patients and families (when mRS 5/6 are grouped to a single worst-outcome level). The study combined data from time-tradeoff (patient/caregiver-centered) and person-tradeoff (clinician-centered) studies.[23, 24, 25] According to this assessment, all one-step mRS transitions have health utility values that range from 0.09 to 0.33, all exceeding the minimally clinically important difference (MCID) of 0.03 for health utility. [13]

The following figure illustrates the value of each mRS transition:

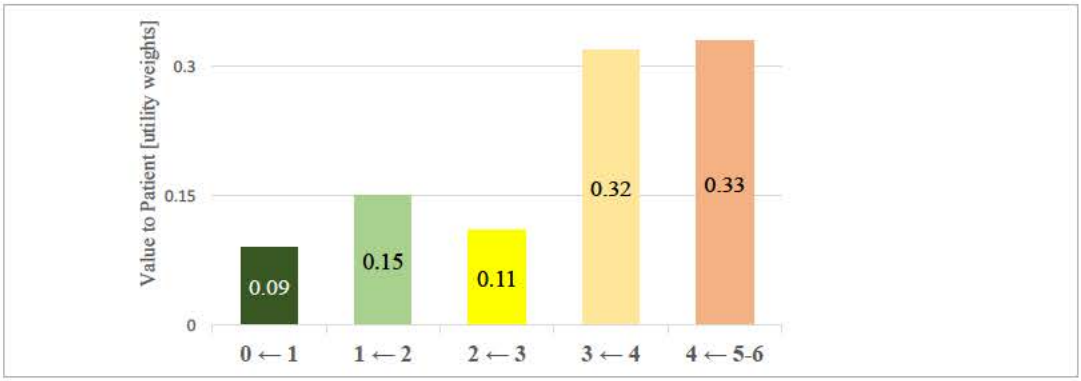

Figure 30 – Patient-Centric Utility Weights for mRS Disability Levels

3.1.4 Infarct Dynamics

Infarct dynamics after stroke vary widely between patients. In large part, this variability is determined by the degree and extent of the pial collateral network. Patients with a poor collateral filling are the so-called "fast progressors" and their degree of permanent tissue damage evolves over minutes. [26]

However, in most people the brain vasculature is richly collateralized and as a result their stroke progresses more slowly allowing time to administer treatment. Experimental data shows that as many as half of patients with acute stroke will still have salvageable tissue up to 24 hours after last known well (or stroke onset). [2]

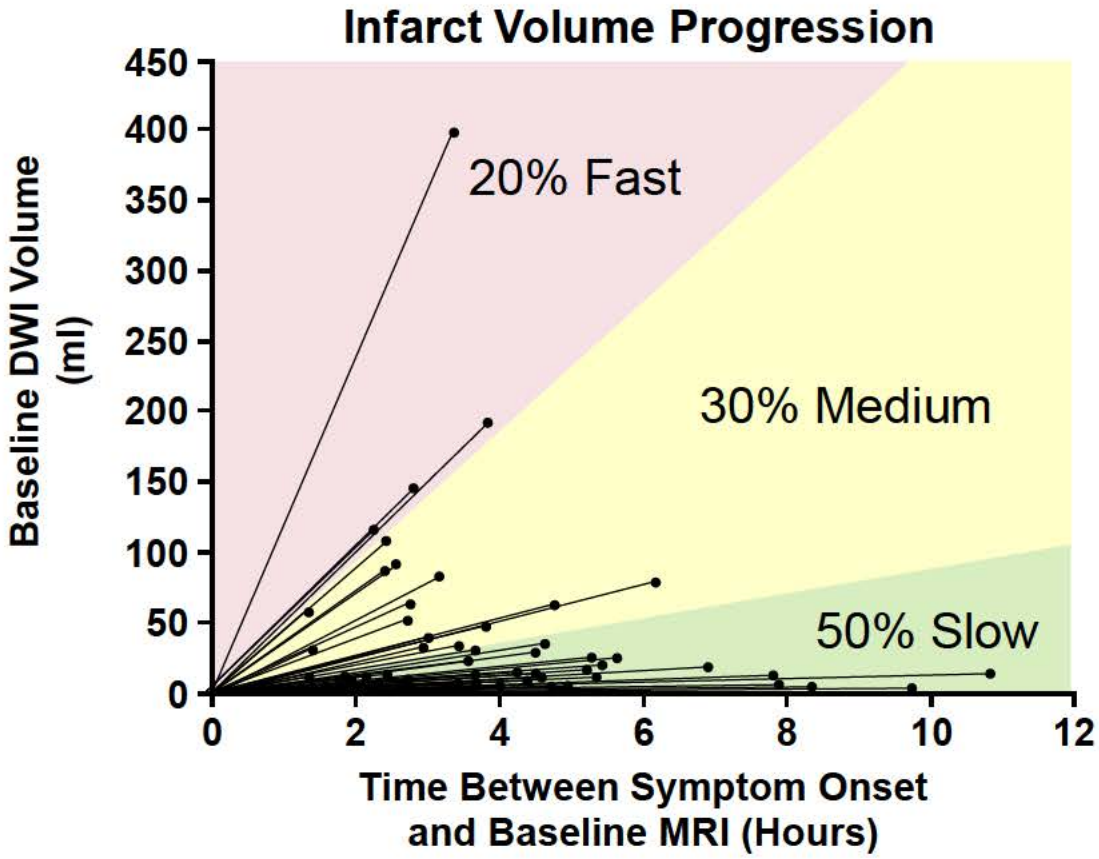

Figure 31 – Infarct Volume Progression by Time from Onset [27]

The degree of tissue damage and speed of core growth are directly related to the degree of blood flow reduction. Inter-arterial connections allow blood to get to the tissue by different routes, bypass the obstruction through the pial arterial network, and supply oxygen to the penumbral region.

Good collateral blood flow is associated with slower infarct expansion, and improved prognosis in patients with acute ischemic stroke.[3, 10, 4]

The following figure illustrates the importance of the collaterals in maintaining the penumbra, comparing a case of poor collaterals (left) to a case of better collaterals (right).

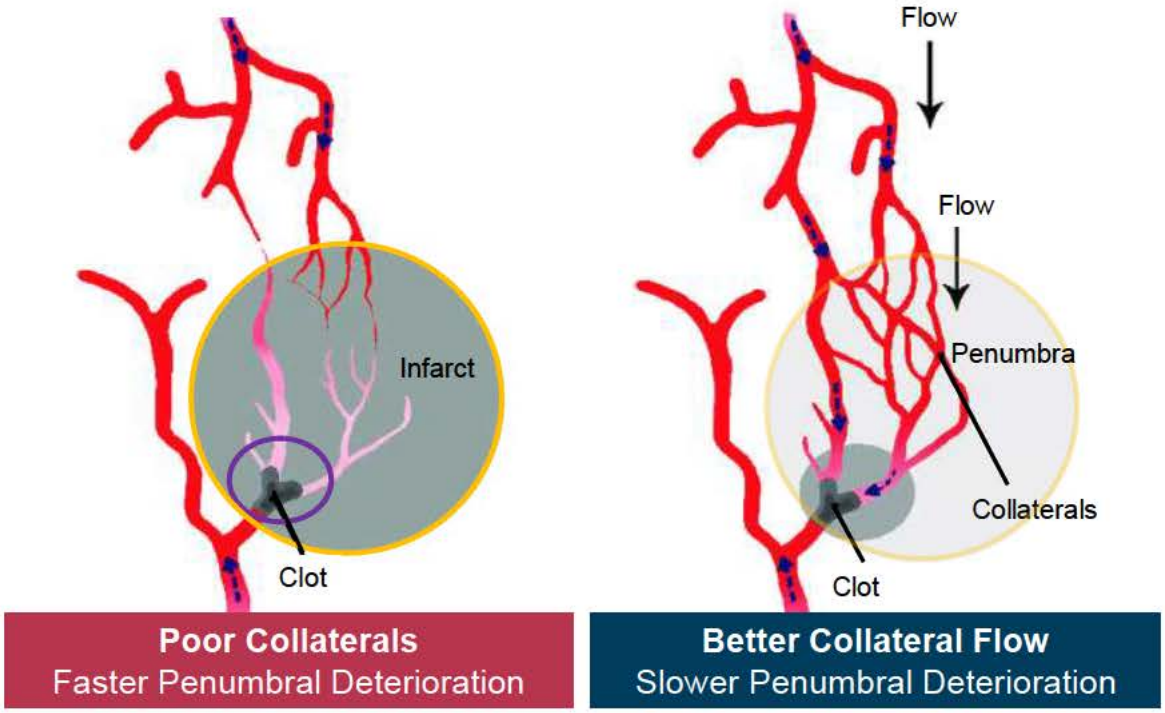

Figure 32 – The role of collateral blood flow in stroke

3.1.5 Disruption of the BBB

The blood–brain barrier (BBB) is a highly selective physical and biochemical border that separates the CNS from the systemic circulation. [6]

During an ischemic stroke, the affected area suffers oxidative stress and the intracellular tight junctions (TJs) are disrupted, resulting in compromised BBB integrity, increased permeability and poor regulation of transfer of molecules and ions across the BBB. Often, when BBB integrity is disturbed, neuronal dysfunction, neuroinflammation, and neurodegeneration may occur.

BBB disruption after ischemia also increases influx of fluid from the system circulation to the cerebral compartment, producing extracellular, vasogenic edema that adds to cytotoxic edema from ischemic cellular injury, increasing mass effect and herniation risk. [6] This cascade of cellular and molecular events elaborates tissue injury is correlated with stroke progression and functional outcome. [28]

The time course of the post stroke BBB opening is not clearly understood. Some studies have shown that BBB disruption peaks between 24-72 hours after stroke and persists for

several days, while more recent studies have shown that BBB opening is bi-phasic, and the second peak occurs between at 12–72 hours after stroke onset. [7, 5, 29]

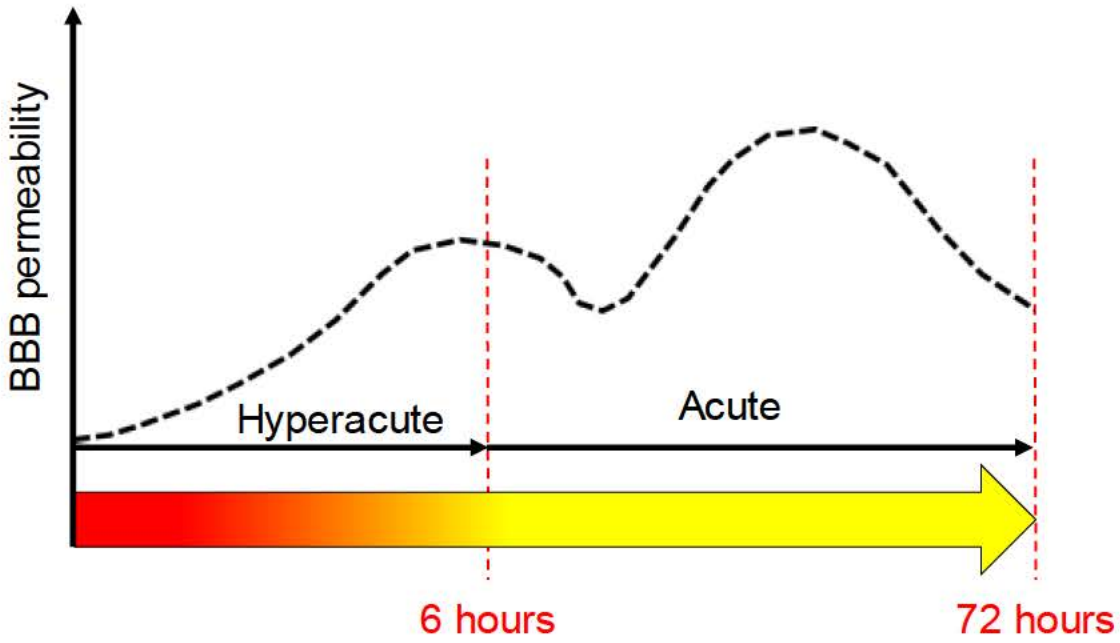

Figure 33 – BBB Disruption After Stroke [7]

3.2 Current Treatment Options

Timely reperfusion is associated with improved neurological outcomes, and recanalization therapies, including intravenous thrombolysis (IV-tPA and endovascular thrombectomy (EVT), are recommended by current clinical guidelines for the management of eligible patients with acute ischemic stroke.[30, 20]

IVT has clear therapeutic value, but its benefits are limited by a large number of contraindications, a short time to treatment window when using standard imaging, relatively low recanalization rates of 30% of visualized cerebral artery occlusions,[31] and increased rates of hemorrhagic transformation following treatment.

In a systematic review of the literature,[32] a significant 4-fold increase in symptomatic intracerebral hemorrhage (sICH) was observed in patients randomized to thrombolysis versus controls (7.5% vs. 1.7%, OR 3.75, 95% CI 3.11 to 4.51).

Indications for stroke reperfusion therapy were widened following the results of recent studies showing that the time window for treatment could be extended to up to 24 hours after stroke onset in highly selected patients. Selected patients are those with large vessel occlusion and salvageable brain tissue, presenting 6–24 hours after they were last seen well and who had small core and large potentially salvageable penumbral brain regions identified by multimodal CT or MRI imaging.

Recent studies demonstrated that this highly selected population had better functional outcome after endovascular treatment compared with patients who received medical therapy alone.[33, 34, 35, 36, 37]

3.3 Unmet Clinical Need

EVT has proven to be effective in the management of AIS. However, 86% of AIS patients may be ineligible for EVT [38], as eligibility criteria require catheter-accessible large vessel occlusions either:

1) Treatable within 6 hours of onset, or
2) Accompanied by small ischemic cores and large penumbras and treatable within 24 hours of onset.

Also, EVT requires intracranial vessel imaging, neuro interventional facilities, and neuro-endovascular medical expertise, which are available only in a small proportion of hospitals worldwide. [4]

Figure 34 shows the effectiveness of EVT as a function of time from onset when patients are not selected for this treatment based on core and penumbra volumes and it shows no benefit beyond 8 hours from stroke onset. [39]

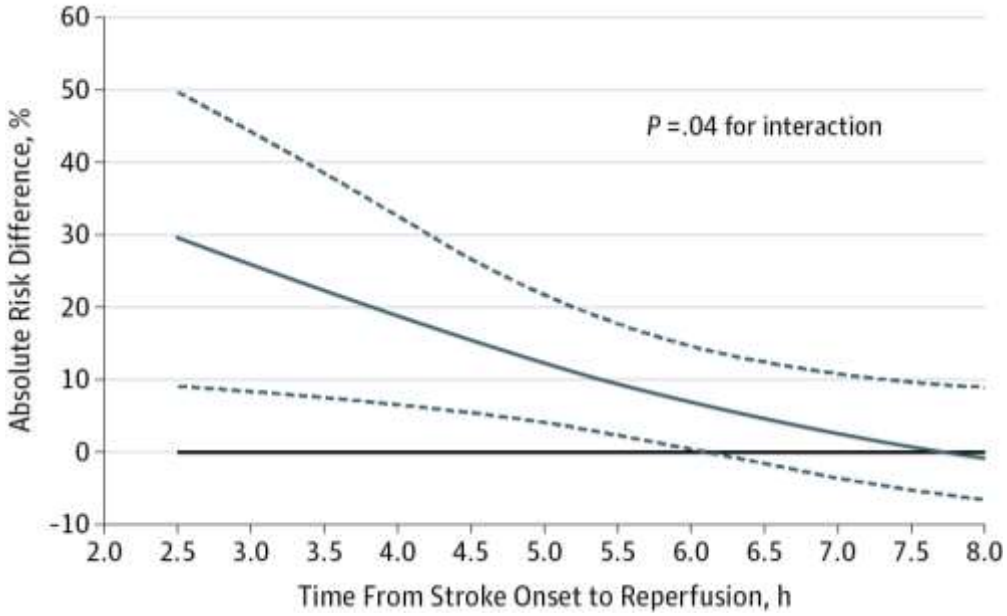

Figure 34 – Efficacy of Endovascular Thrombectomy (with 95% CI) vs Time from Stroke Onset [39]

Many other patients arrive to hospitals that do not perform EVT, have contraindications to IV-rtPA (e.g., active anticoagulation) and to EVT (e.g., non-navigable aortocephalic arteries) or arrive late and have established core.

As discussed above, the efficacy and the safety of direct reperfusion therapies more than 6 hours after onset depend on a small volume of irreversible infarction (ischemic core) and a large volume of salvageable tissue (penumbra). As the time from stroke onset elapses, the core grows and the penumbra disappears, diminishing the potential benefit and increasing the risk of symptomatic intracranial hemorrhage (see Figure 34 and Figure 33).

When using the common perfusion imaging definition of penumbra (Tmax6 volume) and target mismatch of 1.8, only 2%–3% of the patients arriving between 6 and 24 hours from last seen well are eligible for treatment (red curve in Figure 35).[1]

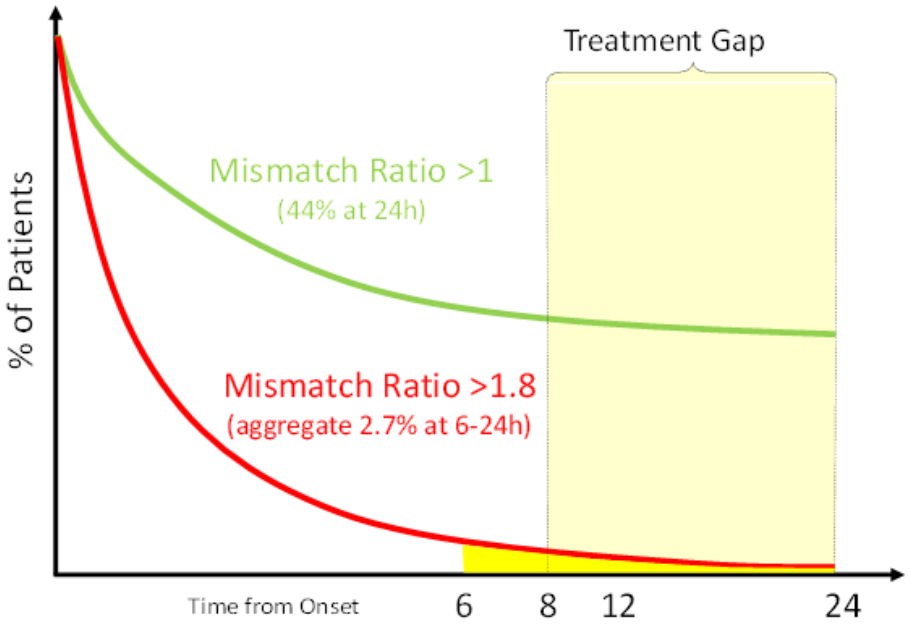

Figure 35 – Infarct Dynamics – the evolution of the penumbra and salvageable tissue

As a result, despite significant progress in direct reperfusion techniques in the last few years, only 8–12% of all acute ischemic stroke patients are being treated. [1, 40] Nonetheless, up to 44% of the patients have some salvageable tissue (and lower mismatch ratios) within 18–24 hours after stroke (green curve in Figure 35). These patients may not be eligible for late EVT but may still benefit from treatment. [2]

In the US, most patients live within a one-hour helicopter flight to an EVT-capable center. However, recent studies have shown that 40%-73% of the hospital transfers for EVT in the US are futile, as patients are no longer eligible for EVT after transfer. [41, 42]

Recent data from a large comprehensive stroke center who already used tissue-based criteria for late EVT shows that 31% of the patient present within 24 hours from stroke

onset with large or medium vessel occlusion (LVO/MVO) and are currently not treated by EVT and/or IV-tPA, as shown in Figure 36. [43]

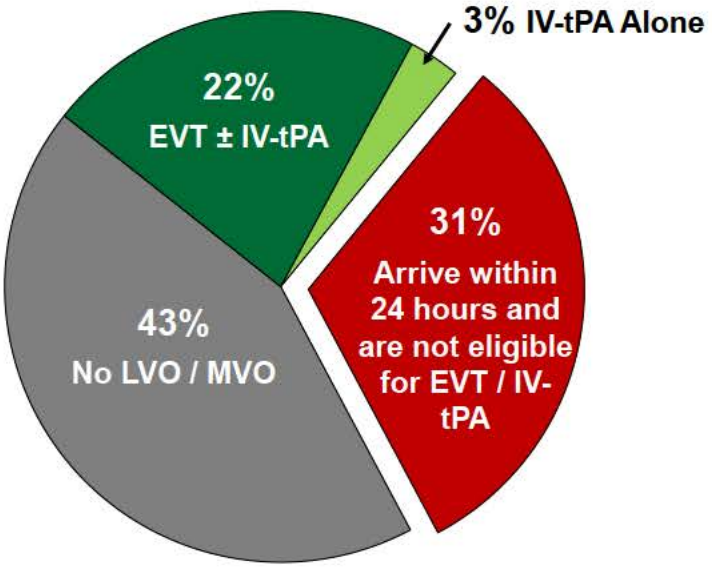

Figure 36 – Treatment Gap in Large Comprehensive Centers [43]

According to the same study, these 31% of patients, who present with LVO/MVO and were ineligible for EVT, had median ASPECTS 7 (same as the CCI population in ImpACT-24B), indicating that most of this group had confirmed cortical involvement. Based on that, it is conservative to assume that 35%-50% of these patients would be eligible for SPG stimulation (10%-15% of all AIS patients in comprehensive centers).

In summary, there is a need for treatment that is simple to administer and is safe and effective in an 8- to 24-hour window in patients who are ineligible for or don't have access to available therapies.

4 SPG Stimulation to Treat Ischemic Stroke

Summary:

- The SPG "manages" vasodilation of the anterior cerebral circulation
- SPG stimulation leverages this mechanism to reduce disability after stroke
- Collateral enhancement affects mostly the cortical regions
- SPG stimulation aims to stop the ischemic cascade and preserve the BBB

4.1 SPG Pathophysiology

The Sphenopalatine Ganglion (SPG) is the source of parasympathetic vasodilatory innervation to the collateral network of the anterior cerebral circulation and electrical stimulation of the SPG has been known to increase blood flow in the collateral arterial networks through vessel dilation and augmentation of collateral flow in the cortex. [6, 8]

In humans, there are two SPGs, located behind the maxillary sinuses; each innervates its ipsilateral hemisphere (see Figure 37).

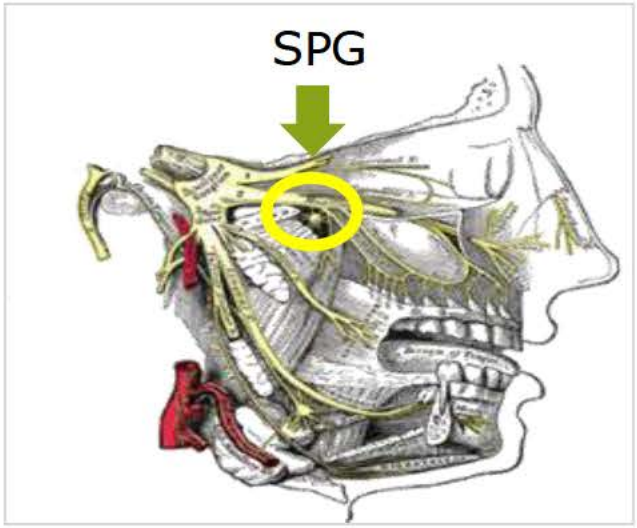

Figure 37 – The Sphenopalatine Ganglion

Multiple interacting regulatory systems control cerebral blood flow (CBF). CBF and cerebral metabolism are tightly linked at the local level by the influence of local substances such as oxygen, ensuring rapid matching of blood supply to metabolic demand. [6]

The nervous system also contributes substantially to CBF regulation. The parasympathetic innervation of the cerebral vasculature is the most potent vasodilatory neural influence, capable of altering CBF independent of current metabolic demand and perfusion pressure. [6]

Parasympathetic fibers from the SPG directly innervate the carotid artery, cerebral vessels, and choroidal vessels. Nerve density is greatest at branching points. The neurotransmitters released at vessel end organs by parasympathetic nerves across species all have vasodilator effects, and include NO, VIP, peptide histidine methionine, and acetylcholine. [6]

In pre-clinical stroke models, blood flow augmentation using SPG stimulation resulted in improved functional outcome. The magnitude of benefit was highest in the hyper-acute time window (0–3 hours), but the benefit persisted when treatment was initiated up to 24 hours from onset, without dependency on the time from onset within a late 9–24 hours window. This was the basis for the design of ImpACT-24A and ImpACT-24B clinical trials, and the same finding was observed in both trials.

4.2 SPG Stimulation Mechanisms of Action

Four neurovascular/neurobiological mechanisms likely contribute to SPG Stimulation benefit in AIS with confirmed cortical involvement in the 8- to 24-hour time window:

a. Collateral enhancement and increased cerebral perfusion in the cortex
b. Blood–brain barrier stabilization in large strokes, involving the cortex
c. Activation of central cholinergic and noradrenergic network neuroprotection
d. Neuroplasticity, neurogenesis, and enhanced neural repair

The following sections focus on the first two mechanisms, which have the most supporting pre-clinical and clinical evidence.

4.2.1 Collateral Enhancement and Increased Cerebral Perfusion

Increased blood flow by SPG stimulation is demonstrated in Figure 38 which shows normal blood flow before stimulation (A), compared to increased blood flow during stimulation (B) in the same pre-clinical model (Adult male Sprague-Dawley rats).

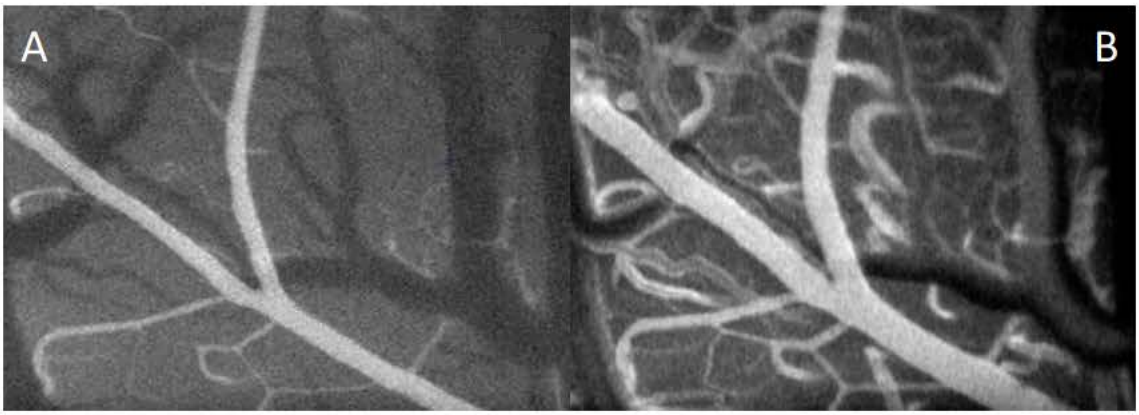

Figure 38 –Blood flow before (A) vs. during SPG stimulation (B) in preclinical model

The degree of CBF increase depends on the level of stimulation in an inverted U-shaped dose-response relationship. [44] This effect in stroke models is shown in Figure 39. The

black line shows the relative change in the vessel diameter and the red line shows the relative change in the peak-to-peak (arterial-venous) interval (Mean Transit Time).

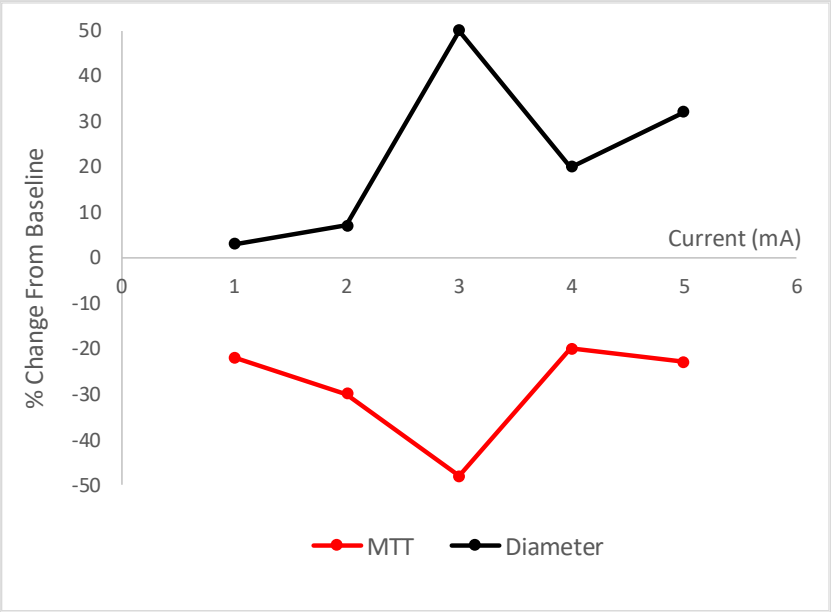

Figure 39 – Dose Response in Pre-clinical Study

Similar dose response relationships were demonstrated in stroke patients in ImpACT-24B between stimulation level and disability outcomes in all endpoints (see Figure 85 in Section 7.2.6.4 below).

An increase in blood flow was also seen in pre-clinical stroke models [44]. The left image in Figure 40 shows the flow before inducing stroke in a rat. The center image shows the reduction of flow when stroke is induced, and the right image shows the increase during stimulation. The white circle marks the penumbra. The bottom graph shows the reduction

of flow through the carotid artery when stroke is induced, and the increased flow during stimulation.

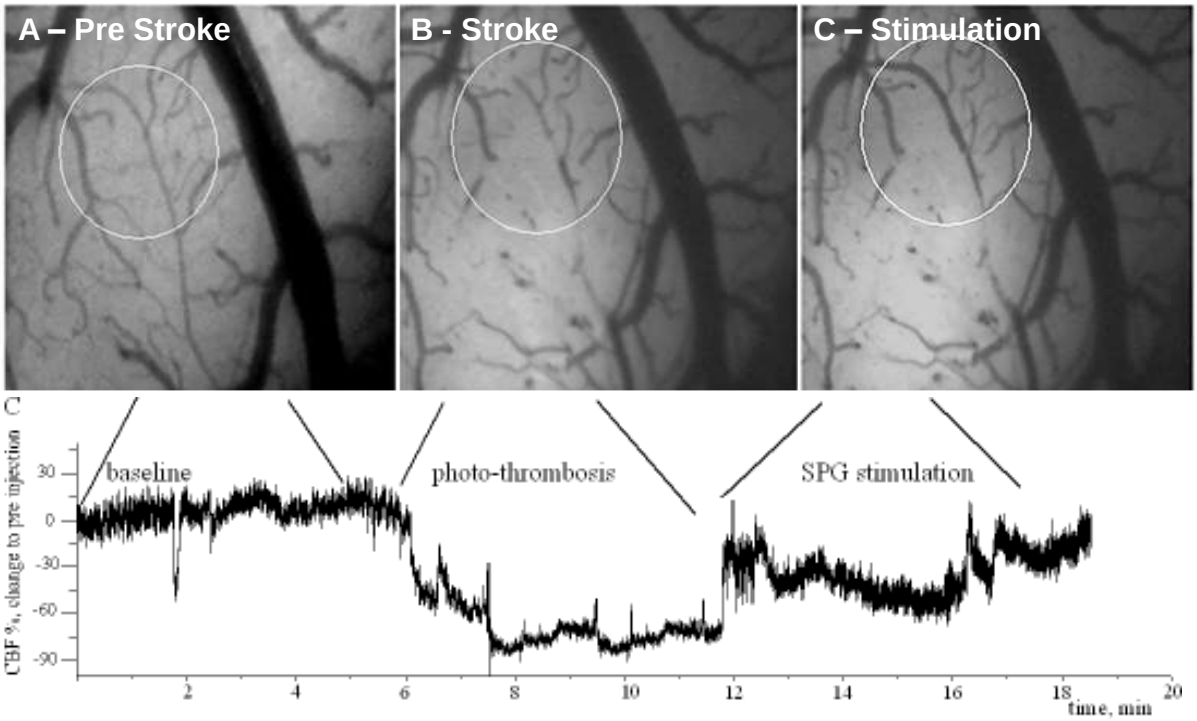

Figure 40 – Pre-clinical Stroke Model Before and During Stimulation (brain surface microscope images)

Figure 40 demonstrates that the total CBF to the affected hemisphere is increased during stimulation, confirming that collateral flow augmentation by SPG stimulation is not a "zero sum game" (not increasing flow in one region by reducing blood flow to other regions). The increased CBF can also be seen in angiographic images (Figure 41):

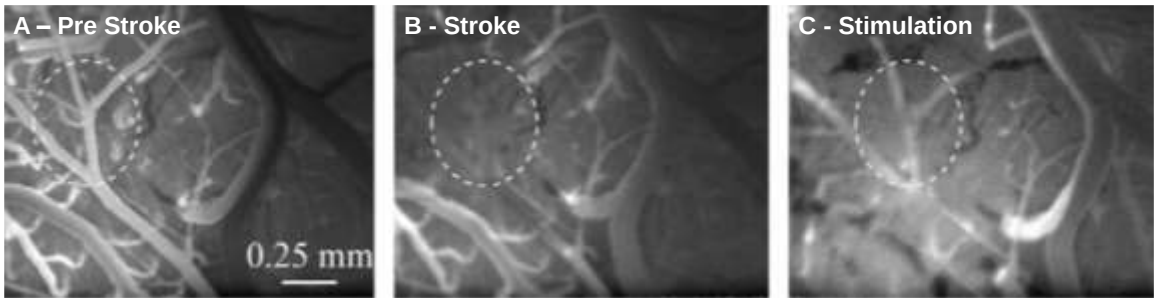

Figure 41 – Fluorescent angiography in a stroke model

Increased cerebral blood flow was also seen in stroke patients, in the ImpACT-24M clinical study (see Figure 114 in section 7.5.3.4).

In most people, the vasculature in the cortex is richly collateralized. Inter-arterial connections allow blood to get to cortical tissue by different routes, so that when an artery is blocked and there are low levels of perfusion, blood can bypass the obstruction through the pial arterial network.

Better pial collateral flow leads to slower penumbral deterioration, hence slower evolution to permanent brain and tissue death. [3, 10] Improving pial collaterals allows retrograde flow to preserve the cortical regions of the brain when anterograde glow is cutoff. This therapeutic approach differs from direct reperfusion therapies, which rely on opening the occluded vessel (Figure 42).

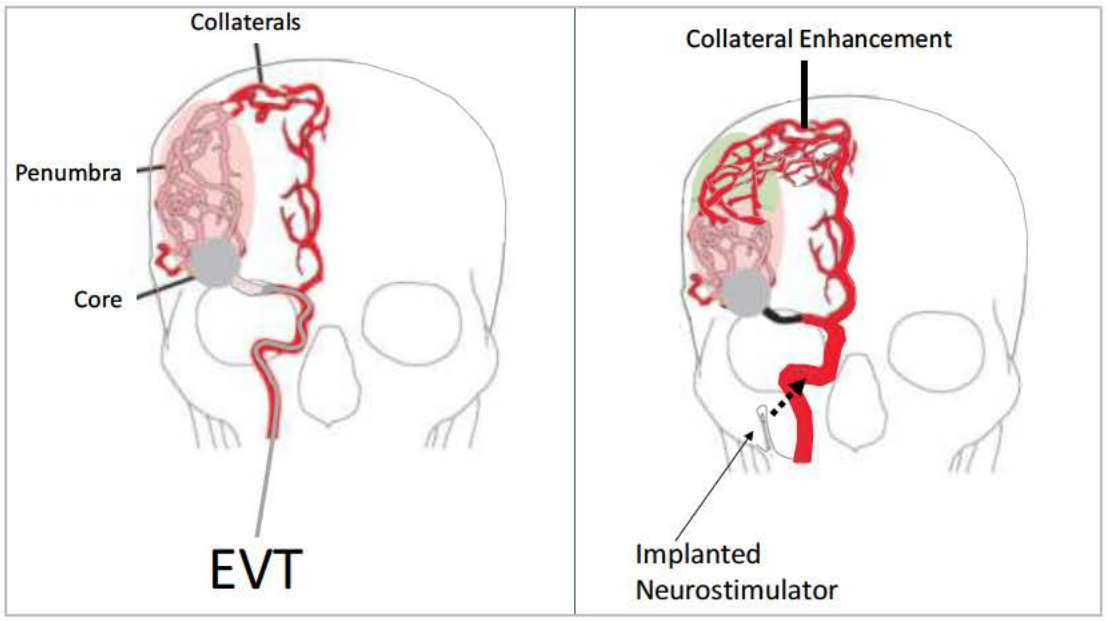

Figure 42 – Direct Reperfusion (A) vs Collateral Flow Augmentation (B)

Collateral enhancement may not be able to completely prevent core growth (Figure 43, blue region), but it may reduce the volume of tissue at risk and salvage some of the penumbra (Figure 43, yellow region).

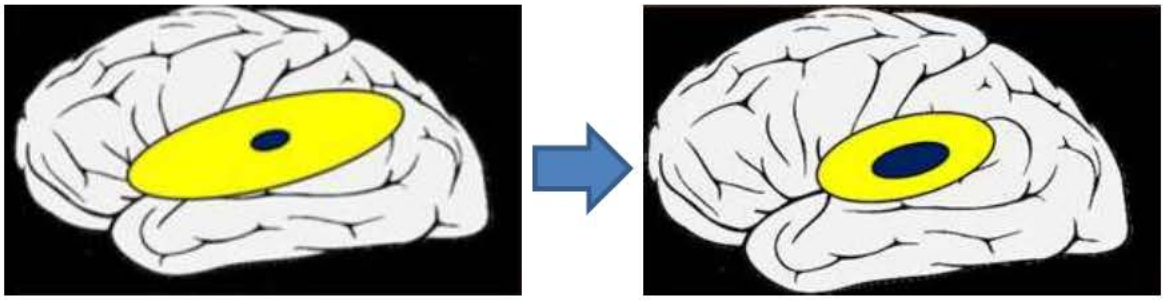

Figure 43 – Collateral Enhancement Effect on the Penumbra

Since SPG stimulation augments blood flow to the cortex, clinical benefit was expected to be greatest in patients with Confirmed Cortical Involvement. This was observed in the pilot ImpACT-24A study, and repeated in the pivotal ImpACT-24B.

An example of the stimulation effect in a CCI patient is shown in Figure 44 using CT Angiography. The occlusion (yellow circle on the left) reduced blood flow in the cortical region downstream (left image). Repeated imaging after the first stimulation session showed that the vessel was still occluded (yellow circle on the right image) but blood flow was increased in the ischemic cortical region through the collateral circulation.

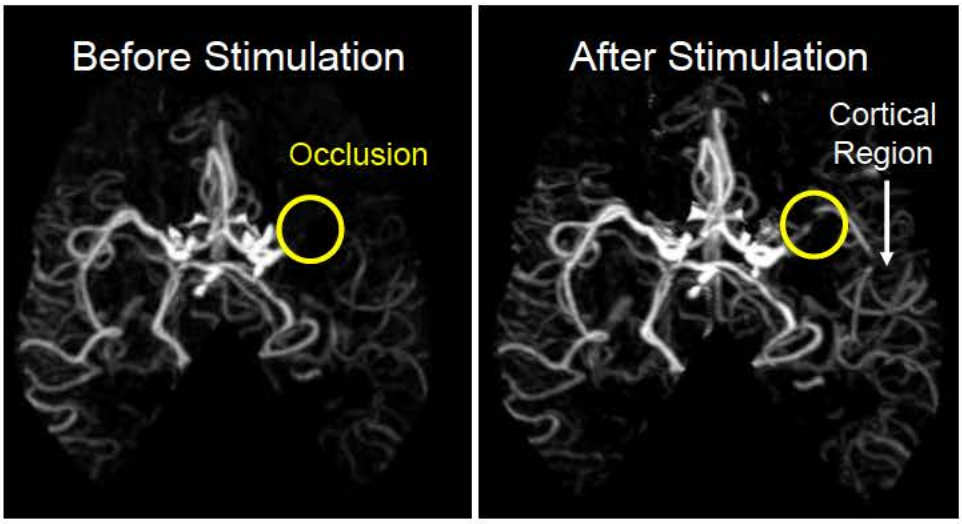

Figure 44 – CT Angiograpy of a CCI Patient Before and After SPG Stimulation

The increased blood flow to the cortical region is also evident in CT perfusion scans of the same patient, before and after stimulation. Substantial improvement in perfusion after stimulation is demonstrated in the cortical region (Figure 45, right), compared to the baseline scan before stimulation (Figure 45, left).

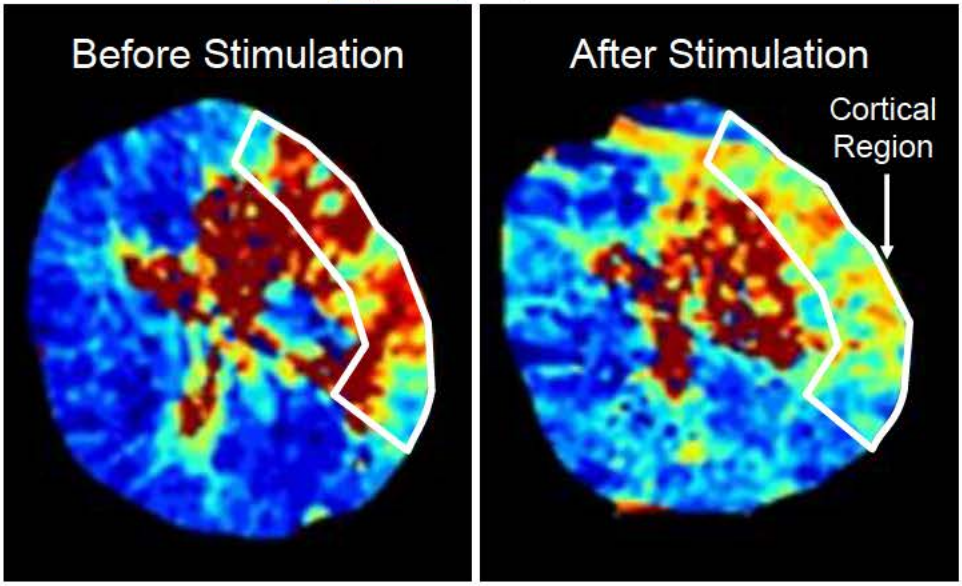

Figure 45 – CT Perfusion of a CCI Patient Before and After SPG Stimulation

4.2.2 Blood–Brain Barrier Stabilization

This section discusses the mechanism by which SPG stimulation can benefit CCI patients in the late time window without being limited to patients with small core and large penumbra.

BBB breakdown "fuels" the ischemic cascade (Figure 46)[44], results in leakage of fluid into the brain, impairment of local homoeostasis, and entry of serum metabolites toxic to brain cells. This increases brain edema, exacerbates brain damage, and in severe cases causes brain herniation and hemorrhagic transformation of the infarct, and is associated with poor outcome.[28]

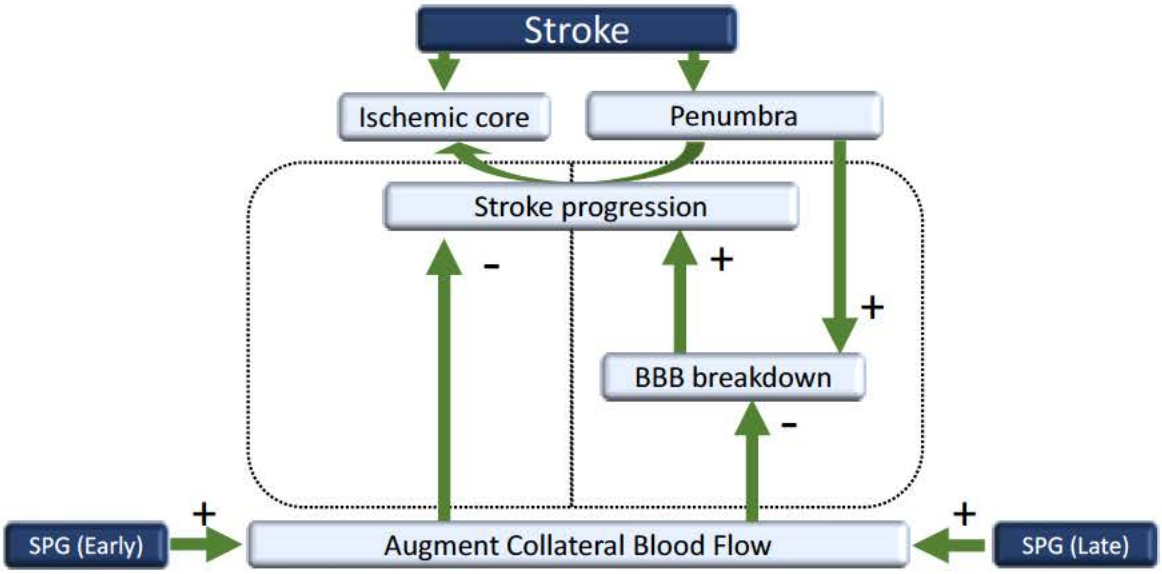

Figure 46 – SPG stimulation aims to slow the ischemic cascade and prevent BBB breakdown [44]

By augmenting blood flow to the cortical ischemic field via collaterals, SPG stimulation aims to slow this ischemic cascade, preserve the BBB, and reduce the ischemic stress, allowing tissue to tolerate the reduction in direct perfusion through the initially occluded artery. This is achieved by supplying more oxygen to the penumbra and by preventing BBB breakdown (Figure 46). [44]

This effect of BBB preservation was demonstrated in preclinical stroke models (adult male Sprague-Dawley rats Figure 47):

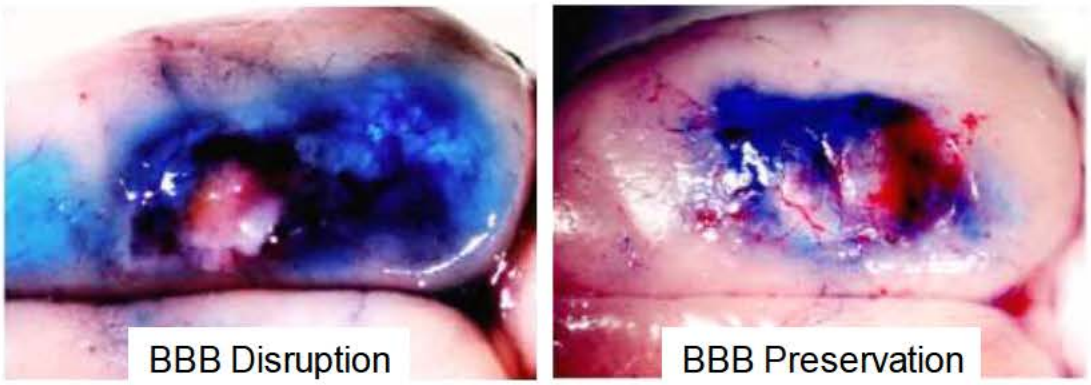

Figure 47 – BBB Disruption in control animal (Left) vs BBB preservation by SPG stimulation (Right)

The extent of BBB disruption, as indicated by the blue dye is markedly smaller in animals treated with SPG stimulation compared to control animals. [44] BBB protection by SPG stimulation was also demonstrated in clinical trials. The rate of sICH was 5x lower in the SPG stimulation group in the pooled dataset compared to sham controls.

As discussed in section 3.1.5 - Disruption of the BBB, the damage to the BBB peaks between 12-72 hours after stroke onset, directly overlapping the ISS500 treatment window (5 days of treatment, where the first treatment is initiated between 8-24 hours after stroke). This may explain why treatment benefit in the two randomized trials was independent of the time from stroke onset (within the 8- to 24-hour window).

4.3 SPG Stimulation and Severe Ischemia

An MR spectroscopy study showed a significant difference in the levels of NAA (a marker of neuronal activity) in the severely ischemic regions, 8 days and 28 days after stroke, in adult male Sprague-Dawley rats treated with SPG stimulation compared to the control group.

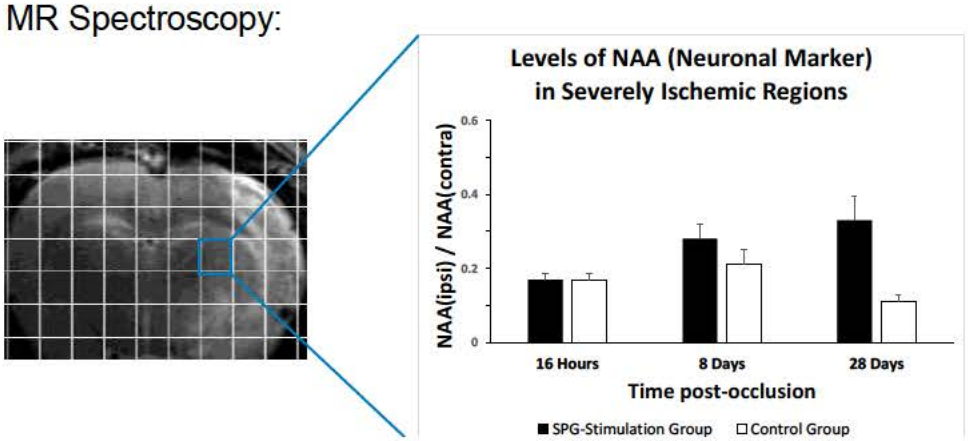

Figure 48 – Increased levels of NAA (marker of neuronal activity), SPG stimulation vs Control

In an exploratory pre-clinical stroke model, SPG stimulation 18 hours after onset reduced the levels of lactate in the severely ischemic region. [45] Figure 49 compares the composition of a severely ischemic region by MR spectroscopy. The upper images are divided by grids, and each graph represents one square in the grid. Lactate levels are represented by negative peaks (marked with blue rectangles on the graphs).

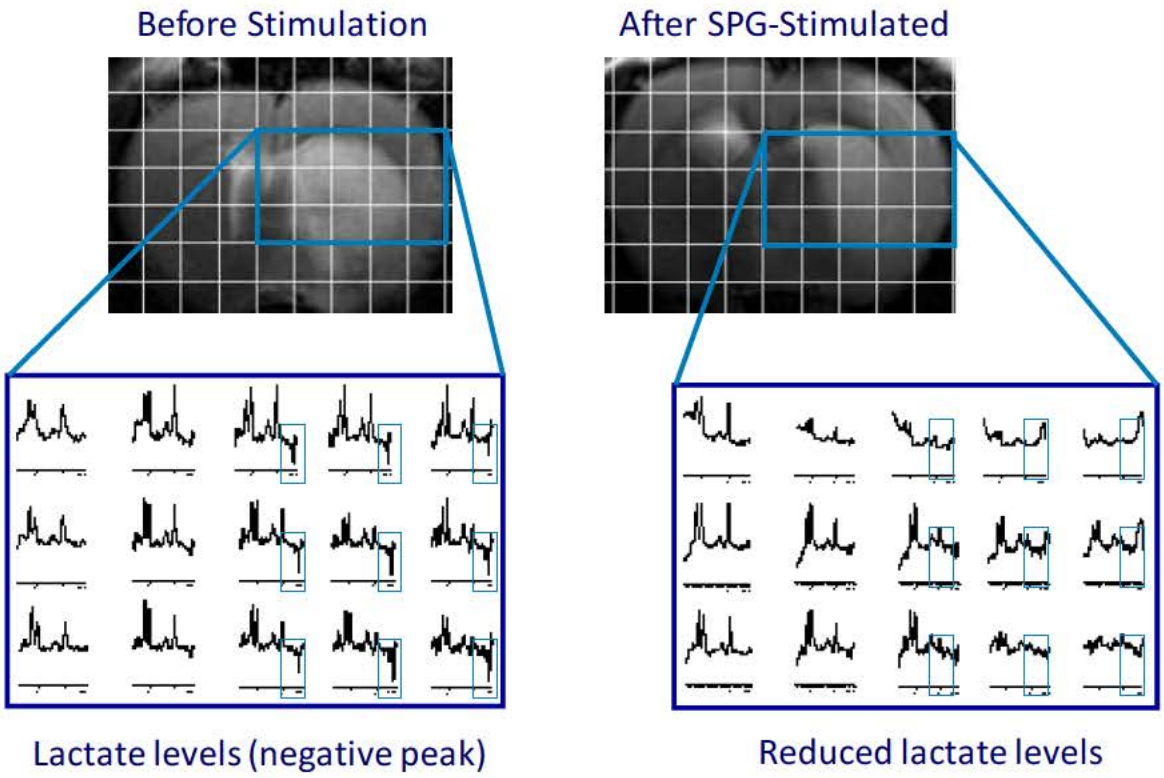

Figure 49 – Reduced lactate levls (negative peak in blue rectangles by SPG Stimulation (MR Spectroscopy)

The lower lactate levels and increased neuronal activity in the severely ischemic regions suggest that SPG stimulation may be effective in patients with large areas of severely ischemic tissue in the cortex.

Consequently, the ISS500 clinical trials population included ischemic stroke patients with baseline infarct core up to 2/3 of the MCA territory and treatment was initiated up to 24 hours from onset.

Both studies showed that the treatment effect is not limited to patients with small core.

The ImpACT-24A and ImpACT-24B studies population is substantially different than the late-window thrombectomy trials population. The following table compares the time from Last-Known-Well (LKW) to treatment initiation and baseline NIHSS (indicative of the penumbra volume) of the CCI population to those of the late-window EVT candidates in the DAWN and DEFUSE-3 trials.

	DAWN / DEFUSE-3	ImpACT24-CCI
Median Time from LKW	11-12h	19h
Median NIHSS	17	13

Table 3 – Baseline Characteristics - SPG vs. EVT [33, 34]

Patients in the late-window EVT trials had larger penumbra, as well as shorter time from onset. Additionally, only patients with small core volumes were included in the EVT trials (median infarct volume <10ml in both trials), while this was not a requirement in the ImpACT-24A and ImpACT-24B trials.

4.4 SPG Stimulation Addresses the Unmet Need

As discussed above, EVT was shown to be effective up to 24 hours from stroke onset in patients with small core and large penumbra, which represent a small subset of the patients in the 8- to 24-hours window.

However, their use is time-dependent and is limited in the late time window to 2-3% of the patients who have small core and large penumbra (Figure 50).

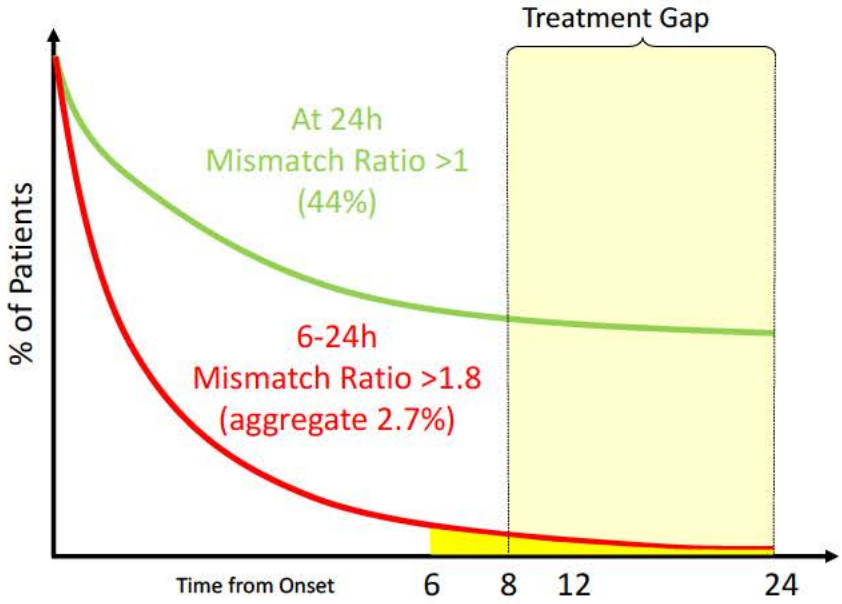

Figure 50 – Infarct dynamics in the first 24 hours after stroke

At the same time, the risk of BBB damage increases, and peaks between 12-72 after onset:

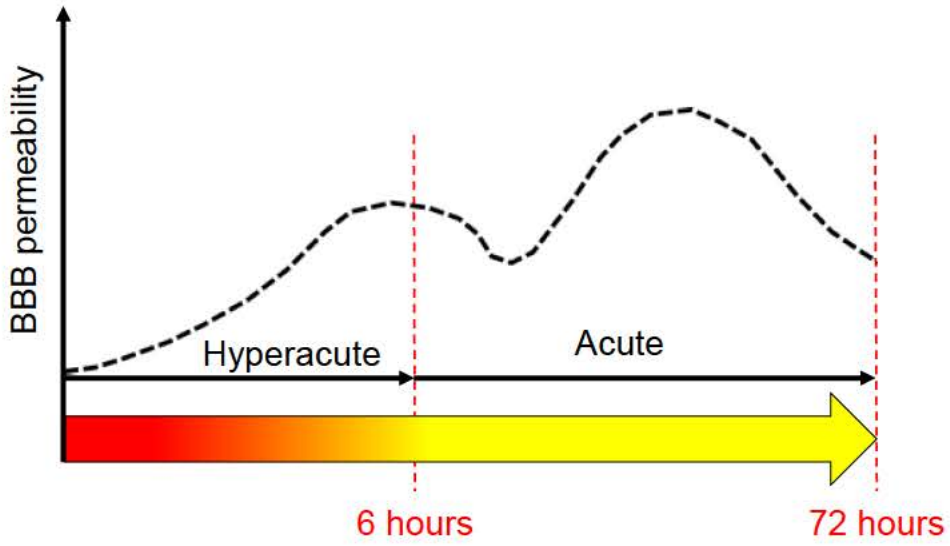

Figure 51 – Evolution of the penumbra, salvageable tissue and BBB disruption

The pre-clinical and clinical data demonstrate that SPG stimulation benefits additional patients that are not eligible for EVT. In summary, SPG stimulation improves outcome by two related mechanisms – preserving the penumbra by increasing cortical blood flow through the collateral circulation and preserving the BBB. Both mechanisms are most significant in large territorial strokes, that involve the cortex.

Some of the benefit of delayed SPG stimulation may be explained by the existence of salvageable tissue in the late time window which might not meet the strict definition of EVT eligibility (see section 3.1.4). This may explain, for example, the improvement in motor function during stimulation in ImpACT-24M measured up to 24 hours from onset (see Figure 113 in section 7.4 below) but the benefits of blood flow augmentation that do not depend on the time from onset or on the baseline infarct size are likely the result of the protection of the BBB.

The clinical studies were designed to demonstrate that the combination of these two mechanisms allows SPG stimulation to be safe and effective when initiated in the 8- to 24-hour time window without being limited (as EVT) to patients with a favorable penumbra/core volume ratio.

If approved, SPG stimulation will extend the therapeutic window for patients who do not meet the criteria for late EVT (Figure 52).

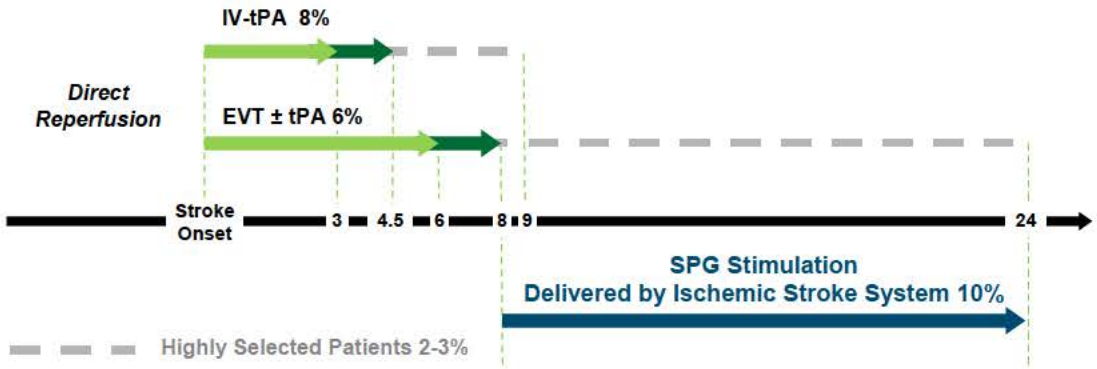

Figure 52 – The extended therapeutic window

It is roughly estimated that ~10% of US ischemic stroke patients will be eligible for SPG stimulation (see Appendix L – Estimated Number of Eligible US Patients for details).

5 Device Description

Summary:

- A first of its kind injectable neurostimulator
- Smart implant with miniature ASIC[i] communicates the actual patient current
- 20 years of technology development, in parallel with the clinical evaluation
- Injected to the SPG fossa in a 5-minute bed-side procedure
- Patient-specific stimulation by physiologic markers of SPG activation
- As with many first-of-a-kind devices, the ISS500 system components and implant technique have evolved over the years, with redesigns to mitigate potential risks.

The Sphenopalatine Ganglion (SPG) is the source of parasympathetic vasodilatory innervation to the collateral network of the anterior cerebral circulation and electrical stimulation of the SPG has been known to increase blood flow in the collateral arterial networks through vessel dilation and augmentation of collateral flow. [8]

The ISS500 is intended to treat stroke by SPG stimulation, under the following IFU:

"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 ISS500 system is comprised of three main components: an acutely implanted neurostimulator, an external treatment subsystem, and an implantation subsystem.

[i] ASIC - Application Specific Integrated Circuit (dimensions: 0.6mm x 1.8mm x 0.25mm), a technology leap that enabled the development of the final implant.

5.1 Injectable Neurostimulator

The injectable neurostimulator (INS) is a 23.5mm long temporary implanted device that delivers electrical stimulation to the SPG (Figure 53).

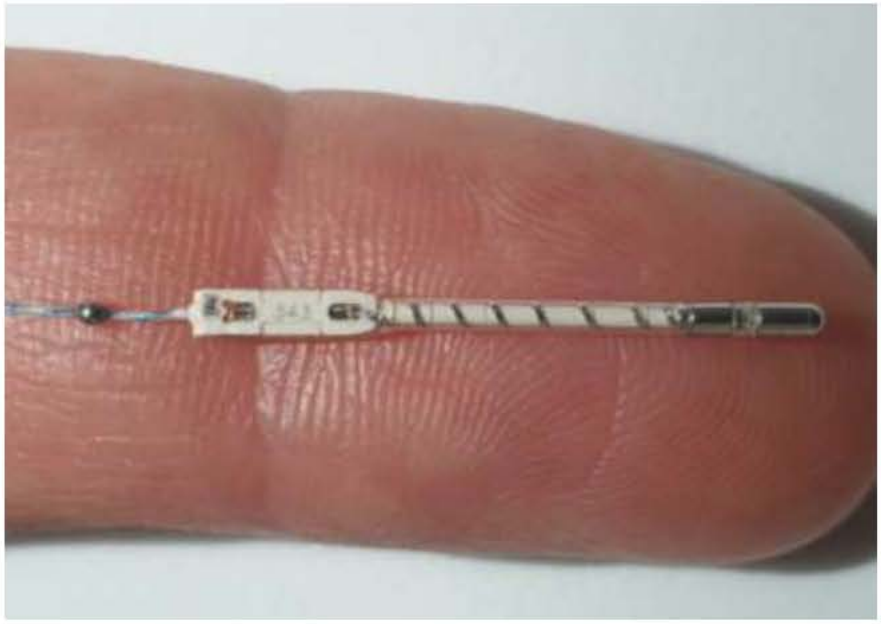

*Figure **53** – Injectable Neuro Stimulator (INS)*

Its flexible "neck" allows it to be injected into curved canals.

The INS has an integrated electronic circuit which verifies that the intended stimulation is delivered successfully to the SPG by measuring the actual current. Any treatment interruption is detected immediately and reported through the treatment system to the user.

5.2 Treatment Subsystem

The purpose of the external treatment subsystem is to manage the patient's treatment, and it includes the following external components:

- **Transmitter** – an RF antenna positioned on the patient's cheek that communicates with the temporarily implanted neurostimulator
- **Driver** – transmits RF energy through the transmitter to the INS (Injectable Neuro Stimulator)
- **Controller** – provides the treatment subsystem's programmable user interface.

The treatment subsystem is illustrated in Figure 54.

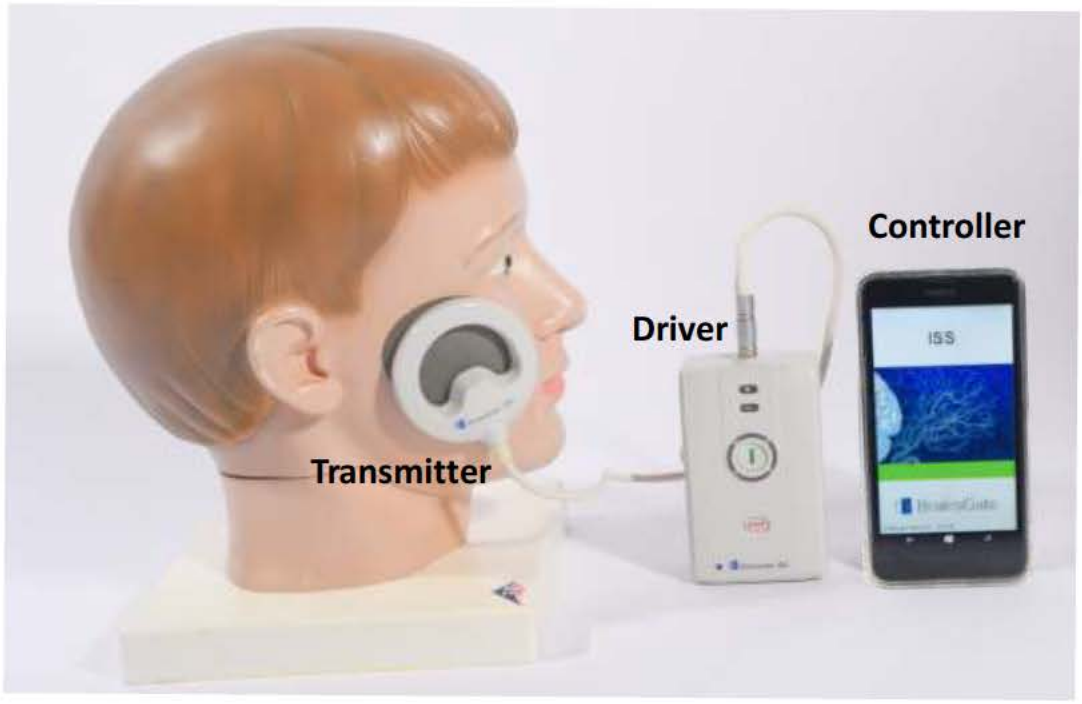

Figure 54 – Treatment subsystem

Treatment is delivered for 5 consecutive days, with 4 hours of stimulation per day, as illustrated in the following figure:

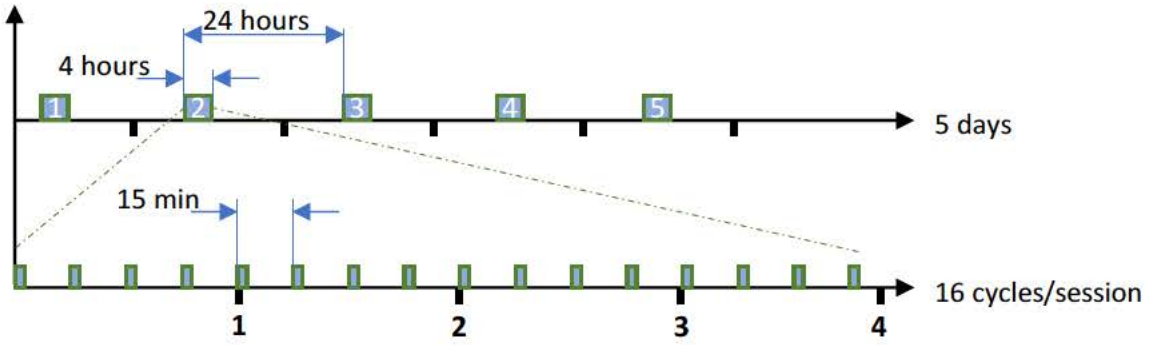

Figure 55 – The ISS500 Treatment Protocol

The stimulation level is set at the beginning of every treatment session by a trained caregiver, based on unique physiologic signs of SPG activation, such as unilateral lacrimation and tingling facial sensation on the stimulation side. The process of identifying the stimulation level by the physician at the patient's Comfortable Tolerance Level (CTL), based on these biomarkers, is illustrated in Figure 56.[i]

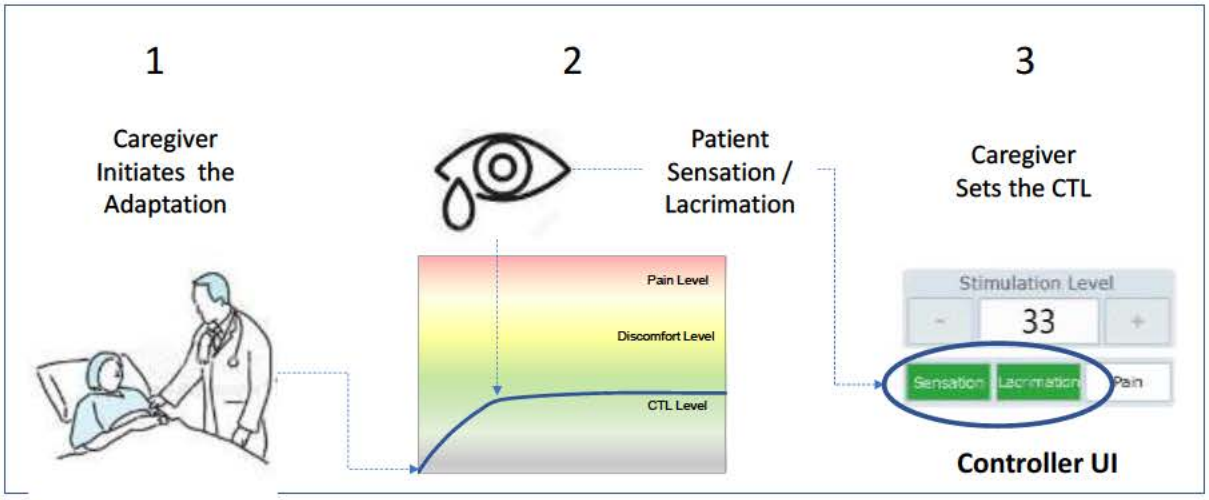

Figure 56 – Setting the Stimulation Level ("Adaptation")

When stimulation level begins to increase, the first sign to appear is the tingling sensation, then the lacrimation. If stimulation is further increased, facial pain appears. Pain should be avoided as it indicates that treatment is applied at a "too high" level. Tingling sensation always precedes pain.

The system limits the search for the CTL to the non-noxious physiologic range (the range in which non-noxious signs of SPG activation appear in >90% of the patients according to ImpACT-24M. In the same range, the effectiveness of SPG stimulation was highest in ImpACT-24B, see section 7.6).

[i] Physiologic signs could not be used in the double-blind trials, due to blinding considerations.

5.3 Implantation

The implant is injected through the Greater Palatine Canal (GPC) in the hard palate of the mouth (Figure 57):

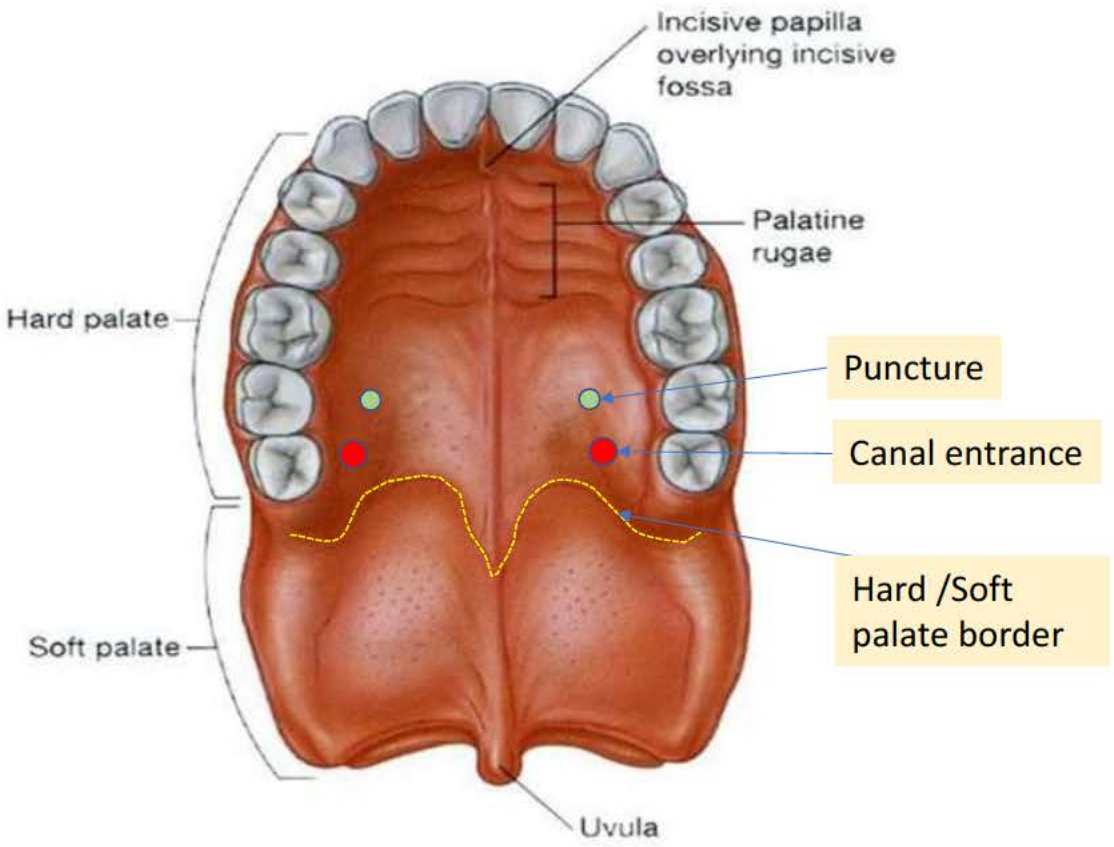

Figure 57 – The Upper Palate

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

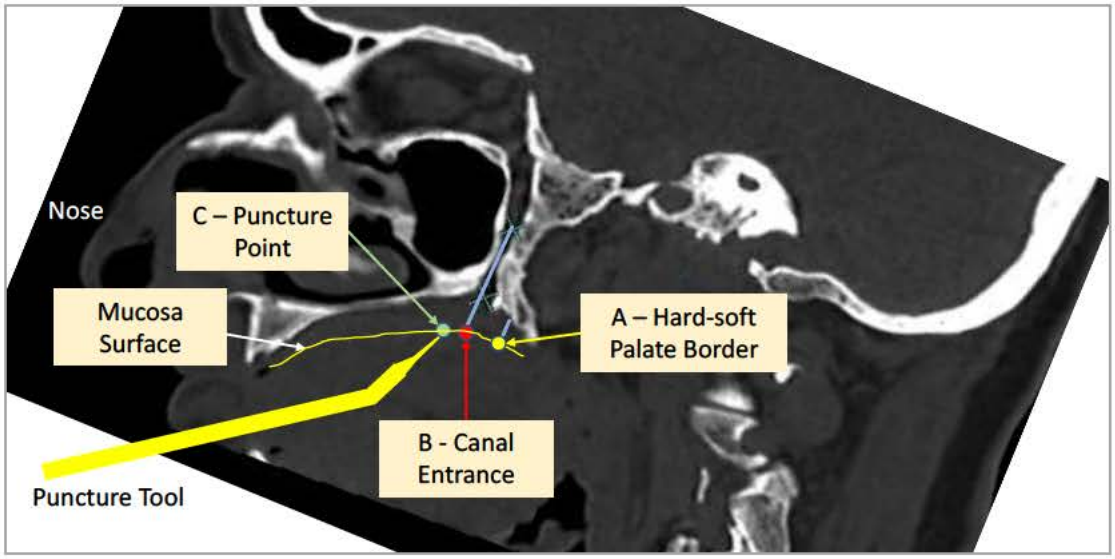

Figure 58 – The Upper Palate – Sagittal View

Injection of the INS is performed using a pre-loaded, single-use injector called Introducer (Figure 59), under local anesthesia. The flexible and robust structure of the INS allows its injection directly into the canal.

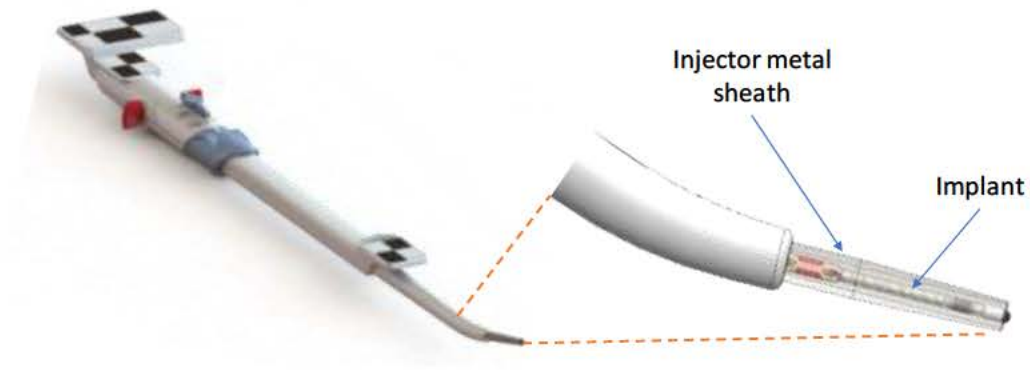

*Figure **59** – Introducer*

INS implantation is performed using the ISS GuideView implantation subsystem which is based on image guided navigation. The concept of optical navigation using markers (on the patient and on the implantation tools) is illustrated in Figure 60.

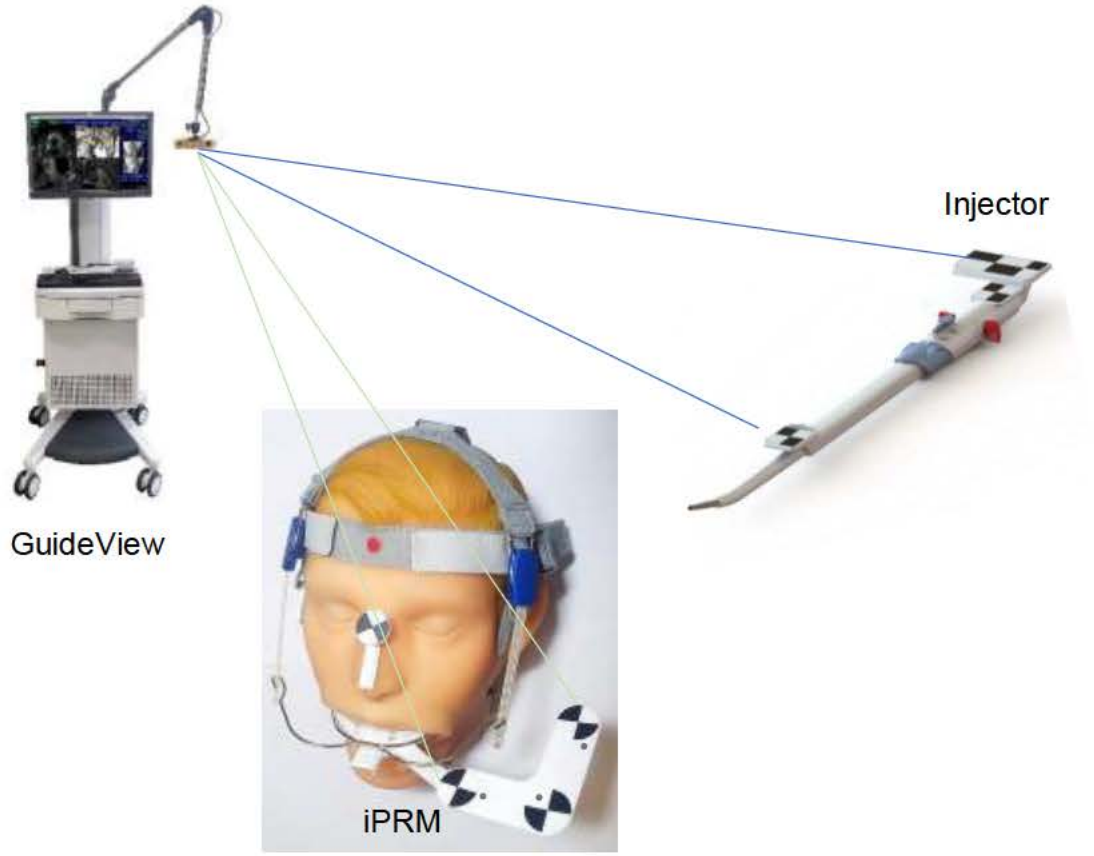

Figure 60 – Navigation using Optical Tracking of the Patient and Tools

Guidance accuracy is ensured by the iPRM (Figure 60), which includes an embedded CT-visible marker and optical markers. It allows GuideView (the image guided navigation system) to automatically match between the CT scan and the patient ("Registration").

Using a patient-specific imprint, the iPRM is attached to the patient's teeth or gum-lime. The patient-specific imprint material (Thermofix), has two unique properties:

1) When it is warm, it adapts itself to any shape, including the shape of the teeth and even the gum line with no teeth.
2) When it is cool, it hardens and maintains its shape.

To increase stability even further and prevent movement, the iPRM is fixed to its place using the head strap. This design ensures that the iPRM is stable regardless of the patient's teeth and gum condition.

If, despite these mechanisms, the iPRM moves, the software detects this movement and notifies the user. When this happens, the unique shape of the imprint allows the user to return the iPRM to its place and verify the registration accuracy again.

The implantation is a bedside procedure, performed by trained medical doctors, typically neurologists (see details in Appendix E – Training Program Overview) and does not require special infrastructure. After the last treatment on day 5, the implant is removed using forceps, by pulling the extraction thread. No anesthesia is needed for removal.

The following images show the implantation site immediately after injecting the implant, (left) and after the implant is removed by pulling the extraction thread (right).

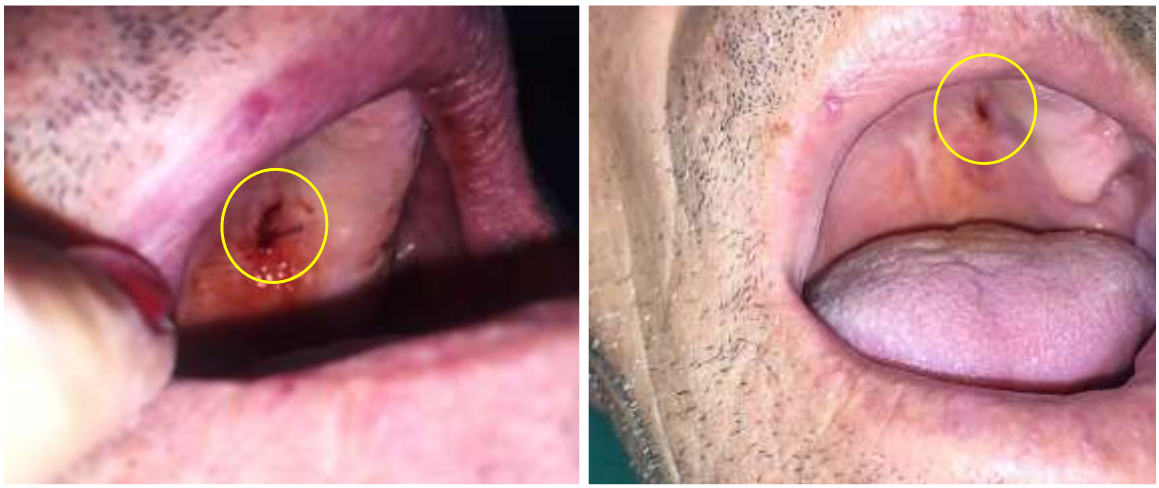

Figure 61 – Implantation site after implant injection (left) and after implant removal on day 5 (right)

Prophylactic antibiotic is administered to prevent infection.

6 FDA Interaction

Summary

- BrainsGate has worked interactively with the FDA since 2006
- Main topics of interactions with the FDA were:
  - Device changes
  - Blinding of control patients
  - The primary endpoint analysis method
  - The modified Intention to Treat (mITT) analysis
  - The CCI primary analyses population

The novelty of the ISS500 system required a long development process and the interaction between FDA and BrainsGate have spanned over 15 years, starting in 2006 as illustrated below.

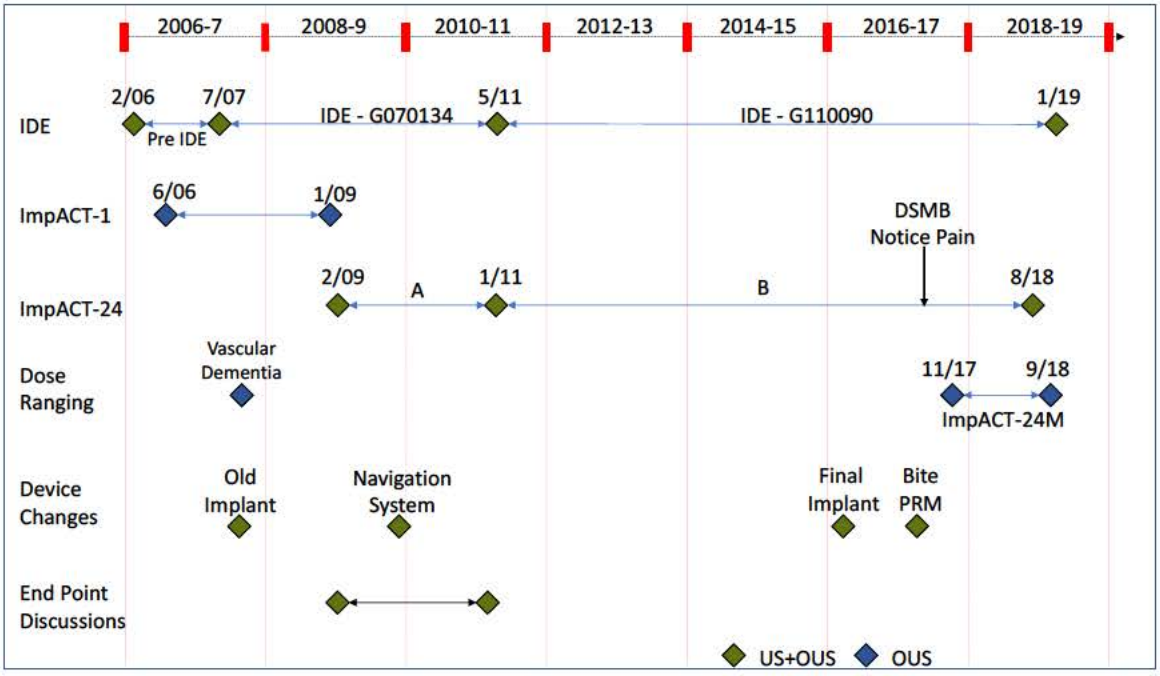

Figure 62 – Interactions Timeline

The main topics of interaction with FDA during the IDE phase included:

1. Device Changes – Several generations were needed to develop the technology to simplify the procedure and prevent misplacements
2. Study Design
    a. Blinding of control patients– How to make control patients believe they were treated
    b. The primary endpoint analysis method (sliding dichotomy)
    c. The modified Intention to Treat (mITT) analysis
    d. The CCI primary analysis population

The following sections summarize these topics.

6.1 Device Changes

Reducing implant misplacements and implantation simplification were the primary reasons for device changes during the 15 years of interaction with FDA, and none of the changes affected the treatment (no change in the electrodes or the stimulation parameters). The key changes are described in this section.

6.1.1 Implantation System

6.1.1.1 The GuideView Navigation System

The first 143 implantations in ImpACT-24A were based solely on anatomic markers, without image guidance. The result was a high rate of implant misplacements, and it became apparent that a guidance system is required.[i] The GuideView navigation system was introduced in late 2009 and was used in the remaining 160 procedures in ImpACT-24A and in >550 procedures in ImpACT-24B and ImpACT-24M. Over the years a few software updates were made, simplifying the registration process, and helping the implanter navigate to the correct place.

6.1.1.2 Patient Reference Marker (PRM)

The PRM is a component equipped with optical markers that is attached to the patient, allowing the guidance system to identify the position of the patient and match it to the patient's CT image.

In ImpACT-24A and ImpACT-24B, the PRM was strapped to the patient's forehead (see Figure 63). An updated PRM which is attached to the patient using a dental impression

[i] Implant misplacement rate reached 30% before introducing the guidance system.

(Bite PRM) was approved by FDA towards the end of the ImpACT-24B study and was validated in ImpACT-24M. The Bite PRM provides a stable attachment to the patient even in cases of completely or partially edentulous patients.

Figure 63 – Previous PRM (left) vs. updated Bite PRM (right)

6.1.1.3 Automatic Registration and Quality Control

The quality of guidance provided by the implantation system is highly dependent on accurate registration between the CT image and the patient, and the stability of the PRM attachment to the patient. In ImpACT-24A and ImpACT-24B, automatic registration was based on markers attached to the patient's face (Figure 63 left), and markers on each side of the nose were used for registration quality control.[i]

In ImpACT-24M, a Bite-PRM with embedded CT Marker were used to facilitate more accurate and stable automatic registration of the patient to the CT image, replacing the previously used markers. The CT marker is detected in the patient's CT image automatically by the GuideView software which then matches its CT location to its optically tracked physical location resulting in highly accurate registration.

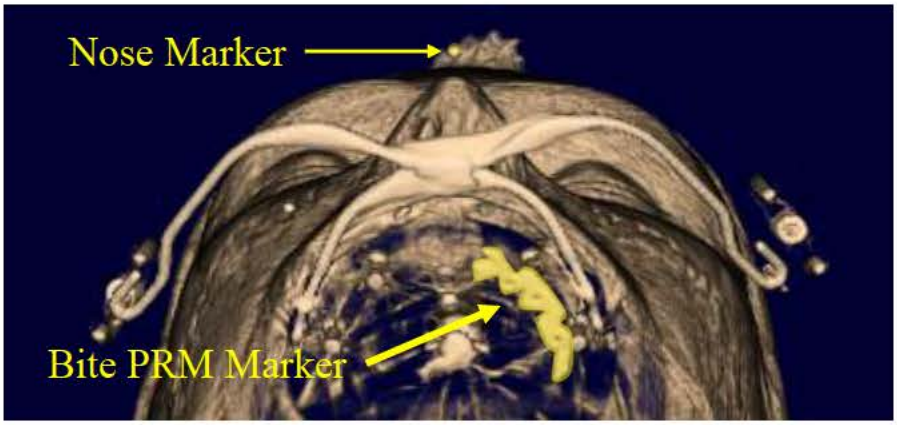

Figure 64 – Automatic Detection of the Embedded CT Marker

[i] The markers were positioned on the soft cheek surface and were prone to facial movement. In the final device these markers were replaced by the nose marker.

6.1.1.4 Registration Quality Control

A CT visible optical nose marker replaced the facial markers in ImpACT-24M (see Figure 64), allowing the GuideView software to track the relative position of the marker and the PRM, to detect any relative movement between the two during the procedure and to notify the implanter of such movement.

6.1.1.5 Implantation Tools

The first generation of the implant was fragile and had to be inserted to the canal with "zero force". Since the canals are often narrow and/or curved (see Figure 65), the canal had to be carefully dilated before the implant could be inserted.

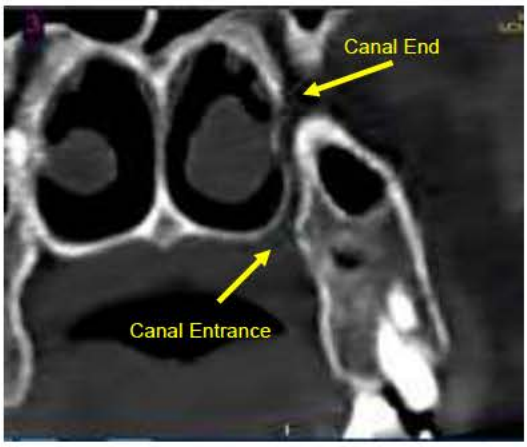

Figure 65 – Example of a curved canal

The canal dilation was performed using a set of rigid trocars, having tips designed to grind the canal wall:

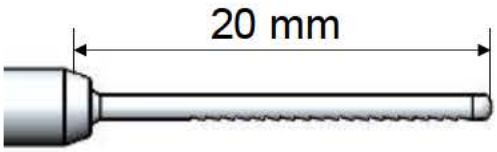

Figure 66 – Old Trocars Tip

Canal preparation started with the smallest trocar (1mm tip), followed by 1.5mm, 1.8 and 2mm. Before trying to insert the implant, the implanter had to verify that the canal is ready, using a Template tool. Nonetheless, occasionally the canal was not sufficiently dilated resulting in mechanical implant failures that led to adverse events (see Table 4).

Fault Mode	Number of Events
Torn Thread	16
Implant Crack/Break	14
Electrodes Bent	3

Table 4 – First generation implant mechanical failures in ImpACT-24A and 24B

Torn thread failures typically occur due to insufficiently dilated canal, resulting in a "stuck" implant. A sequence of these events triggered the development of a mechanically stronger design, with identical treatment (same stimulation protocol and pulse shape) that eliminated the mechanical failures risk.

The modified implant (the "Final Implant") was introduced into the ImpACT-24B study in 2016 to resolve the mechanical failures risk and eliminate the related adverse events (see Figure 67 showing 1st generation implant vs the final implant).

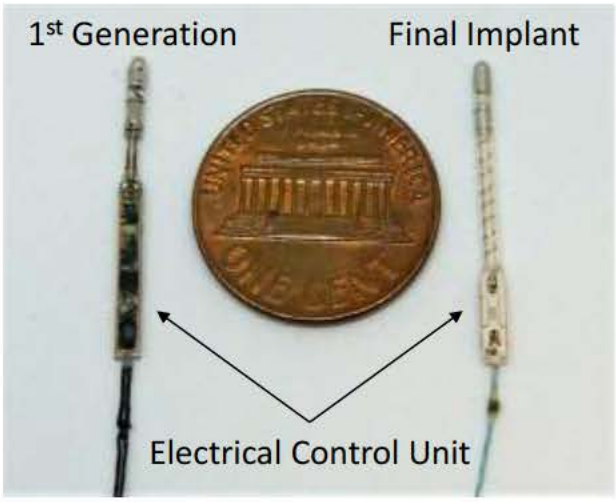

Figure 67 – First generation vs. Current Implant

The final implant is flexible and has a robust mechanical structure that can withstand significant forces, allowing it to be inserted to all canals without the use of trocars. Implantation of the final implant requires only the Puncture tool, reducing the number of tools used in the procedure from 6 to 1 as illustrated in Figure 68.

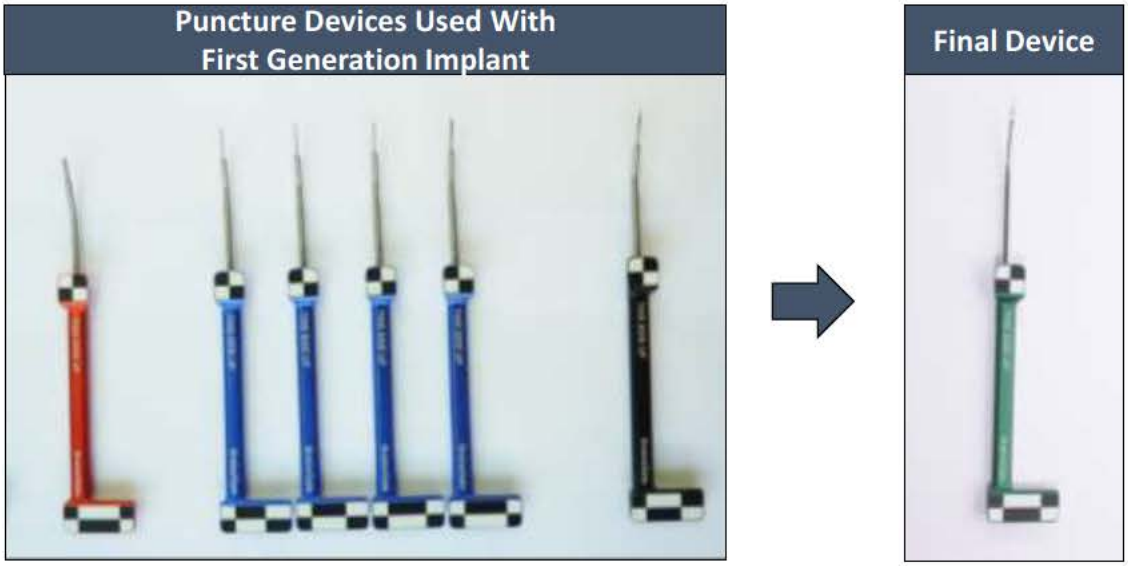

Figure 68 – Implantation Tools - Old vs. New

The Puncture tool is used only to puncture the mucosa and clear the first 8 mm of the canal (see Puncture tool's tip in Figure 69). The first 8mm of the canal are accessible in all patients based on analysis of >750 implantation CTs from ImpACT-1, ImpACT-24A, ImpACT-24B, and ImpACT24M.

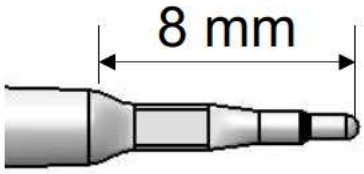

Figure 69 – Puncture Tool Tip

The robust structure of the final implant resolved the mechanical vulnerabilities and implantation complications of the first-generation implant (see safety results in section 7.2.5.4), and significantly simplified the implantation procedure.

The final implant (with its Introducer, Figure 59) was used in 247 patients (the last 197 in ImpACT-24B, and all 50 in ImpACT-24M).

6.1.2 Treatment System

The implant and the Controller were changed during the course of the ImpACT-24B study. The changes had **no** effect on the treatment provided by the system.

6.1.2.1 Controller

The IPAQ based Controller that was developed prior to the ImpACT-24A study, became obsolete requiring its replacement. In 2016 a new Controller based on smartphone was introduced. The smartphone enabled the incorporation of real-time remote treatment monitoring, but in all other respects was identical to the replaced Controller.

6.1.2.2 Implant

The implant is part of both the implantation and the treatment systems. The implant changes that relate to the treatment system are its improved accuracy in reporting the stimulation current provided to the patient, and coded communication with the Driver making it immune to external interference. The treatment itself is identical to the first-generation implant in all aspects. The final implant was used in 247 patients (the last 197 in ImpACT-24B, and all 50 in ImpACT-24M).

6.1.3 Summary of Previous Versions Use in Studies

The following table summarizes the use of previous device versions in the studies.

Replaced Devices	ImpACT-24A	ImpACT-24B	ImpACT-24M	Total
Trocars without optical markers	143	-	-	143
Trocars with optical markers	160	339	-	499
Forehead PRM + facial makers	160	339	-	499
First generation Implant	303	339	-	642

Table 5 – Use of Replaced Devices in the Clinical Studies

6.1.4 Summary of Gained Experience with Final Device

The experience gained with the final device is summarized below:

GuideView System – introduced in ImpaCT-24A following a 30% misplacement rate experienced with the first 143 patients enrolled into the study. GuideView was used in over 725 implantations in three clinical studies.

Updated PRM and Nose Marker – attached to the patient, the PRM allows GuideView to identify the position of the patient. As described in Section 6.1.1.3, the updated PRM in the submitted system combines the roles of PRM with the registration function. The nose marker provides registration quality control during the procedure. This final configuration was used in 50 patients in ImpACT-24M.

Implantation Tools – the current generation implant (Section 6.1.1) can be inserted to the canal without the use of trocars. As a result, the number of tools used dropped from six tools to a single Puncture tool. This simplified procedure was used in 247 procedures (last 197 in ImpACT-24B and all 50 in ImpACT-24M).

Implant (INS) – developed to overcome the fragility of the first-generation implant, the current generation INS was used in 247 procedures.

Table 6 summarizes the number of patients in each study and in total for each part of the final system:

Final Device	ImpACT-24A	ImpACT-24B	ImpACT-24M	Total
GuideView	160	536	50	746
iPRM + Nose Marker	-	-	50	50
Puncture Tool	-	197	50	247
Implant[i]	-	197	50	247

Table 6 – Gained Experience Final Device

It is important to emphasize that all changes were driven by the need to prevent implantation-related adverse events.

None of these affected the treatment, and it was therefore unjustified to stop the pivotal trial and start a new one with the final device.

The implantation safety data in section 7.2.5.5 represents a worst-case, as the rates of adverse events in the last 197 procedures are much lower than in the first 339 procedures.

[i] Including its dedicated Introducer

6.2 Study Design

6.2.1 Control Patients Blinding

One of the important trial design considerations was how to maintain patient blinding to randomization assignment. A full description of blinding in the pivotal trial can be found in Section 7.2.1.11.

The focus of the discussion was how to mimic the sensation of SPG stimulation in Control patients. One approach, suggested by FDA, was to have the ISS500 deliver sub-therapeutic stimulation to mimic treatment for Control patients in ImpACT 24A. However, this was not possible because blood flow is increased at lower stimulation levels than those that trigger sensation. This was observed in an OUS exploratory study of vascular dementia patients (in 2007), where blood flow measurements using common carotid doppler (CCD) were taken during stimulation.

An alternative blinding method was developed, using mechanical vibration of the Transmitter on the patient's cheek.

In ImpACT-24A, all patients were implanted before randomization and all had transmitter vibrations, but only patients in the SPG stimulation group received actual electrical stimulation.

This approach had disadvantages:

a. It was not possible to assess the risks of implantation when both groups are implanted.

b. There was also a concern, which was later ruled out, that the implant might cause some level of mechanical activation of the SPG that might mask some of the treatment effect.

c. It was difficult to obtain IRB approval for implantation of the control arm (due to the complexity of the procedure at the time)

In ImpACT-24B, patients were randomized first, and then underwent actual implantation or sham procedure. Patients in both groups had transmitter vibration on the cheek, as before.

The effectiveness of this blinding method was successfully demonstrated (see formal blinding analysis in section 7.2.6.7).

Blinding impacted the method used to identify the correct stimulation level for each patient (CTL – comfort tolerance level). The preferred method of identifying the CTL is by physiological markers (sensation and ipsilateral lacrimation). This approach cannot be used in a blinded environment as the transmitter vibration mimics the stimulation sensation. For

blinding purposes, an alternative method (the "Blinded Method") was developed in which stimulation is increased up to the level of discomfort, and then decreased to the comfort level (see Figure 70).

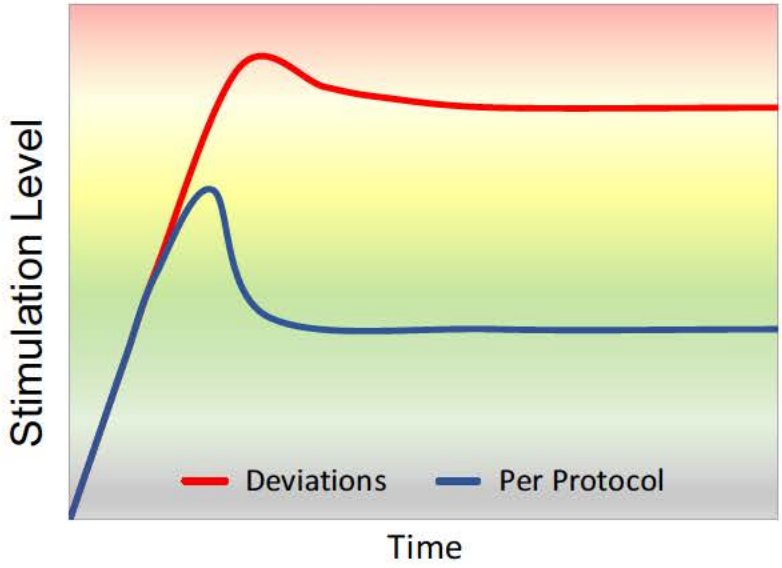

Figure 70 – Setting the Stimulation Level in Blinded RCT Environment

The preferred approach of using the physiological markers of SPG activation was validated in the ImpACT-24M usability study, where blinding is not required.

The following table summarizes which CTL determination method was used in each study.

CTL Determination Method	ImpACT-24A	ImpACT-24B	ImpACT-24M
Blinded Method	X	X	
Physiologic Markers Method			X

Table 7 – CTL determination method by study

6.2.2 The Sliding Dichotomy Primary Endpoint

In discussions with FDA during ImpACT-24A, FDA proposed the use of modified Rankin Scale (mRS) Dichotomy 0-2 as the primary endpoint. The rationale for this recommendation was that an endpoint used for regulatory purposes needs to be a dichotomized endpoint, one in which success/failure are defined at the individual patient level and not only for the study as a whole.

Sliding dichotomy was proposed as a primary endpoint to comply with the requirement for an individual-patient success criteria, while being able to detect clinically meaningful effects at more than one health state transition as opposed to a single transition.

In early interactions with FDA, shift analysis was also discussed as a possible primary outcome but was rejected for not having individual patient success criteria. In retrospect, this method (which was not pre-specified as a primary or secondary endpoint) is less appropriate, as the mRS distributions are not fully consistent with the assumption of a constant treatment effect across strata. According to the literature, the van Elteren test "performs well if the treatment effect is constant across strata, but it can be grossly inefficient otherwise". [46]

The following sections explain the sliding dichotomy endpoint, and the rationale for selecting it as the primary analysis method.

6.2.2.1 Sliding Dichotomy Concept

In the sliding dichotomy analysis, the "success criterion" for a patient (the disability threshold at which the patient will be considered to have a favorable outcome) is set based on the patient's baseline prognostic variables (NIHSS, age and stroke-side), as illustrated in Figure 71.[i]

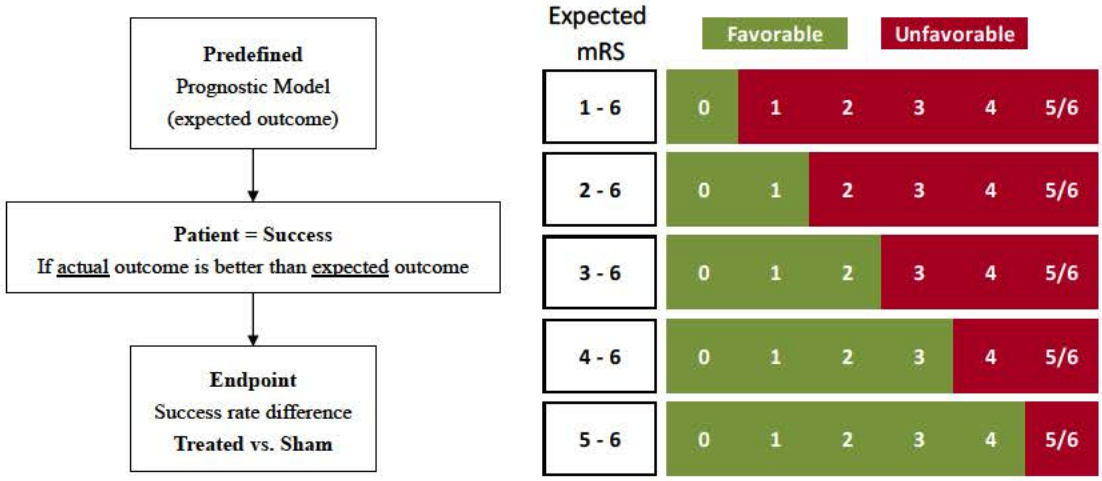

Figure 71 – Sliding (Prognosis-Adjusted) Dichotomy

The prognostic model was built based on the baseline and outcomes data of 1077 control patients with similar characteristics in prior acute ischemic stroke studies (the VISTA archive).

It is important to note that the model predicts, for each patient, the probability of reaching every possible outcome. The most informative dichotomy threshold for each patient is the median of this distribution. Outcomes that are equal or worse than the median are considered failure, and outcomes lower than the median are considered favorable.

[i] The expected outcome is calculated using a model based on the VISTA database of previous stroke trials. The data was from control patients with available NIHSS measurements within 12-24 hours from onset.

The following examples demonstrate how sliding dichotomy is applied.

For example, a 50-year-old patient with NIHSS 9 has >50% probability of reaching mRS 0-2 even if untreated.[i] In such a patient, only mRS 0-1 would be considered success (second row in Figure 71, expected mRS 2-6).

On the other hand, a 65-year-old patient with NIHSS 16 has >50% probability[ii] of reaching mRS 4-6 and would be considered success if their actual mRS is 0-3 (4th row in Figure 71, expected mRS 4-6).

6.2.2.2 Sliding Dichotomy Discussion

Were we to have been forced to choose a single fixed dichotomous cut-point for the CCI population, from physiologic reasoning it would have been most appropriate to choose a 0-3 vs 4-6 cut-point. As we are treating patients in the late window, with larger cores than DEFUSE/DAWN, and with some irreversible damage that already occurred, it might well have been expected that the treatment effect would cluster more at mRS 0-3 rather than mRS 0-2.

Indeed, the mRS 0-3 endpoint showed nominally stronger effects than both the mRS 0-2 and the shift analysis in 24B (62.3% vs 51.1%, OR 1.58, 95CI 1.11-2.25, p = 0.01). If one is going to consider the fixed dichotomy endpoints, one must consider both that were prespecified, not only the one with slightly less effect (mRS 0-2), but also the one with slightly more effect (mRS 0-3).

We recognized that we had some uncertainty regarding where the treatment effect would cluster and that is why we chose the sliding dichotomy. Since it detects effects at more than one health state transition, not a single transition, it is a more appropriate choice when one cannot confidently predict where benefits will cluster. [47]

The two fixed dichotomy endpoints (0-2 and 0-3) were added as secondary endpoints following the steering committee's recommendation.

As it turned out, the benefits clustered more at 0-3 vs 0-2. Had we chosen 0-3, the p value would have been slightly lower; had we chosen 0-2 the p value would have been slightly higher; the sliding dichotomy, detecting effects at both these transitions (and elsewhere), gave a p-value in between.

Use of the sliding dichotomy analysis in acute stroke trials has been endorsed as a standard and often desirable analytic approach by both of the major international consensus groups on acute stroke clinical trial design: i) the North American Stroke Therapy Academic Industry Roundtable (STAIR) [48] and ii) the European Stroke Organization Outcomes

[i] In the ImpACT-24B control group, 67% of the patients with NIHSS <10 had mRS 0-2 on day 90.

[ii] In the ImpACT-24B control group, 78% of the patients with NIHSS>15 had mRS 4-6 on day 90.

Working Group.[49] The noted advantages of sliding dichotomy include providing improved study power, reducing the impact of unanticipated case mix and straightforward conversion to number needed to treat.

6.2.3 The mITT Analysis

As pre-specified in the protocol and statistical analysis plan, the primary efficacy analysis excluded patients who did not receive at least one treatment session (modified Intention-to-Treat approach – mITT). The rationale for this approach and its compliance with ICH guidelines [50] are discussed below.

Since there was no previous experience in placing electrodes near the SPG, an implantation technique had to be developed in parallel with the clinical evaluation of the device. The ICH guidelines [50] allow, under special circumstances, exclusion of patients for reasons such as "failure to take at least one dose of trial medication". The pre-specified (and most logical) approach given the unique challenges of the implantation procedure was to exclude patients who were not treated due to implantation failure and not confound the true treatment efficacy with implantation failures which tend to improve over time.

The "one dose" was defined as non-zero stimulation (determined blinded to outcome based on implant position), and at least 60 pulse sequences of non-zero current, as determined by the device log files.

In order to stimulate the SPG, the electrodes have to be inside the SPG fossa, and if the electrodes are farther than 5mm from the fossa there is no stimulation of the SPG (because the bones surrounding the fossa isolate it).[i]

Implant misplacements in the range between 5-15mm were caused by the rigid trocars used with the old implant. The old implant was fragile and required the canal to be dilated with a set of rigid trocars (up to 2mm diameter). In some cases of curved canals or wrong alignment of the trocars, the thin canal wall was breached, and the electrodes reached the maxillary sinus or the nasal cavity.

The final implant is flexible and is not fragile, and trocars are no longer used in the procedure (see section 6.1 above).

Once experience was gained with the final implant, verifying that its mechanical design indeed allows it to be inserted without trocars and that misplacements >5mm can no longer occur, the mITT implant position definition was updated to 5mm, to exclude all patients that did not receive stimulation due to misplacement.

[i] This was specified in the per-protocol analysis set definition

6.2.4 The CCI Primary Analysis Population

This section explains the rationale and external events that led to the definition of the CCI population as a primary analysis population in the pivotal study, and why this population was pre-specified after the trial was started (before unblinding the results). The generalizability of study results in this population to clinical use is discussed in section 8.

6.2.4.1 Background

Collateral arterial networks are most robust in the circle of Willis and superficial leptomeningeal arteries supplying the cortical layers and less robust at the level of small penetrating arteries.[3, 10, 11] Therefore, the increase in CBF is greatest in the brain's cortical regions.

Preclinical studies showed that SPG stimulation decreases the damage to the brain-blood barrier, which typically occurs in large territorial strokes, involving the cortex. The damage to the BBB peaks around 24 hours from onset.

Therefore, a treatment based on augmentation of collateral flow is expected to benefit patients with cortical involvement, including patients with large territorial strokes.

The idea that SPG stimulation is most beneficial in strokes that involve the cortex was supported by the results of the ImpACT-1 single-arm feasibility study. In ImpACT-1, a larger effect was noticed in patients with aphasia, a symptom of involvement of the cortical language areas. In ImpACT-24A (the pilot RCT), a pre-specified secondary endpoint of patients with Aphasia showed again a larger effect in this population.

However, it was clear that aphasia alone was not a good definition as the language areas are typically in the left hemisphere and this definition would exclude approximately 70% of the target population. There are no clear clinical symptoms that are specific to cortical involvement in the right hemisphere.

Patients were enrolled in both ImpACT-24A and ImpACT-24B using non-contrast CT[i], without relying on the use of advanced perfusion imaging that might not be available in all hospitals. Non-contrast CT is very sensitive in ruling out hemorrhages but is not sensitive to ischemic changes in the first few hours after stroke. Therefore, a definition that relies solely on imaging was not considered to be robust enough to detect large strokes that involve the cortex. In the lack of a better definition of the CCI population, ImpACT-24B was initiated with a broader definition that included all moderate-severe strokes in the anterior circulation, not restricted to those with confirmed cortical involvement.

[i] non-contrast CT is not sensitive and specific enough to detect ischemia in the first few hours after stroke

6.2.4.2 The CCI Definition

The concept of a "Cortical" definition that combines a clinical assessment (NIHSS), and imaging (CT, ASPECT), was suggested only when the DAWN study results were published. [33] This late-window EVT trial showed 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. Based on this idea to combine clinical and imaging criteria, and based on the results of ImpACT-24A (Figure 100), the "confirmed cortical involvement" (CCI) population was defined in ImpACT-24B as baseline NIHSS ≥ 10 and signs of cortical involvement on baseline non contrast CT imaging (involvement of at least one of the following ASPECTS[i] regions: M1-M6, Insular Cortex). This definition is practical for clinical application, as NIHSS and non-contrast CT are performed routinely on stroke patients.

By the time the DAWN trial results became available, enrollment in the pivotal ImpACT-24B study was already under way, but results were fully blinded. Accordingly, the study analytic plan was refined to specify two primary analysis populations – one including all patients (the mITT[ii] population) and one including only those with confirmed cortical involvement (CCI, the target population of this PMA). The timeline of these events is illustrated in Figure 72 below.

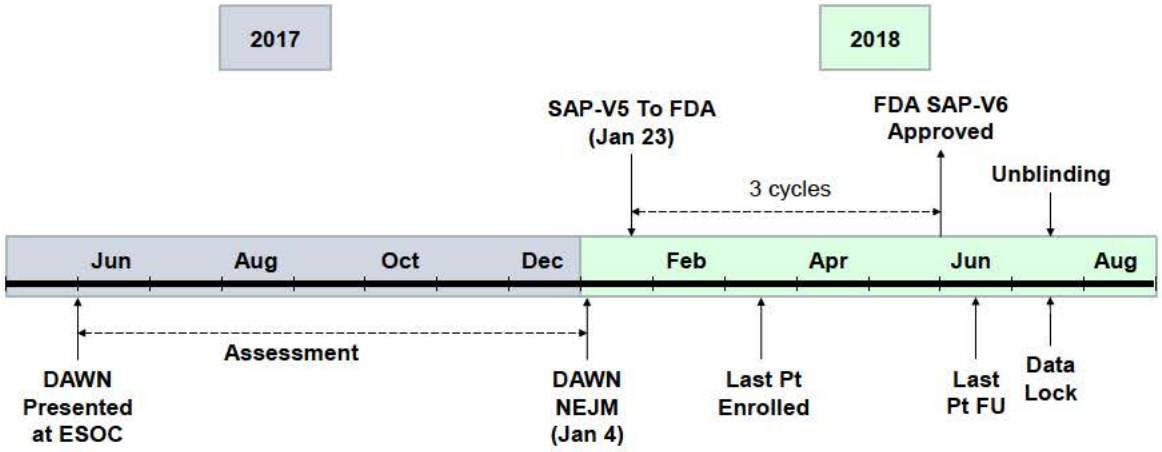

Figure 72 – Timeline to SAP approval – CCI Primary Endpoint

Chronologically, the decision to add the CCI population as a primary endpoint occurred after two interim analyses in 2014 and in 2016. However, this decision was triggered by external events, as explained above, and not by the interim analyses, which included no subgroup analyses. Please note that the DSMB (which was the only one that was exposed to interim efficacy data) was not involved in any subsequent changes in the analysis plan.

[i] ASPECTS - Alberta Stroke Program Early CT Score

[ii] Modified Intention to Treat

6.2.4.3 Multiplicity of Primary Endpoints

Two guidance documents define the needed statistical methodologies for regulatory evaluation in case of multiplicity of primary endpoints:

- FDA guidance on multiple endpoints [51]
- EMA guideline on multiplicity issues in clinical trials [52]

According to these guidance documents, the issue of multiplicity must be addressed (for example, using the Hochberg method) to prevent inflation of the overall type I error.

Based on these guidance documents, the clinical and statistical rationale for a multiple primary population analysis were discussed with FDA and an updated statistical analysis plan was accepted without study design considerations in supplement G110090/S025, pre-specifying the Hochberg procedure for multiplicity adjustment (see the Multiplicity of Primary Endpoints section 7.2.2.1).

6.2.5 Study Design Interactions – Summary

In summary, the following main study-design topics were discussed with FDA and led to changes during the clinical evaluation program:

Topic	ImpACT-24A	ImpACT-24B
Control blinding	Full implantation + sham treatment	Sham implantation + sham treatment
Primary endpoint	Changed to sliding dichotomy	Sliding dichotomy
Modified intention to treat	Definition changed to <5mm of fossa after verifying that the problem of implant misplacement was resolved	
CCI population		Added as primary analysis with multiplicity control following the publication DAWN (late-EVT study)

Table 8 – Main Study Design Interactions with FDA

7 Clinical Studies

7.1 Introduction

The neurostimulator was evaluated in over 1400 patients in 4 studies, the largest device studies in stroke. All four studies focused on expanding the therapeutic window and included patients 8-24 hours after stroke, who were ineligible for or had no access to IV-tPA and endovascular thrombectomy (EVT).

The following table summarizes the clinical evaluation of the ISS500:

	ImpACT-1 (N=98)	ImpACT-24A (N=253)	ImpACT-24B (N=1,000)	ImpACT-24M (N=50)
RCT	No	2:1	1:1	No
Type	Feasibility	Pilot	Pivotal	Usability
Dates	2006-2008	2009-2011	2011-2018	2017-2018
IDE	OUS	G070134 + OUS	G110090 + OUS	OUS
Main Findings	Feasible, Tolerable	Safe, signal of Effectiveness	Safe, effective in CCI[i] patients	Simple to find CTL[ii], <5 min. skin to skin

Table 9 – ISS500 Clinical Evaluation

ImpACT-1 was a single-arm study which showed the feasibility and tolerability of SPG stimulation for stroke patients. It also showed a signal of efficacy (compared to historical controls), especially in patients with aphasia (a typical symptom of cortical involvement).

ImpACT-24A was a pilot RCT trial. The study started as a confirmatory trial with planned sample size of 660 patients but was stopped at 300 patients due to high rate of implant misplacement. It was therefore underpowered to confirm efficacy, but it demonstrated the safety and signal of efficacy of the ISS500 for stroke patients. Benefit was highest in patients with aphasia (a pre-specified secondary endpoint) and in patients with confirmed cortical involvement.

ImpACT-24B was the pivotal RCT. The study had two primary analysis populations, one including all eligible patients and one including those with confirmed cortical involvement (CCI), the target population of this PMA. The final implant was used in the last 40% of the patients in ImpACT-24B.

ImpACT-24M was a usability study with 7-day follow up period. The study validated the simplicity and accuracy of implantation of the final implant using the final implantation

[i] CCI – Confirmed cortical involvement (a pre-specified primary analysis population and the target of this PMA)

[ii] CTL (comfortable tolerance level) is the stimulation level at which the SPG is activated without pain

system and validated a simple method to identify the correct stimulation level based on physiological signs of SPG activation. This study also directly measured the increased blood flow and improved motor function during stimulation.

ImpACT-24A and ImpACT-24B spanned over >10 years and were conducted under IDE. All changes in the device and protocols during this period were reviewed and approved by FDA. Both studies were prospective, double-blind, sham-controlled parallel arm studies.

The studies were monitored by a Data and Safety Monitoring Board (DSMB) and all serious adverse events (SAEs) were adjudicated both by the local investigators and by an external blinded adjudicator to assess possible relationship to the device.

Assessment of the modified Rankin Scale (mRS), the primary endpoint, was performed using the Rankin Focused Assessment (RFA) structured mRS form which was shown to minimize inter-observer variability.[22] In the pivotal study, the final assessment (on day 90) was video-recorded for quality control purposes and was reviewed by native-language speaking central assessors[i] (for details of this process see section 7.2.1.7).

Central review of radiology data (including baseline scans and follow-up scans on day 5) was performed blinded to treatment allocation and outcomes.

There were 96 US patients in total in ImpACT-24A and ImpACT-24B, including 46 CCI patients (see details in section 7.7).

The following figure helps navigate through discussion of the clinical development program:

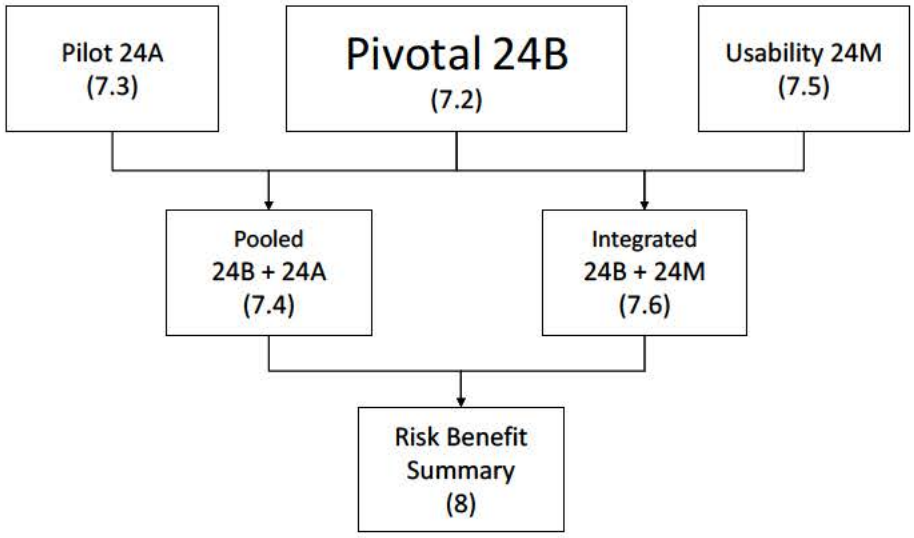

Figure 73 – Clinical Studies "Map"

[i] Both assessors were blinded to treatment allocation. The site assessor's score was the one used for the primary and secondary analyses.

7.2 Pivotal Clinical Study - ImpACT-24B

7.2.1 Study Design

7.2.1.1 Overview

ImpACT-24B was a prospective, randomized double-blind, sham-controlled, parallel-arm multicenter study. The primary objective was to assess the safety and effectiveness of SPG stimulation with the ISS as an adjunct to standard of care in subjects with acute ischemic stroke. [53]

Patients were recruited beginning June 10, 2011 and last follow-up visit was on June 6, 2018.[i]

7.2.1.2 Inclusion/Exclusion Criteria

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

Parameter	Criteria
TFSO (time from stroke onset)	Initiate treatment within 8-24h since last known well
Infarct Topography	Visible infarct on baseline CT/MRI, non-lacunar topography, <2/3 of the MCA territory
NIHSS	7-18
Prior Intervention	No IV-tPA or mechanical thrombectomy
Age	40-80 (men); 40-85 (women)

Table 10 – Main Eligibility Criteria

7.2.1.3 Randomization

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

- Group 1: implantation and SPG stimulation during 5 consecutive days, and standard of care
- Group 2: sham implantation, sham stimulation during 5 consecutive days, sham removal, and standard of care

Treatment duration was 4 hours per day for both groups.

[i] Data unblinding was performed on July 18, 2018

7.2.1.4 Study Flow

Patients with clinical signs and imaging evidence of acute ischemic stroke in the anterior circulations were screened for the study. After signing the informed consent, patients were randomized to one of the treatment groups. Treated patients needed to be scanned for the Image-Guided implantation procedure. In order to match the time from stroke onset, Control patients waited 1.5 hours. Then, NIHSS was re-assessed and the implantation/sham procedure was performed. Following successful implantation, Stimulation/Sham treatment began. To mitigate the risk that scanning for the implantation procedure could lead to unblinding, the informed consent notified subjects that the need for a CT was determined by the implanting physician.

The following diagram details the patient flow during the first day:

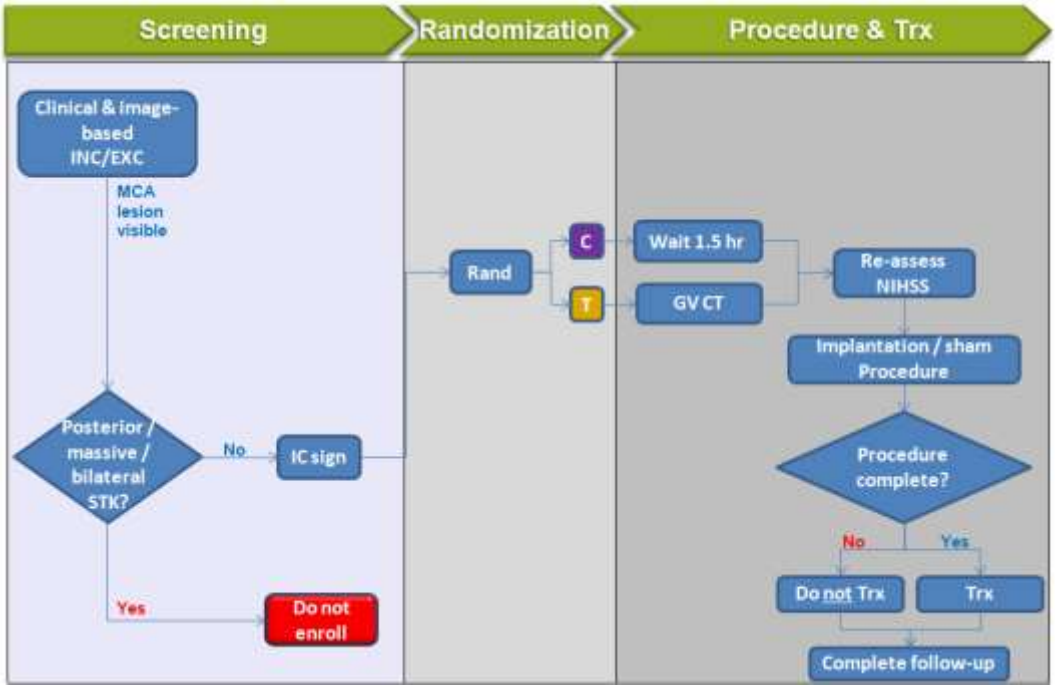

Figure 74 – Screening to Treatment[i]

The first active/sham stimulation was initiated within 24 hours of the stroke onset. All subjects were to be treated according to the standard of care for treatment of acute ischemic stroke in accordance with the general management of ischemic stroke and secondary stroke prevention guidelines. [54] Additional active/sham treatments were delivered on Days 2–5 of stroke onset. Each treatment was initiated within 18–26 hours from the preceding treatment.

During all study periods, patients will receive Standard of Care in accordance with the general management of ischemic stroke and secondary prevention, following the guidelines

[i] Figure Abbreviations: Inc/Exc = Inclusion/Exclusion, MCA = Middle cerebral artery, STK = Stroke, IC = Informed consent, GV CT = Implantation CT, used by the GuideView navigation system

of the American Heart Association/American Stroke Association and of the European Stroke Organization (ESO), including the use of antiplatelets, management of secondary stroke, dyslipidemia, hypertension, diabetes and counseling regarding smoking cessation.

Off-label uses of drugs and devices was prohibited during any of the study periods.

7.2.1.5 Follow-Up

After the last active or sham stimulation session on Day 5, imaging was performed to assess ischemic lesion size, detect cases of hemorrhagic transformation, and verify correct implant position, and then the implant was removed by pulling the implant's extraction thread using forceps. For subjects in the control group, a sham removal procedure was performed. The following chart details the follow up schedule:

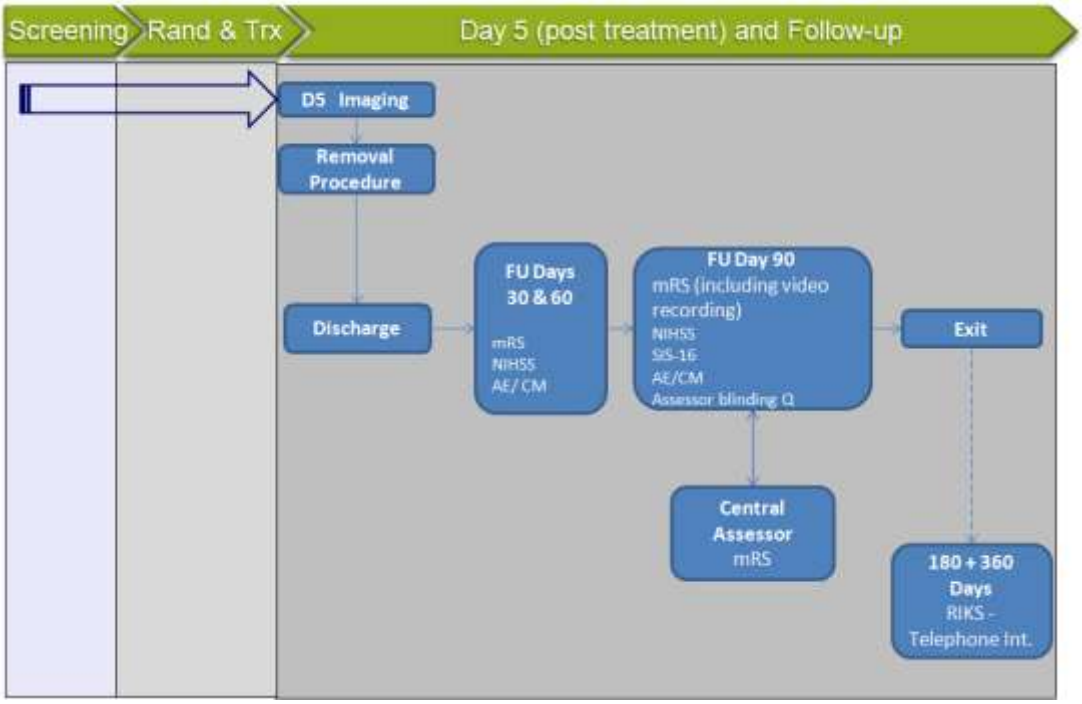

Figure 75 – Post Treatment and Follow Up[i]

Patients were followed up for a period of 90 days from enrollment. Follow-up sessions were performed on days 30±7, 60±7, and 90±7, to assess both safety and efficacy endpoints including mRS, NIHSS, Stroke Impact Scale-16 (SIS-16) and safety parameters (adverse events, mortality).

Patients were also contacted via telephone on Day 180±7 and on Day 360±7 to assess their quality of life status using a 5-caterogy questionnaire (RIKS). [14]

At all times, assessors were blinded to the type of treatment received by the patients.

[i] "Exit" in this figure indicates the end of all efficacy and safety follow-up except for the phone interviews

Radiology data was collected and reviewed by blinded central radiologists to ensure patient eligibility and assessment of cortical involvement (which is key to the classification of CCI).

7.2.1.6 Blinding Method

The goal of the blinding measures used in the study was to have all patients believe they were randomized to the treatment group. Table 11 summarizes the blinding measures in the study.

Study Procedure	Treated Arm	Control Arm
Baseline CT	Brain + Implantation	Brain
Patient Reference Marker	Y	Y
Navigation markers	Y	Y
Local anesthesia	Y	Y
Implant placement	Mucosa puncture + Implant placement	Mucosa Puncture
5 days treatment	Stimulation + Vibration	Vibration
Transmitter sticker	Y	Y
Transmitter positioning	Y	Y
Stimulation adaptation	CTL	Max tolerable vibration
Day 5 follow up CT	Brain + Implant position	Brain
Implant removal	Y	sham procedure
D30, D60, D90 blinded assessment	Y	Y

Table 11 – Blinding Measures

During implantation/sham procedure, puncture of the mucosa was performed in both groups following local anesthesia. The only person unblinded to the allocation was the implanter, who had no additional roles in the study other than the initial implant and implant removal.

It is important to note that the informed consent form stated that the need for a CT was determined by the implanting physician. Therefore, the lack of CT was not an indicator of randomization status.

4 hours of treatment were delivered each day to both groups. Actual SPG stimulation was delivered only to the treated group. Treatment sensation was mimicked in control patients using transmitter vibration as illustrated in Figure 76. Vibration was used in both groups to blind the health care professional.

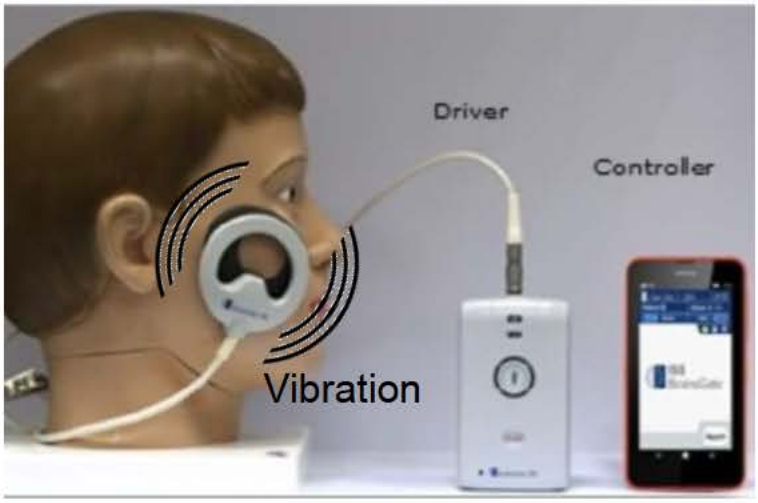

Figure 76 – Sham treatment

Implant removal and sham removal procedures were performed following the 5th treatment session.

7.2.1.7 mRS Assessment Process

The mRS assessment was performed by a Blinded Assessor (BA) on site using the Rankin Focused Assessment (RFA) structured mRS form [22], to minimize inter-observer variability. The final assessment (on day 90) was video-recorded for quality control purposes and was reviewed by native-language speaking, blinded Central Assessor (CA).

In the event of discrepancy between the BA and CA assessments, the system automatically informed the CA of the gap, and the CA initiated communication with the BA to ensure all relevant information was available to both (such as pre-stroke disabilities and observations prior to the video recording).

A Central Endpoint Quality Assessor (Figure 77) supported the process as follows:

- Informed both BA and CA of patient's pre-stroke disabilities prior to the assessments
- Reviewed the technical quality of the recordings and reminded the BA to include all relevant information in the video
- Verified that the mRS assessment questionnaire was followed and the mRS rationale was clearly documented
- Identified mistakes that could lead to discrepancy and provided periodic training to BAs and CAs

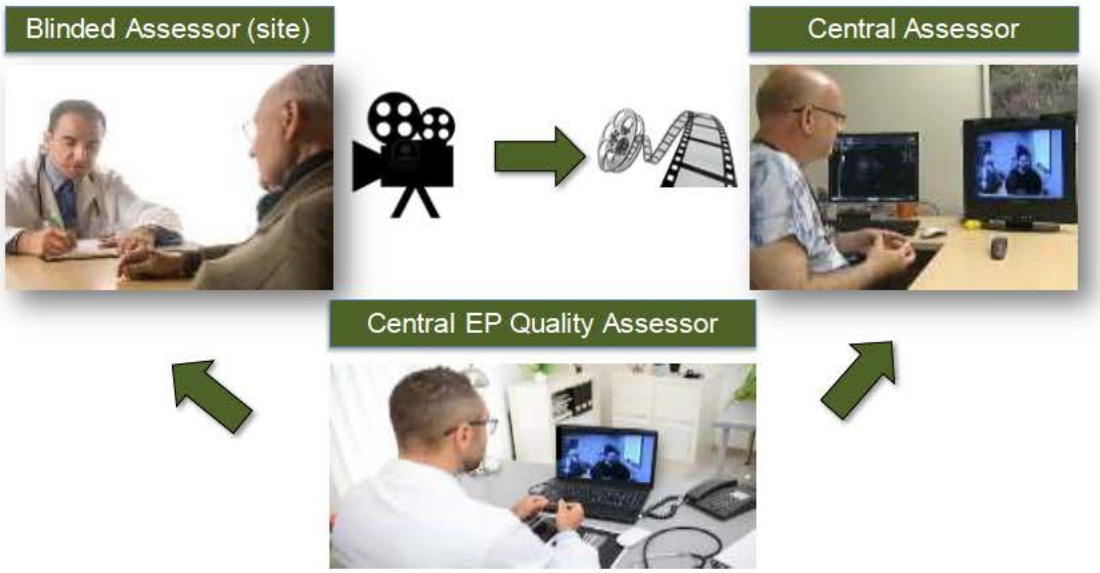

Figure 77 – mRS primary endpont assessment process

The BA's mRS assessment (the local site assessor's score) was the one used for both primary and secondary end point analyses.

7.2.1.8 Analysis Sets

Safety Analysis Set

The pre-specified safety analysis is performed on the Safety Analysis Set which includes all patients in whom the implantation procedure was initiated.

Primary Efficacy Analysis Sets

According to the pre-specified statistical analysis plan, the primary efficacy analysis is performed on the mITT cohort (see definition below) and on the CCI population (mITT patients with Confirmed Cortical Involvement).[i]

The modified intent-to-treat (mITT) population consists of randomized subjects receiving at least the minimal exposure of one treatment (ISS Stimulation or Sham Control) session out of the five planned sessions (in accordance with ICH E9 Statistical Principles for Clinical Trials)[50].[ii]

An ISS Stimulation session is defined as follows:

Non-zero stimulation as determined blinded to outcome based on implant position, and at least 60 pulse sequences of non-zero current (out of a maximum of 64 sequences), as determined by the device log files.

Implant position is assessed blinded to outcome according to the following criteria:

1. In place (inside the fossa) or within ≤5 mm from the fossa
2. Electrodes in contact with tissue (not in air)

Subjects with unknown implant position will be regarded as "not in place", unless the reason for not performing imaging of implant position is a Serious Adverse Event (SAE).

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.

[i] Chronologically, the decision to add the CCI population as a primary endpoint occurred after two interim analyses. However, this decision was triggered by external events and not by the interim analyses, which included no subgroup analyses. See details in section 6.2.4.

[ii] Given the improvement in implantation accuracy and simplicity (zero misplacements in 50 patients with the final implantation system), this approach of excluding patient who were not treated because of failed implantation is suitable for this study.

Secondary Efficacy Analysis Sets

A secondary analysis is performed on the Per Protocol cohort.

The Per Protocol cohort was defined as:

1) The completion at least 4 complete treatment sessions, including days 1 and 2;

2) At least a 30-day follow-up evaluation of mRS and NIHSS

3) The absence of major protocol violations:

   a) No stroke in the anterior circulation (no signs of ischemia, or pure posterior circulation stroke)

   b) Massive stroke at baseline imaging, defined as infarct >2/3 of the MCA territory.

   c) No source records for key data that might affect outcome (baseline NIHSS, Age, Stroke Side, mRS)

7.2.1.9 Efficacy Endpoints

According to the approved protocol and statistical analysis plan, the pre-specified primary endpoint was the favorable global disability outcome (mRS scale, sliding dichotomy) at Day 90 ± 7, assessed in the two primary analytic populations (see section 7.2.1.8):

- mITT population (all subjects receiving at least one treatment)
- CCI (those with confirmed cortical involvement, the target of this PMA)[i]

Additional analyses included:

- Stroke-related quality of life using the Stroke Impact Scale (SIS-16), at day 90 ± 7
- RIKS – patient-reported stroke-impact assessment at 180 ± 7 and 360 ± 7 days
- Functional independence (mRS 0-2 vs. 3-6) at day 90 ± 7
- Able to walk + do body self-care (mRS 0-3 vs. 4-6) at day 90 ± 7
- Global disability level at 90 days (post-hoc, utility-weighted mRS)

Missing data were imputed using the last observation carried forward method.

[i] Chronologically, the decision to add the CCI population as a primary endpoint occurred after two interim analyses. However, this decision was triggered by external events and not by the interim analyses, which included no subgroup analyses. See details in section 6.2.4.

Pre-specified subgroup analysis of the primary endpoint was performed for the following 8 covariates: NIHSS strata, ischemic lesion extent at presentation, brain side of stroke, diabetes, atrial fibrillation, time from stroke onset strata, sex, and age strata.

7.2.1.10 Safety endpoints

All adverse events were collected and events were classified by the investigators as related to the implantation, treatment, or unrelated.

A serious adverse event (SAE) is any adverse event that:

- Is life-threatening or results in persistent or significant disability or death
- Requires inpatient hospitalization or prolongation of existing hospitalization

The following are the pre-specified descriptive safety endpoints:

- 90-day Mortality
- Incidence of Serious Adverse Events (% of patients with at least one event).
- 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
- Implantation Complications
- Adverse Events classified by the investigator as device related
- Serious Adverse Events that are adjudicated as device-related or procedure-related
- Proportion of failed implantations (%)

Additionally, serious adverse events of special interest (identified in the risk analysis and reviewed routinely by the DSMB):

- Pneumonia
- Symptomatic intracranial hemorrhage (sICH)

The safety evaluation included all patients in whom implantation was attempted (the pre-specified Safety Analysis Set) and was performed separately on all patients and on CCI patients (the target of this PMA).

7.2.1.11 Blinding

Analysis of Patient Blinding

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 answered if they think they received actual treatment, sham treatment, or “don’t know”.

A patient blinding was considered successful if he/she believed he/she received actual treatment, or if the answer was incorrect or "don't know."

At the study level, the blinding of patients is adequate if at least 90% of the patients had successful blinding as defined above (see results in section 7.2.6.7).

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 answered if they think the patient received actual treatment, sham treatment, or "don't know".

An assessor's blinding for a specific patient was considered successful if the answer to the above question was incorrect or "don't know" or if the mRS score was equal to the central assessor's score.

At the study level, the assessors blinding is adequate if blinding was successful (as defined above) in at least 90% of the patients (see results in section 7.2.6.7).

7.2.1.12 Dose Response and Pain Analysis

As will be shown in the stimulation safety results section (7.2.5.4), an increase in stimulation level caused increase in pain adverse events which was noted by the DSMB in 2017.

The DSMB requested to analyze the relationship between this phenomenon and treatment efficacy as part of the efficacy analysis.

The dose-response analysis was done using polynomial and restricted cubic splines (RCS) for stimulation level (continuous) in logistic regression models on the primary and secondary endpoint outcome in the CCI population. Continuous secondary endpoints were assessed using RCS in generalized linear regression models (utilizing maximum likelihood estimation methods). Control subjects were included in the analysis with a stimulation level of zero. The models assessed were: restricted cubic splines (with 4 and 5 knots), 3rd degree polynomial and 4th degree polynomial. The AIC[i] values were very similar across the 4 models (the two models with fewer degrees of freedom were less noisy and had better

[i] Akaike Information Criterion, an estimator of the relative quality of statistical models for a given set of data.

AIC values). The model chosen for further analysis was based on the RCS model with 4 knots.

Significance level for the presence of a dose-response relationship was calculated using the likelihood ratio test.

The outcomes of mRS 0-2, mRS 0-3, SIS and utility-weighted mRS were also evaluated using RCS models (same knots). The dichotomous endpoints were assessed using logistic regression while the continuous endpoints (SIS and utility-weighted mRS) were assessed using generalized linear models. The results of this analysis are detailed in section 7.2.6.4 in the Efficacy Results

7.2.2 Statistical Methods

7.2.2.1 Multiplicity of Primary Endpoints

The primary efficacy parameter was tested using the Chi-square two-sided procedure at $\alpha = 0.05$ level. Multiplicity was handled using the Hochberg multi-step, step-up testing procedure:[i]

- The test *P* values were compared to alpha critical values of α/m, $\alpha/(m-1)$, …, α, where $\alpha = 0.05$ and m is the number of primary analysis populations ($m = 2$ in this study).
- The procedure starts with the largest p-value, which is compared to the largest population-specific critical value (α).
- If the first test is significant, the Hochberg procedure provides a conclusion of statistically significant treatment effects for both populations.
- If the first test of hypothesis does not show statistical significance, testing proceeds to compare the second-largest p-value to the second adjusted alpha value, $\alpha/2$ (0.025).
- If this second is significant the Hochberg procedure provides a conclusion of statistically significant treatment effects for the second population only.

This step-up procedure strongly controls the family-wise type I error rate.

7.2.2.2 Sample Size and Interim Analysis

The study followed an adaptive design, with a sample size between 450-1000 (prespecified sample size adjustment rule at interim analysis of 350 patients).

There were two interim analyses:

[i] Based on FDA guidance on multiple endpoints [51] and an EMA guideline on multiplicity issues in clinical trials.[52]

1. Pre-specified futility analysis and sample size adjustment while controlling the type I error rate (350 patients)

2. Futility analysis (600 patients)

Sample size re-estimation was done based on the Per Protocol analysis set.

The independent Data and Safety Monitoring Board (DSMB) were responsible to review the results of the interim analysis and make one of the following recommendations for the study:

1. Trial continuation as planned
2. Trial continuation with modification to the sample size
3. Early trial termination due to lack of efficacy (futility)

The Sponsor and Investigators remained blinded to the interim analysis results.

The second interim analysis included futility analysis only without the possibility to stop the study on success or to adjust the sample size.

The first interim analysis was performed on Feb. 27th, 2014. The study was non-futile, and the sample size was adjusted to 1,000 patients.

The second interim analysis was performed on May 12, 2016. This interim analysis was a futility analysis only (no possibility of termination on success and no sample size adjustment). The study was found to be non-futile.

7.2.3 Patient 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 patients receiving at least one study treatment: 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 because no follow-up was available.

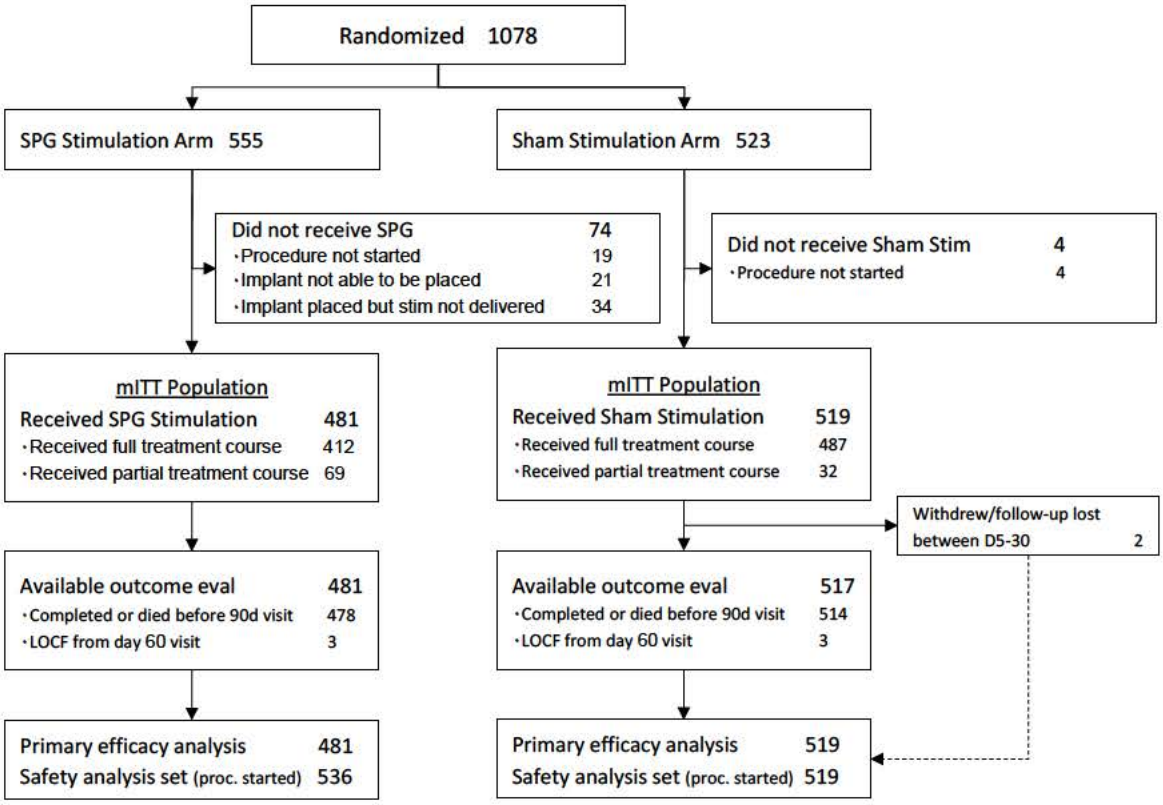

Figure 78 – CONSORT Chart – All Patients

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). All other reasons are detailed in the clinical investigation report. 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 (see Appendix G1 – Baseline Characteristics of non-mITT Patients).

The following CONSORT chart shows the CCI patient disposition:

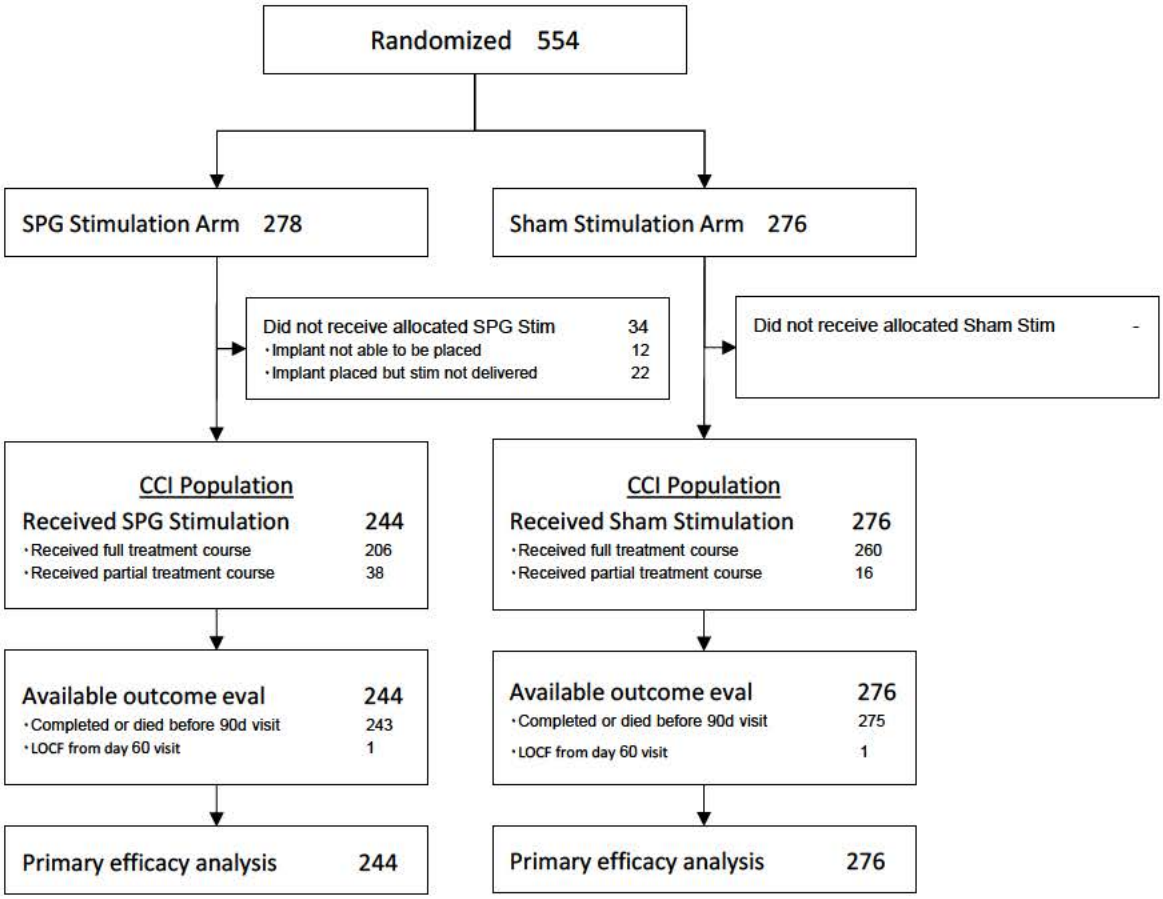

Figure 79 – CONSORT Chart – CCI Patients

7.2.4 Demographics and Baseline Characteristics

Most baseline characteristics were well balanced between treatment groups in both analysis populations.

7.2.4.1 Patient Demographics

	mITT Population		CCI Population	
	SPG Group	Sham Group	SPG Group	Sham Group
N	481	519	244	276
Median age, years (IQR)	70 (62, 77)	71 (63, 77)	70 (63, 77)	72 (64, 77)
Sex (female)	49.5%	52.2%	48.4%	48.9%

Table 12 – Demographics

7.2.4.2 Medical History

	mITT Population		CCI Population	
	SPG Group	Sham Group	SPG Group	Sham Group
N	481	519	244	276
Pre-stroke mRS = 0	91.5%	94.4%	91.4%	93.8%
Hypertension	87.1%	84.4%	87.3%	85.1%
Diabetes	23.7%	27.4%	22.1%	23.9%
Atrial Fibrillation	24.7%	26.0%	33.6%	30.8%
Smoking	10.2%	8.7%	9.0%	9.4%
Alcohol	2.3%	3.9%	2.9%	4.3%
Obesity	5.6%	4.6%	6.1%	3.6%
Systolic Blood Pressure, mean (SD)	148.1 (18.6)	148.7 (18.3)	148.2 (18.0)	148.9 (18.5)
Diastolic Blood Pressure, mean (SD)	82.7 (11.3)	82.9 (11.9)	83.2 (11.6)	83.3 (11.3)
Heart Rate, mean (SD)	77.7 (13.5)	78.2 (13.5)	78.0 (15.1)	79.2 (14.2)
INR, mean (SD)	1.1 (0.2)	1.0 (0.1)	1.1 (0.2)	1.0 (0.1)
aPTT, mean (SD)	29.0 (6.8)	28.6 (6.9)	29.2 (6.7)	27.8 (6.4)
Glucose, mean (SD)	135.3 (49.7)	134.3 (46.7)	135.2 (51.2)	134.5 (42.7)
Pre-Stroke Residence (home without assistance)	97.7%	98.8%	97.5%	98.6%

Table 13 – Medical History

There are 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%).

7.2.4.3 Baseline Stroke Characteristics

	mITT Population		CCI Population	
	SPG Group	Sham Group	SPG Group	Sham Group
N	481	519	244	276
Median NIHSS (IQR)	12 (9, 14)	12 (9, 14)	13 (12, 15)	13 (11, 15)
Stroke side (left brain)	56.5%	50.1%	57.4%	52.2%
Median ASPECTS (IQR)	7 (6, 9)	7 (6, 9)	7 (5, 8)	7 (5, 8)
Median time from last-known-well to 1st stim, hrs (IQR)	19.9 (16.0, 22.6)	18.7 (15.7, 21.8)	19.7 (15.8, 22.5)	18.5 (15.5, 21.1)
Median time from last-known-well to rand., hrs (IQR)	16.7 (13.4, 20.2)	16.6 (13.7, 19.9)	16.3 (13.2, 19.5)	16.4 (13.6, 19.2)

Table 14 – Baseline Stroke Severity

There are more left-hemisphere strokes than right-hemisphere strokes in the study in general (53%) and specifically in the treated group (57%). Since the NIHSS is more sensitive to left- than right-hemisphere deficits, for the same presenting NIHSS score, left-hemisphere strokes tend to have on average more favorable final mRS scores.[55] This is accounted for in the primary analysis (sliding dichotomy) - the prognostic model adjusts for stroke side, so that the expected mRS outcome under standard care is also lower for left-hemisphere patients. Stroke side therefore does not increase (or decrease) the predicted success probability (see details in section 6.2.2 - The Sliding Dichotomy Primary Endpoint).

In both the mITT and CCI populations, time from last known well to randomization was balanced, and time from last known well to first stimulation/sham treatment was longer in the active treatment group, by a mean of 56 minutes[i]. This difference arose from the longer time needed to complete the genuine versus sham implantation procedure with the 1st generation implant used in the first 621 enrolled patients. This difference was lessened with the introduction of the injectable implant (see section 6.1-Device Changes).

As expected, 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%, $p<0.0001$).

[i] Endpoint assessors were blinded to the procedure time and to the time from last-known-well to treatment

7.2.5 Safety Results

Safety events were collected until the last follow-up visit on day 90±7. All adverse events were classified by the investigators as related to the implantation, treatment, or unrelated and were coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Serious adverse events were also adjudicated by central reviewers, blinded to treatment arm.

The safety results are presented in the following structure:

1) Mortality rates - 7.2.5.1
2) SAE rates - 7.2.5.2
3) Rates of pre-specified SAEs of interest - 7.2.5.3
4) Event details by SOC/PT and relationship to the device - 7.2.5.4
   a) Related to stimulation
   b) Related to implantation (grouped by implant model)
   c) Unrelated

The summary and discussion of the overall safety of the ISS500 is in section 9 - Risk Benefit Summary.

7.2.5.1 90-day All-cause Mortality

The following table summarizes the number of fatal adverse events:

	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
Categorical data compared via Chi-square tests (continuity corrected)				

Table 15 – 90-day Mortality

The table below details the SOC and PT classification of frequent fatal events (>1%). Classification of all events is provided in appendix G2 – Mortality by SOC/PT.

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
Nervous system disorders	Stroke in evolution	6 (1.1%)	10 (1.9%)
	Cerebral infarction	9 (1.7%)	7 (1.3%)
Cardiac disorders	Cardiac arrest	6 (1.1%)	5 (1.0%)
General disorders and administration site conditions	Death	9 (1.7%)	8 (1.5%)

Table 16 – Frequent (>1%) fatal events by SOC/PT

7.2.5.2 All Serious Adverse Events

The following table shows the SAE rates in the two groups:

	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
Categorical data compared via Chi-square tests (continuity corrected)				

Table 17 – 90-Day Incidence of Serious Adverse Events (% of patients with at least one event)

The table below details the SOC and PT classification of frequent SAE's (>1%). 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. Classification of all SAEs is provided in appendix G3 – SAE by SOC/PT.

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
Nervous system disorders	Cerebral infarction	25 (4.7%)	16 (3.1%); 17
	Stroke in evolution	19 (3.5%)	20 (3.9%)
	Hemorrhagic transformation stroke	8 (1.5%)	11 (2.1%)
Respiratory, thoracic and mediastinal disorders	Pneumonia	12 (2.2%); 14	12 (2.3%); 13
Cardiac disorders	Cardiac arrest	7 (1.3%)	5 (1.0%)
Gastrointestinal disorders	Clostridium colitis	1 (0.2%)	6 (1.2%); 7
General disorders and administration site conditions	Death	9 (1.7%)	8 (1.5%)
Infections and infestations	Sepsis	7 (1.3%)	3 (0.6%)

Table 18 – Frequent (>1%) SAE's by SOC/PT

7.2.5.3 Pre-specified Events

Neurological Deterioration (ND)

ND was defined by an increase of 4 or more points on the NIHSS related to any neurological event within the first 10 days.

	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
Categorical data compared via Chi-square tests (continuity corrected)				

Table 19 – 90-Day Neurological Deterioration

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
Categorical data compared via Chi-square tests (continuity corrected)				

Table 20 – 90-Day Pneumonia Serious Adverse Events

Symptomatic Intracranial Hemorrhages (sICH)

sICH was defined as any ICH event within the first 5 days, 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
Categorical data compared via Chi-square tests (continuity corrected)				

Table 21 – 5-Day Symptomatic ICH Rates

7.2.5.4 Stimulation-Related Events

Stimulation-Related Serious adverse events:

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
Nervous System Disorders	Stroke in evolution	1 (0.2%)	1 (0.2%)
	Hemorrhagic transformation stroke	1 (0.2%)	1 (0.2%)
	Epileptic seizure	1 (0.2%)	-
Total		3 (0.6%)	2 (0.4%)

Table 22 – Serious Adverse Events, Possibly Related to Stimulation

Note: all stimulation-related SAE's were classified as "possibly related" to the stimulation, and no SAE was classified as definitely- or probably- related to the stimulation.

Stimulation-Related Non-Serious adverse events:

The following table shows non-serious stimulation-related events that occurred in at least 1% of the patients in either group. 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. A list of all events is provided in appendix G4 – Stimulation-Related Non-Serious Adverse Events

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

Table 23 – Frequent (>1%) Non-Serious Adverse Events Related to Stimulation

Lacrimation is a known sign of SPG activation which resolves at the end of the treatment session and was not considered an adverse event by most investigators (it appears in ~60% of the patients according to ImpACT-24M data).

Headache, which occurred in 3.5% of the patients, may be a side-effect of SPG activation[i]. All headache cases resolved without sequela.

The remaining frequent non-serious events are pain or discomfort. According to the protocol, stimulation should be given at the patient's comfortable tolerance level (CTL) and pain during treatment shall be avoided. Following the introduction of the modified implant in 2016 (see FDA Interactions section 6.1), the DSMB noted an increase in the number of pain adverse events occurring during treatment in some sites.

Study sites were retrained not to exceed the CTL (see Table 24).

Model / Period	Start Date	N	Pain AE (%)
First implant	Jun. 2011	293	18.8%
Modified implant, before retraining	Aug. 2016	134	47.8%
Modified implant, after retraining	Oct. 2017	54	1.9%
Modified implant, ImpACT-24M	May 2018	50	0%

Table 24 – Stimulation Levels and Pain Adverse Events in ImpACT-24B (Treated Patients) and 24M

[i] SPG inhibition is being used to relieve cluster headaches.

Due to these changes in the way stimulation levels were set during the study, the DSMB requested an analysis of outcomes vs dose/pain. The results showed a strong U-shaped dose-response relationship between stimulation levels and outcomes (see details in sections 7.2.6.4 and 7.6 in the Efficacy Results section below).

The above problem of over stimulation is applicable only in randomized trials where blinding prevents the use of physiologic signs (such as ipsilateral lacrimation) for identification of the correct stimulation level. It does not apply to the final version of the device and did not occur in the single-arm ImpACT-24M study. For details of how stimulation level is set, see section 5.2 in the Device Description above.

7.2.5.5 Implantation-Related Events

Implantation-related Serious Adverse Events

The following table lists all serious adverse events that occurred during the study and were related or possibly related to the implantation or implant removal procedures. Overall, there were few implantation-related serious adverse events and all 3 cases resolved without sequela.

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 25 – Implantation / Implant removal Serious Adverse Events by Implant Type

Implantation-related non-Serious Adverse Events

The following table lists frequent (>1%) non-serious adverse events that occurred during the study and were related or possibly related to the implantation or implant removal procedures, grouped by the type of implant. 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. Classification of all events is provided in appendix G5 – Implantation-Related Non-Serious Adverse Events.

SOC	PT	Old Implant (N=339)	Modified Implant (N=197)	All Treated (N=536)
Injury, poisoning and procedural complications	Implant site pain	32 (9.4%); 36	2 (1.0%)	34 (6.3%); 38
	Implant site hemorrhage	13 (3.8%); 16	-	13 (2.4%); 16
	Application site pain	7 (2.1%)	-	7 (1.3%)
General disorders and administration site conditions	Complication of device removal	8 (2.4%)	1 (0.5%)	9 (1.7%)
Psychiatric disorders	Agitation	10 (2.9%)	5 (2.5%)	15 (2.8%)

Table 26 – Frequent (>1%) non-serious implantation adverse events

Proportion of Failed Implantations:

The following table reports the proportion of failed implantations in ImpACT-24B (compared to the more recent ImpACT-24M study, which used the same implant with the final navigation system. For more details on the evolution of the device during and after ImpACT-24B see section 6.1). There were no failed implantations in the ImpACT-24M study.

	Old Implant (N-339)	Modified Implant (N=197)	ImpACT-24M (N=50)
Incomplete Procedures, %(n)	5.0% (17)	2.0% (4)	0.0% (0)
Misplacements, %(n)	8.3% (28)	2.0% (4)	0.0% (0)
Total Failed Implantations	13.3% (45)	4.1% (8)	0.0% (0)
Skin to skin time, Median (IQR) [min.]	35 (25-52)	17 (12-23)	4 (3-7)

Table 27 – Implantation Success Rate and Skin-to-skin time (Treated Patients) – ImpACT-24B vs ImpACT-24M

The table shows that there were no incomplete procedures and no misplacements with the final configuration of the implant and navigation system, and the median skin-to-skin time was 4 minutes.

The rate of implantation failures dropped from 13% with the old implant to 4% with the final implant and reached 0% with the final PMA configuration (in ImpACT-24M).

For more details on implantation safety see Appendix C – Implantation Risks – Detailed Analysis.

7.2.5.6 Unrelated Events

Unrelated Serious Adverse Events

The following table shows frequent unrelated SAE's that occurred in 1% or more of patients (in either group). Classification of all events is provided in appendix G6 – Unrelated Serious Adverse Events.

SOC	PT	SPG Stim. (N=536)	Sham (N=519)
Nervous system disorders	Cerebral infarction	25 (4.7%)	16 (3.1%)
	Stroke in evolution	18 (3.4%)	19 (3.7%)
	Hemorrhagic transformation stroke	7 (1.3%)	10 (1.9%)
Respiratory, thoracic and mediastinal disorders	Pneumonia	12 (2.2%)	12 (2.3%)
Cardiac disorders	Cardiac arrest	7 (1.3%)	5 (1.0%)

Gastrointestinal disorders	Clostridium colitis	1 (0.2%)	6 (1.2%)
General disorders and administration site conditions	Death	9 (1.7%)	8 (1.5%)
Infections and infestations	Sepsis	7 (1.3%)	3 (0.6%)

Table 28 – Unrelated Serious Adverse Events

Unrelated Non-Serious Adverse Events

The following table shows frequent unrelated non-serious adverse events that occurred in at least 3% of the patients in either group. 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. Classification of all events is provided in appendix G7 – Unrelated Non-serious Adverse Events.

SOC	PT	SPG (N=536)	Sham (N=519)
Psychiatric disorders	Insomnia	39 (7.3%)	53 (10.2%); 56
	Depression	49 (9.1%)	36 (6.9%)
	Agitation	44 (8.2%); 46	34 (6.6%); 35
	Anxiety	24 (4.5%); 25	24 (4.6%); 25
Gastrointestinal disorders	Constipation	57 (10.6%); 59	61 (11.8%); 65
	Diarrhea	23 (4.3%); 24	21 (4.0%); 23
Nervous system disorders	Headache	66 (12.3%); 78	70 (13.5%); 76
	Hemorrhagic transformation stroke	14 (2.6%)	19 (3.7%)
Renal and urinary disorders	Urinary tract infection	89 (16.6%); 103	96 (18.5%); 114
Metabolism and nutrition disorders	Hypokalemia	46 (8.6%); 51	24 (4.6%)
General disorders and administration site conditions	Pyrexia	63 (11.8%); 70	58 (11.2%); 64
Respiratory, thoracic and mediastinal disorders	Bronchitis	20 (3.7%)	9 (1.7%)
	Pneumonia	17 (3.2%)	15 (2.9%)
Cardiac disorders	Atrial fibrillation	31 (5.8%)	25 (4.8%); 26
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	18 (3.4%); 19	15 (2.9%); 16
	Back pain	5 (0.9%)	16 (3.1%)
Vascular disorders	Hypertension	22 (4.1%); 23	18 (3.5%); 19
Blood and lymphatic system disorders	Anemia	21 (3.9%)	11 (2.1%)

Table 29 – Frequent (>3%) Unrelated Adverse Events

Hypokalemia (low levels of potassium in blood serum) was numerically, occurred more frequently in the treated arm. Hypokalemia is easy to diagnose and to treat and none of the 75 cases (in both arms) was classified as severe or life threatening. The post-market surveillance will track the rates of Hypokalemia in the market.

7.2.6 Efficacy Results

7.2.6.1 Primary Efficacy Endpoints

The study had two primary analysis populations – the mITT population and the CCI population. In the mITT population, the primary endpoint was not met. There was no difference between treatment and sham control in the improvement in outcome (Figure 80).

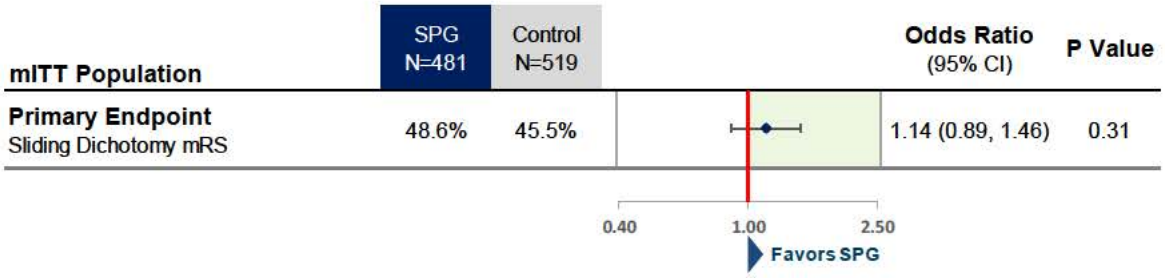

Figure 80 – Efficacy Results – Primary mITT Population

In the CCI population[i] (the target of this PMA), the multiplicity-adjusted primary analysis (Sliding Dichotomy mRS) missed the formal significance level (p=0.0258, compared to the p<0.025 multiplicity-adjusted threshold).[ii]

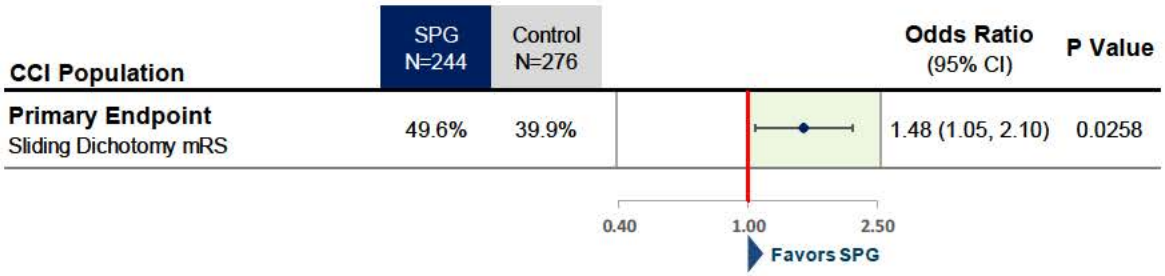

Figure 81 – Efficacy Results – Primary CCI Population (PMA Target)

[i] Chronologically, the decision to add the CCI population as a primary endpoint occurred after two interim analyses. However, this decision was triggered by external events and not by the interim analyses, which included no subgroup analyses. See details in section 6.2.4.

[ii] This small difference in p-value would disappear with an additional ¼ of a single successful patient

7.2.6.2 Secondary Endpoints

The benefit in the CCI Population is supported by consistent results in all secondary endpoints (Figure 82). Note that these endpoints do not test different hypotheses than the primary endpoint, and were specified only to demonstrate the robustness of the results, by analyzing the same 90-day disability data using different analytic methods.

CCI Population	SPG N=244	Control N=276	Odds Ratio (95% CI)	P Value
Functional Independence Dichotomy mRS 0-2	34.8%	27.2%	1.43 (0.99, 2.08)	0.06
Able to Walk & Self Care Dichotomy mRS 0-3	62.3%	51.1%	1.58 (1.11, 2.25)	0.01
Stroke-Related Quality of Life SIS-16	52.2	43.9	1.48 (1.08, 2.02)	0.01
Global Disability Level Utility weighted mRS	50.0	43.9	1.37 (1.00, 1.87)	0.05

Figure 82 – Efficacy Results – Primary CCI Population Secondary Endpoints

These benefits are clinically meaningful. For example, 48.9% of the sham control group were unable to walk or care for their body on day 90 (mRS≥4), compared to 37.7% in the SPG Stimulation group (p=0.01).

7.2.6.3 Long Term 180 and 360 Days

The treatment efficacy in the target CCI population was also demonstrated 180 and 360 days after stroke using the RIKS patient-reported stroke impact questionnaire (Figure 83, Figure 84):

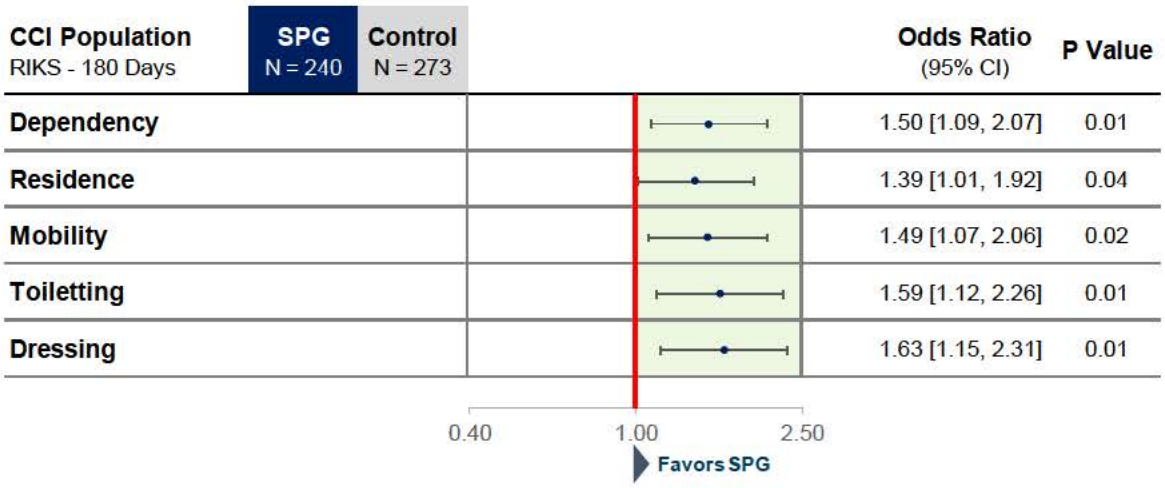

Figure 83 – ImpACT-24B CCI RIKS Results[i] at 180 days

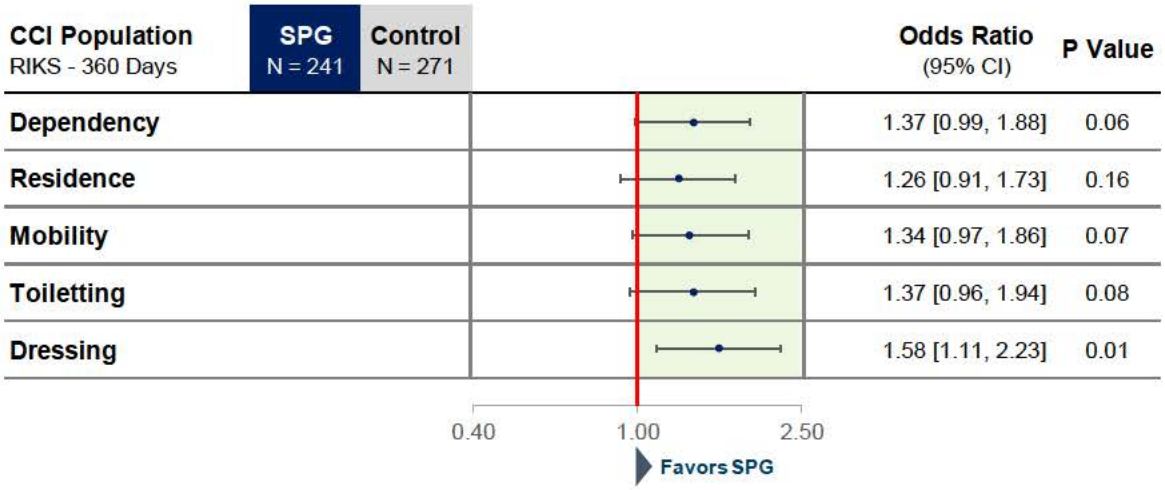

Figure 84 – ImpACT-24B CCI RIKS Results[ii] at 360 days

The RIKS-Stroke is a patient-reported outcome measure that assesses disability, covering both instrumental and extended activities of daily living. Accordingly, it assesses from a patient reported-perspective the same outcome domain (disability) that the modified Rankin Scale assesses from a clinician reported-perspective. The RIKS-Stroke has been validated as having high correlation with concurrently assigned mRS scores (unweighted

[i] Odds ratios and p-values were calculated using ordinal logistic regression.
Day 180 RIKS data is available for 240/244 treated 273/276 control patients (98.4% and 98.9% respectively.
[ii] Odds ratios and p-values were calculated using ordinal logistic regression.
Day 360 RIKS data is available for 241/244 treated and 271/276 control patients (98.8% and 98.2% respectively).

0.82, weighted kappa 0.85). [14] The RIKS-Stroke therefore provides important information on the durability of benefit of SPG stimulation upon patient disability, showing that the benefits shown on the mRS at 3 months are maintained through 6 months and 1 year.

The chief theoretical limitation of the RIKS-Score, as all patient self-reported outcome measures, is that it may be influenced by a patient's values and attitudes, not just objective performance. Conversely, this is also the chief theoretical advantage of the RIKS-Score: it directly reflects the patient's experience of disability, rather than external clinician perceptions. But the close correlation between the RIKS-Stroke and the mRS when measured concurrently suggests that patient judgements and clinician judgements of degree of disability are generally concordant and that therefore the RIKS-Stroke assessment in the trial is a valid indicator of durable treatment benefit upon disability.

7.2.6.4 Dose-Response and Pain Analysis Results

The dose-response analysis (see section 7.2.1.12) revealed an inverted U-shaped relationship in the CCI population (Figure 85). Patients who received stimulation in the medium range had a much higher rate of favorable outcome in all endpoints, compared both to patients whose stimulation level was too high and to sham-control patients (zero stimulation).

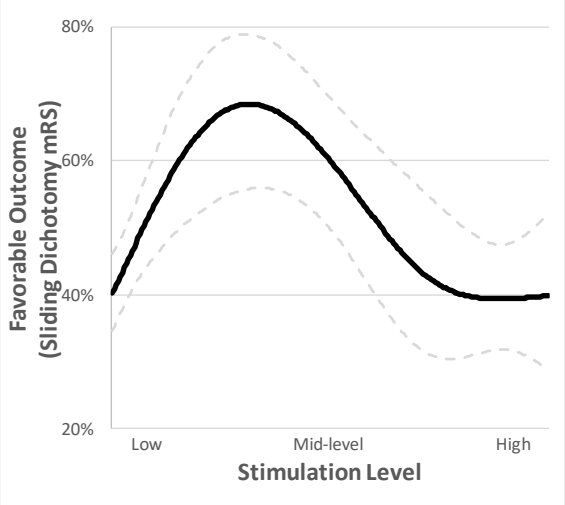

Figure 85. Study ImpACT-24B – Dose response in CCI population (rates of favorable outcome and associated 95% CI; cubic spline model, N=520)

The dose-response relationship was significant in all endpoints, with and without adjustment for all pre-specified baseline prognostic covariates (Figure 86, Table 30).

Covariate analysis showed that implant model was not associated with outcome (p=0.28).

In all figures, stimulation level zero represents the control population, and the dotted lines represent the 95% confidence intervals:

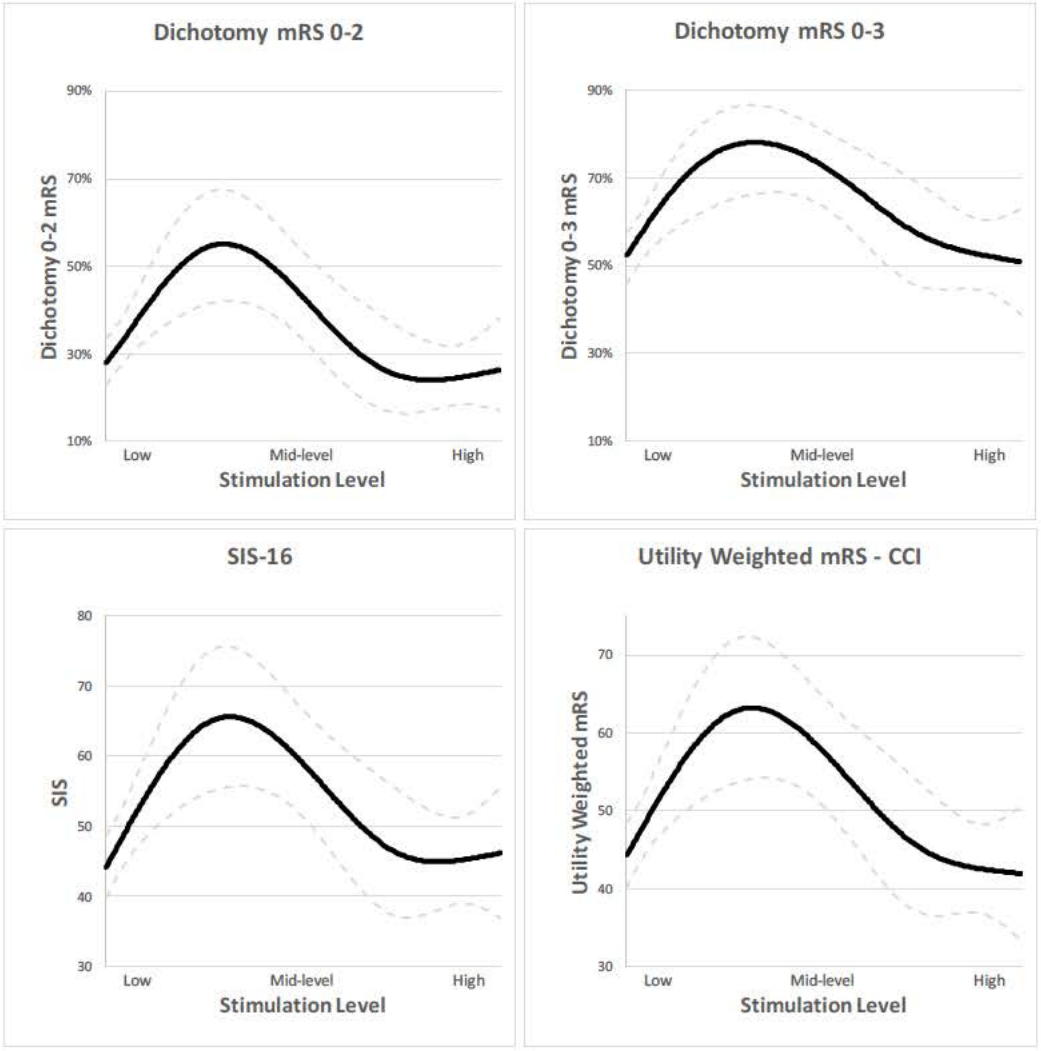

Figure 86 – Dose Relationship for Additional Endpoints (N=520)

	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 30 – Significance of Association between Stimulation Level and Outcome (N=520)

These results show that the relationship between the stimulation-level and patient outcome is robust and does not depend on the choice of endpoint, the implant model or the baseline characteristics of the patients.

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

Inverted U-shaped dose–responses for stimulation intensity are a common feature of electrical stimulation applied to neuronal systems, reflecting tuning of neurobiological systems to respond maximally at low–midrange levels [15, 16], and has also been documented in preclinical studies of stroke in a rodent model (see Figure 39 above).[44].

7.2.6.5 Per Protocol Analysis

The per-protocol analysis set included 458 patients (out of 520 CCI patients). In all endpoints, the results of the per-protocol analysis are directionally the same as the primary analysis, and the magnitude of the benefit is higher.

CCI Population - PPP	SPG N=206	Control N=252	Odds Ratio (95% CI)	P Value
Primary Endpoint Sliding Dichotomy mRS	51.5%	40.9%	1.53 (1.06, 2.22)	0.024
Functional Independence Dichotomy mRS 0-2	37.4%	28.2%	1.52 (1.03, 2.26)	0.04
Able to Walk & Self Care Dichotomy mRS 0-3	65.0%	52.0%	1.72 (1.18, 2.51)	0.005
Stroke-Related Quality of Life SIS-16	54.7	44.8	1.60 (1.14, 2.23)	0.01
Global Disability Level Utility weighted mRS	52.4	44.7	1.49 (1.06, 2.08)	0.02

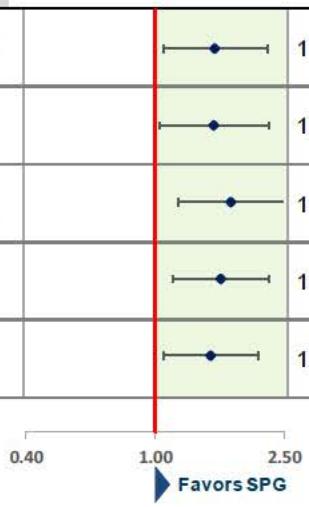

Figure 87 – ImpACT-24B - Per Protocol Analysis - CCI Population

7.2.6.6 Subgroup Analysis

Subgroup analysis showed no heterogeneity of treatment effect with respect to any of the prespecified subgroups for CCI (Figure 88) and mITT (Figure 89).

CCI Population

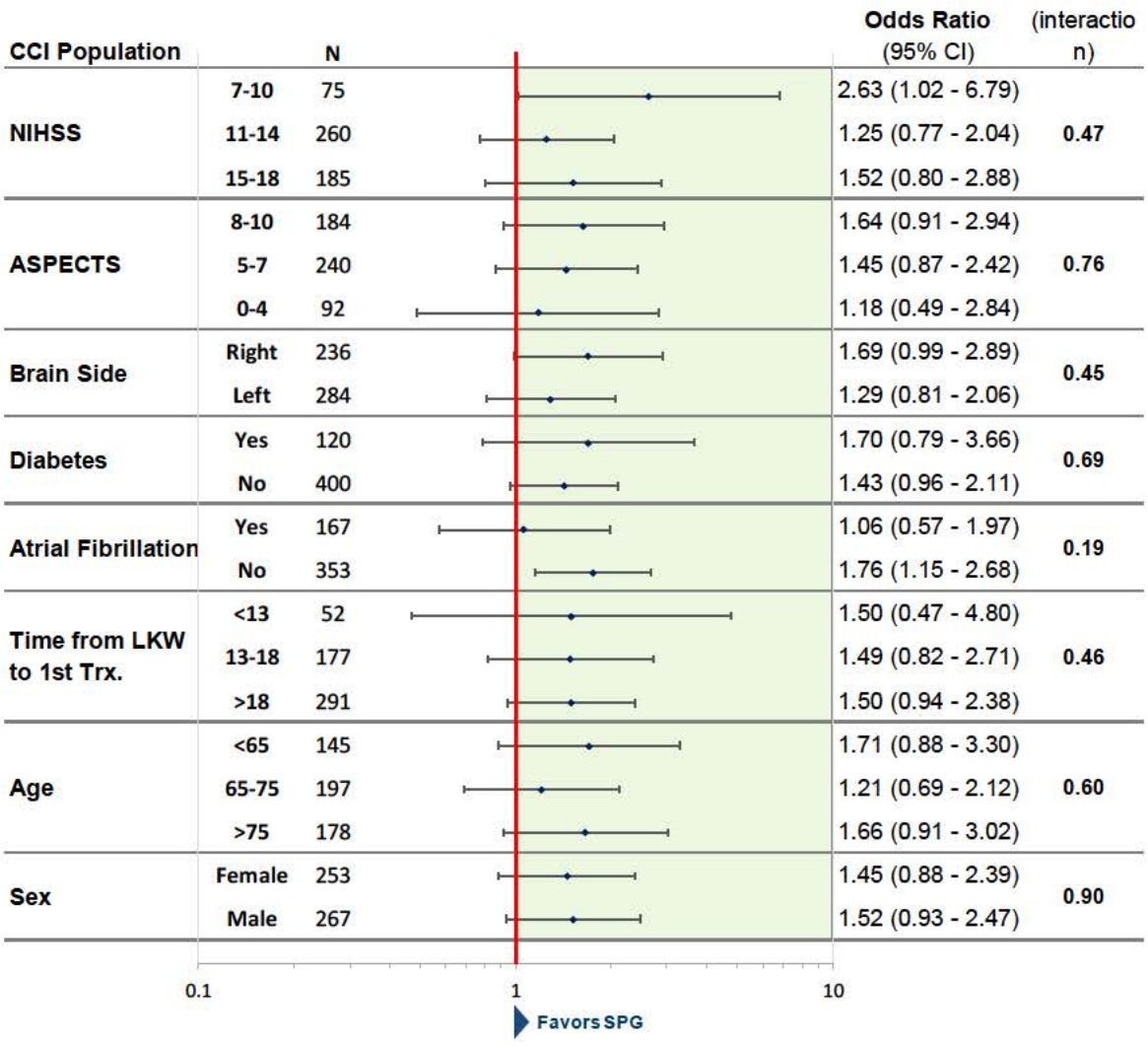

Figure 88 – CCI Subgroup Analysis (ImpACT-24B)

mITT Population

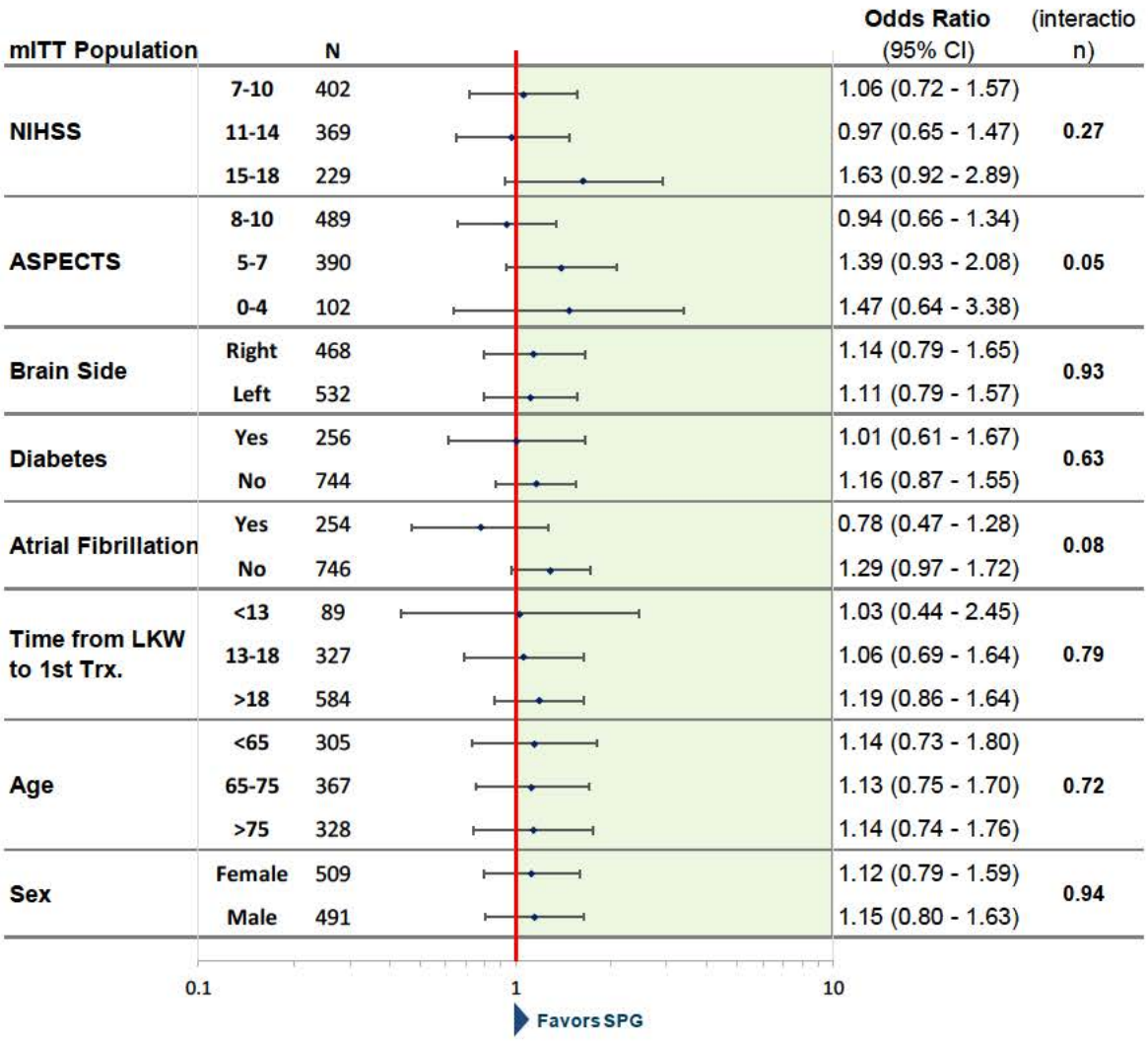

Figure 89 – mITT Subgroup Analysis (ImpACT-24B)

A trend of lower efficacy was noted in the atrial fibrillation group. This trend disappears in the pooled subgroup analysis and is likely a play of chance (see pooled results in section 7.4.4).

The subgroup analysis was repeated in patients treated within the final device dose range.

CCI Population, Final Device Dose Range

CCI Population Physiology Range		N	Odds Ratio (95% CI)
NIHSS	7-10	60	2.96 (0.95 - 9.21)
	11-14	203	1.71 (0.94 - 3.12)
	15-18	130	2.15 (0.90 - 5.10)
ASPECTS	8-10	137	2.40 (1.11 - 5.20)
	5-7	188	2.08 (1.11 - 3.89)
	0-4	65	1.89 (0.62 - 5.78)
Brain Side	Right	185	2.90 (1.50 - 5.58)
	Left	208	1.70 (0.93 - 3.09)
Diabetes	Yes	90	1.90 (0.72 - 5.05)
	No	303	2.23 (1.35 - 3.68)
Atrial Fibrillation	Yes	128	1.30 (0.62 - 2.73)
	No	265	2.97 (1.69 - 5.20)
Time from LKW to 1st Trx.	<13	41	2.67 (0.43 - 16.53)
	13-18	128	1.74 (0.78 - 3.87)
	>18	224	2.36 (1.34 - 4.14)
Age	<65	109	2.06 (0.92 - 4.61)
	65-75	150	2.57 (1.23 - 5.36)
	>75	134	1.91 (0.89 - 4.10)
Sex	Female	191	2.00 (1.06 - 3.76)
	Male	202	2.34 (1.27 - 4.33)

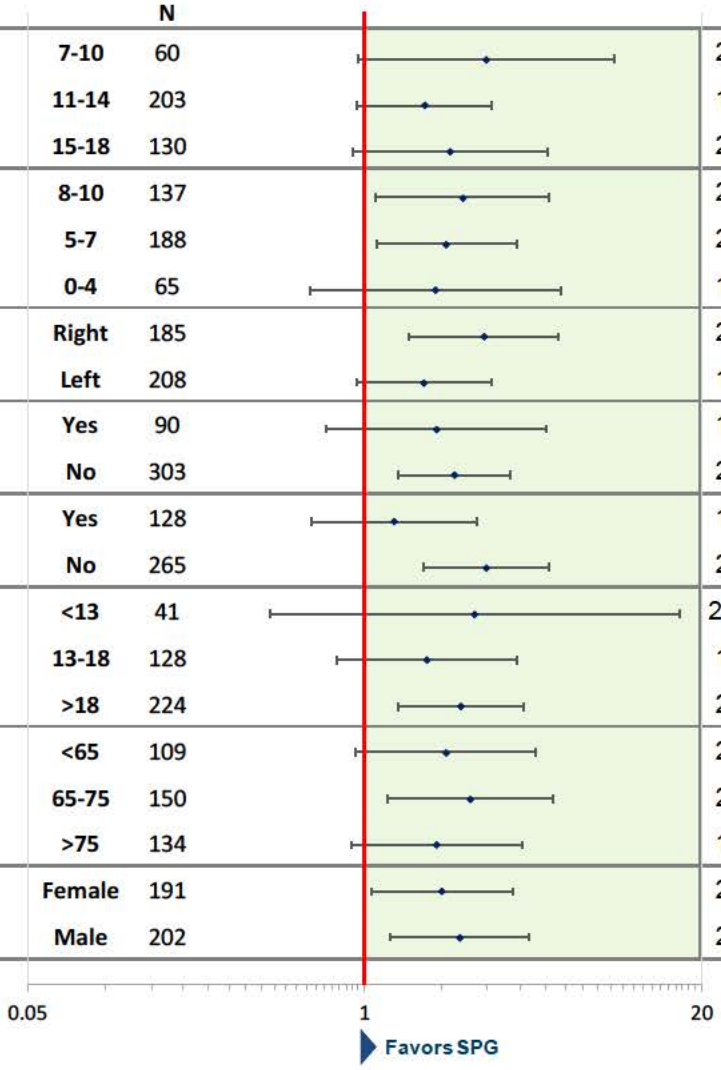

Figure 90 – CCI Subgroup Analysis, Physiology Range (ImpACT-24B)

mITT Population, Final Device Dose Range

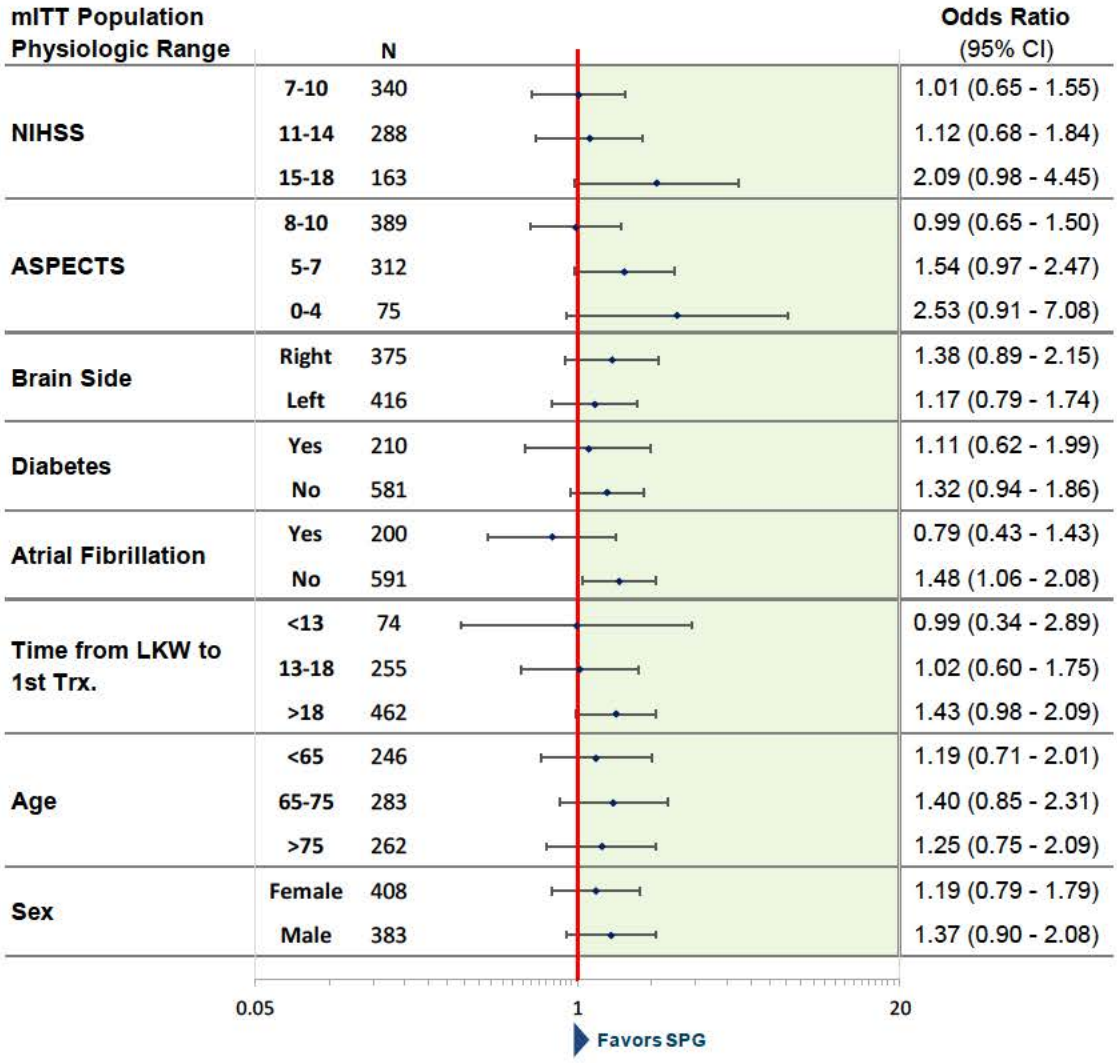

Figure 91 –mITT Subgroup Analysis, Physiology Range (ImpACT-24B)

7.2.6.7 Blinding Analysis Results

The pre-specified criteria for blinding success were:

- A patient blinding was considered successful if he/she believed he/she received actual treatment, or if the answer was incorrect or "don't know."
- The blinding of the Blinded Assessor (BA) for a specific patient was considered successful if the answer to the blinding questionnaire was incorrect or "don't know" or if the mRS score was equal to the central assessor's score.

Results:

- 33% of the control patients and 27% of the treated patients were unable to answer the question due to their medical condition.
- Patient Blinding Results: Of the patients that were able to answer, 98% believed they were treated or didn't know
- BA Blinding Results: In 96% of the cases, BA answer to blinding question was wrong/"don't know" or BA mRS Score was equal to CA mRS Score

Patient blinding and BA blinding success rates were both higher than the pre-specified 90% success threshold.

Blinding was also assessed using the James Blinding Index [56]:

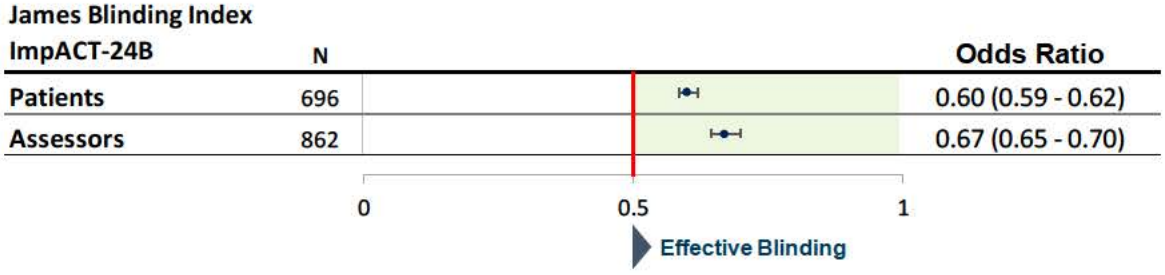

Figure 92 – Blinding Results (James Blinding Index)

The lower 95% confidence limit of the James Blinding Index results is higher than 0.5, indicating effective blinding for both patients and assessors.

Another indication of blinding compliance is the following comparison of the prescribed concomitant medications and rehab/discharge facility in the two groups.

The data show that there is no preference to the SPG stimulation group in either rehabilitation or concomitant medications. Additionally, the rehab center staff did not know

the treatment allocation in the study and thus there could be no influence of treatment allocation on the prescribed rehabilitation.

The only significant difference is in the number of patients who remained in rehabilitation/geriatric centers 180 days after stroke onset (more control patients), while more treated patients returned home[i].

This result does not indicate bias (in favor of the control arm), but rather a treatment benefit.

		SPG Stim. N=244	Sham N=276	OR (95% CI)
Medications	Anti-Platelets/Coagulants	93.4%	95.7%	0.65 (0.30-1.40)
	Anti-Hypertension	88.1%	89.5%	0.87 (0.50-1.50)
	Anti-Hyperlipidemia	79.5%	79.0%	1.03 (0.67-1.58)
	DVT Prophylaxis	60.7%	67.0%	0.76 (0.53-1.09)
	Anti-Depressants	26.6%	26.8%	0.99 (0.67-1.46)
Rehab (discharge)	Home	32.8%	31.9%	1.04 (0.71-1.52)
	Home with rehab	18.5%	16.2%	1.18 (0.74-1.89)
	Rehab/geriatric center	44.4%	48.8%	0.84 (0.59-1.19)
	Dead/unknown	4.3%	3.1%	1.42 (0.55-3.66)
Rehab (180d)	Rehab/geriatric center	3.3%	8.8%	0.36 (0.16-0.81)

Table 31 – Concomitant Medications and Rehab/Discharge Information – CCI Population[ii]

The data support that both the sham and treatment groups received similar recommended care, and all investigators and caretakers were blinded to treatment assignment.

7.2.7 The Patient's Perspective

7.2.7.1 Reduced Disability

Most CCI patients have poor prognosis and are ineligible for currently approved therapies.[iii]

Patients who arrive too late often miss the window of opportunity for treatment as the growing risk of IV tPA and EVT exceeds the diminishing benefit. The problem is even larger outside of urban centers, as it takes more time for the patient to arrive and very few frontline hospitals have the capability to perform EVT. As a result, only a small proportion of stroke patients are currently treated with IV tPA and/or EVT. [4]

[i] In the treated group, 75.0% of the patients lived at home or in a community facility 180 days after stroke compared to 68.5% in the control group (odds ratio 1.38, 95% CI 0.94-2.03).

[ii] This post-hoc analysis was performed in response to FDA's question on possible bias in study results

[iii] The median ASPECTS was 7 (IQR 5-8) indicating that most patients already had established core were unlikely to meet the strict criteria for late EVT. The proposed IFU limits the indication to patients who are ineligible or have no access to EVT

If untreated, patients who suffer moderate-severe stroke, such as the CCI population (the target population of the ISS device), commonly end up in a wheelchair (mRS 4), bedridden (mRS 5), or dead (mRS 6), as evidenced in ImpACT-24B, where 49% of the control CCI patients in the study had mRS ≥4 three months after stroke, compared to 37% in the treated arm.

All one-step transitions in the mRS disability scale are valued by patients and families (when mRS 5/6 are grouped to a single worst-outcome level). The following table illustrates the utility values of each mRS transition (see background in section 3.1.3):

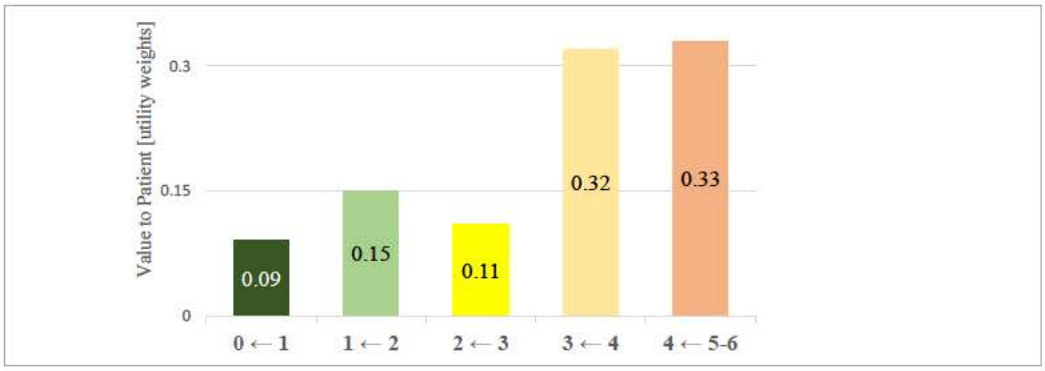

Figure 93 – Patient-Centric Utility Weights for mRS Disability Levels

The mRS transitions at which there was greatest treatment impact in ImpACT-24B, from mRS 4/5/6 to mRS 3, are the transitions with the highest utility value for patients, caregivers, and clinicians (Figure 94). [23, 24, 25]

Figure 94 – mRS Distribution - ImpACT-24B CCI

The absolute risk reduction (ARR) of 9.8% in the primary CCI population is clinically meaningful, higher than the 1.5% Minimal Clinically Important Difference (MCID) in dichotomized endpoints in stroke [12], the 3% MCID for continuous utility-weighted endpoints [13] and higher than the 7% ARR that was pre-specified in the protocol as the minimum desirable effect.

The uncertainty of the benefit of reduced disability is reduced by the 180-day and 360-day RIKS patient-reported outcome which show that the benefits persist for at least one year and that they are meaningful to patients.

7.2.7.2 *Quality of Life*

The benefits of the reduced disability by SPG stimulation directly affect patients' quality of life (QoL), as measured in the study using SIS-16, [57] which is a Patient Reported Outcome (PRO) endpoint.

SPG stimulation increased the mean SIS-16 score in the CCI population from 43.9 (95% CI 39.4-48.4) to 52.2 (95% CI 47.3-57.0), p=0.01. When dichotomizing the SIS results using a 10-point improvement cutoff (10 points is the Minimal Clinically Important Difference at the individual patient level)[58], SPG stimulation increased the success rate of CCI patients from 37.4% to 52.1% (odds ratio 1.82, 95% CI 1.28-2.59, p=0.0008).[i]

An alternative way to understand the improvement in the SIS score from a patient's perspective is to break it down to its individual components. This breakdown shows benefit in all 16 categories, each representing an important aspect of stroke-related disability and quality of life (Figure 95 for CCI, Figure 96 for mITT):

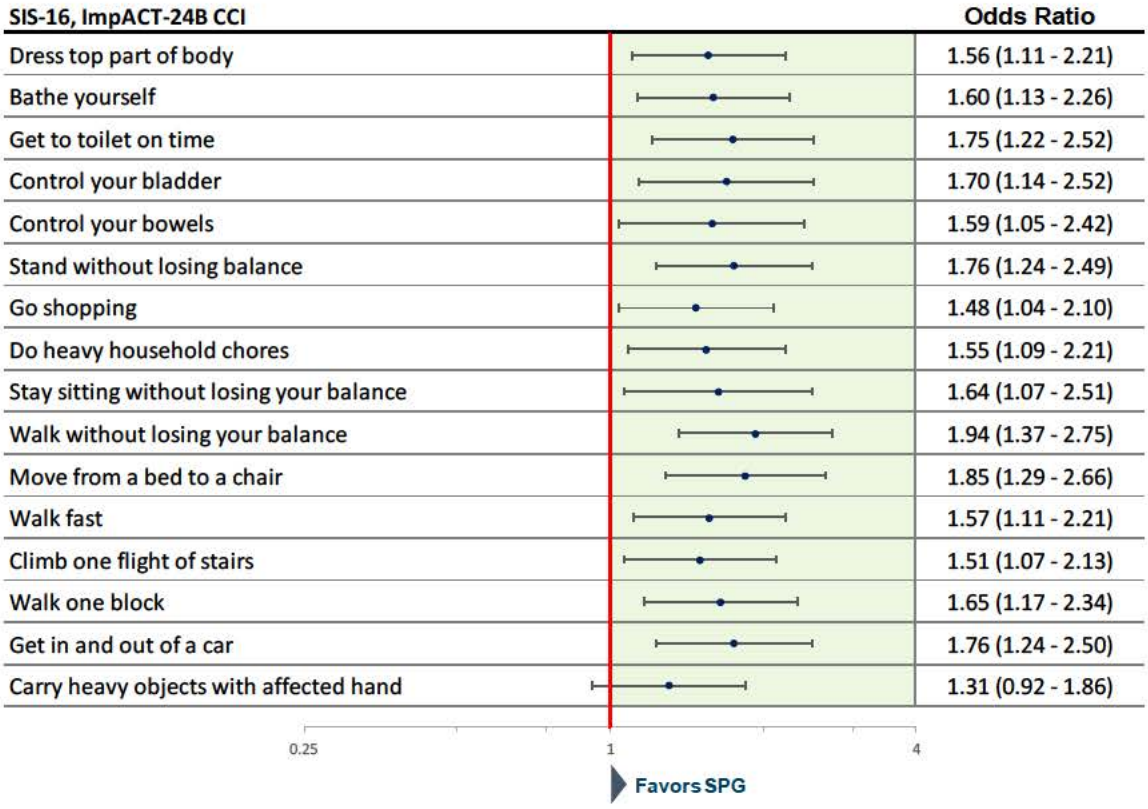

Figure 95 – SIS Results Breakdown (CCI)

[i] Success in the dichotomized SIS score was defined: **Actual Score > Expected Score + 10**. The expected SIS score of each patient was computed using a prognostic model, built from the ImpACT-24B Control population data. The prognostic variables were those used in the Sliding Dichotomy model (NIHSS, Stroke Side, Age). The proportion of success was compared between the Treated and Control populations.

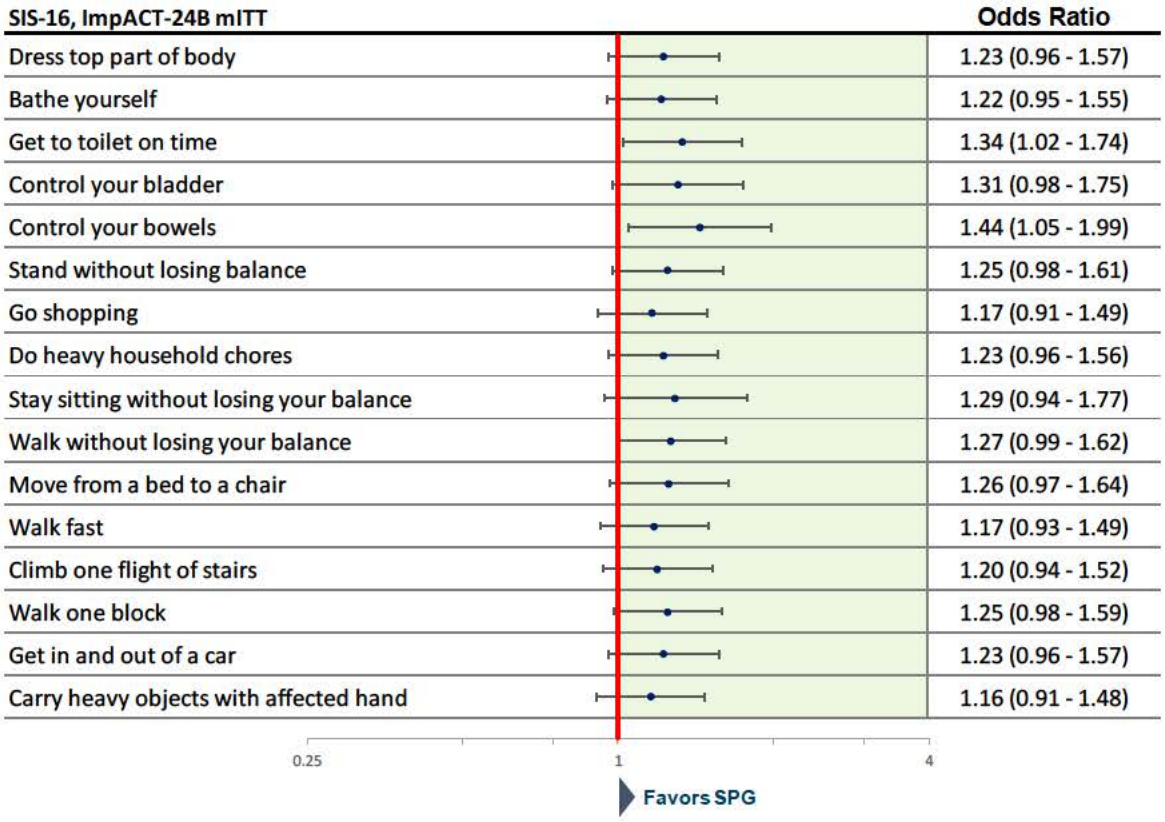

Figure 96 – SIS Results Breakdown (mITT)

7.2.8 Pivotal Trial ImpACT-24B Summary

ImpACT-24B was the largest device trial in stroke, and was a double-blind, sham-controlled, parallel-arm, multi-center trial. Both patients and assessors were successfully blinded.

The primary endpoint missed the formal multiplicity-adjusted statistical threshold (0.0258 vs. 0.025). This uncertainty of the benefit in the CCI Population is reduced by:

- Consistent beneficial effects of reduced disability and improved quality of life on all prespecified additional efficacy endpoints. For example, 49% of the patients in the control arm were unable to walk or care for their body on day 90 (mRS ≥4) compared to 37% in the treated arm.
- The benefit was shown to persist 180 days and 360 days after treatment
- A strong dose-response relationship was demonstrated (Figure 85)
    - Patients who received stimulation in the medium range had significantly better outcome than those that were stimulated too high, consistent with pre-clinical results (inverted U shape dose response is a common feature of electrical stimulation applied to neuronal systems)

  - The dose-response relationship repeated in all endpoints, with and without covariate adjustment, and with both models of the implant

- Similarity of findings with those of the preceding ImpACT-24A trial
  - There was no heterogeneity of treatment effect between the two studies (p=0.88)
  - In both studies, treatment benefit did not depend on baseline core size or on the time from stroke onset, consistent with the device MOA and preclinical results
  - In both studies, the rate of sICH was lower in the SPG stimulation group compared to control, consistent with the BBB protection effect in preclinical studies

The implantation and treatment were both safe, and no safety concerns were identified.

7.3 Pilot Study: ImpACT-24A

7.3.1 ImpACT-24A Study Design

7.3.1.1 Overview

ImpACT-24A was a pilot multicenter, randomized, double blind, sham control, parallel arm trial which followed a similar study design to ImpACT-24B, with the same 5-day treatment protocol.

The primary objective of the study was to assess the safety and effectiveness of SPG stimulation with the ISS. The first patient was enrolled in February 2009 and the last follow-up visit was in January 2011. The planned enrollment was 660 subjects, however the recruitment was halted before reaching the planned enrollment due to a high implant-misplacement rate.

7.3.1.2 Inclusion/Exclusion Criteria

SPG Stimulation augments cerebral blood flow (CBF) in the anterior circulation, and the study was aimed to show that this CBF augmentation improves neurological outcomes in patients diagnosed with acute ischemic stroke, with a treatment window of up to 24 hours following stroke onset.

The inclusion criteria for the study were:

Parameter	Criteria
TFSO (time from stroke onset)	Initiate treatment within 8–24h since last known well
Clinical diagnosis	Acute ischemic stroke in the carotid, middle or anterior cerebral artery territories based on general physical examination and neurological examination
NIHSS	7–18
Age	≥ 18 years and ≤ 85 years

Table 32 – ImpACT-24A Inclusion Criteria

A minimum of 8 hours from stroke onset was defined in order not to overlap even the broadest window for re-canalization at the time the study was conducted.

The exclusion criteria were the same as in ImpACT-24B (see Appendix A – Pivotal Study Inclusion/Exclusion Criteria), including no prior intervention with IV-tPA or mechanical thrombectomy.

7.3.1.3 Randomization

After implantation, eligible subjects were randomized in a 2:1 ratio into one of the following groups:

- Group 1: SPG stimulation during 5 consecutive days, and standard of care
- Group 2: Sham stimulation during 5 consecutive days, and standard of care

7.3.1.4 Study Flow and Follow Up

Patients with clinical signs of acute ischemic stroke in the anterior circulations were screened for the study. After signing the informed consent, patients were scanned for the Image-Guided implantation procedure. Following implantation, patients were randomized to one of the treatment groups and active/sham stimulation began.

After the last stimulation (or sham treatment) session, imaging was performed to assess lesion size, detect cases of hemorrhagic transformation, and verify correct implant position, and then the implant was removed.

Patients were followed up for a period of 90 days from enrollment. Follow-up sessions were performed on days 30±7, 60±7, and 90±7, to assess both safety and efficacy endpoints including mRS, NIHSS, Stroke Impact Scale-16 (SIS-16) and safety parameters (adverse events, mortality).

7.3.1.5 Blinding Method

The goal of the blinding measures used in the study was to have all patients believe they were randomized to the treated arm. Table 33 summarizes the blinding measures in the study.

	Treated Arm	Control Arm
Baseline CT	Brain + Implantation	Brain + Implantation
Patient Reference Marker	Y	Y
Navigation markers	Y	Y
Local anesthesia	Y	Y
Mucosa puncture	Y	Y
Implant placement	Y	Y
5 days treatment	Stimulation + Vibration	Vibration
Transmitter sticker	Y	Y
Transmitter Positioning	Y	Y
Stimulation adaptation	CTL	Max tolerable vibration
Day 5 follow up CT	Brain + Implant position	Brain + Implant position
Implant removal	Y	Y
D30, D60, D90 blinded assessment	Y	Y

Table 33 – Blinding Measures

7.3.1.6 Analysis Sets

Safety Analysis Set

The Safety Analysis Set included all patients who were implanted and randomized. Safety analysis was also performed on the primary efficacy analysis set.

Primary Efficacy Analysis Sets

The efficacy analysis is performed on the mITT cohort which includes all patients receiving at least one active/sham stimulation (same definition as the mITT cohort in ImpACT-24B).[i]

7.3.1.7 Efficacy Endpoints

The primary endpoint was favorable outcome on the mRS (sliding dichotomy, same as ImpACT-24B) at Day 90 ± 7.

The secondary endpoints were:

- Favorable mRS outcome (sliding dichotomy) at Day 90 ± 7 for subjects with baseline aphasia
- NIHSS at Day 90 ± 7, binary, defined as NIHSS ≤ 1 or improved by ≥ 9 from baseline

Additional endpoints were:

- Stroke Impact Scale (SIS)-16;
- Riks-Stroke assessment at 180 ± 7 and 360 ± 7 days.

Additionally, two post-hoc analyses were performed:

- Functional independence (mRS 0-2) at 90 days
- Distribution of mRS level 0,1,2,3,4, and 5/6 disability outcomes at 90 days (utility-weighted mRS)

Primary and secondary endpoints were analyzed in 6 prespecified subgroups of: presenting deficit severity on the NIHSS, presenting ischemic lesion size on ASPECTS, time from stroke onset, sex, brain side of stroke, and stroke location (cortical vs non-cortical).

7.3.1.8 Safety Endpoints

The safety endpoints were:

- Incidence of serious adverse events
- 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
- Implantation complications

[i] According to the protocol, only patients with at least one mRS measurement were included. However, it was later discussed with FDA that patients with no mRS measurements will be assigned the worst possible outcome (mRS 6).

- Stimulation adverse events
- Proportion of failed implantations (%)
- 90-day mortality

7.3.2 Statistical Methods

Dichotomous endpoints were assessed using a chi-squared ($\chi 2$) test, and the SIS-16 efficacy endpoint was assessed using a t-test.

Heterogeneity of treatment effect was assessed in prespecified subgroups of presenting deficit severity (NIHSS), lesion extent (ASPECTS), time from stroke onset, sex, side, and stroke location (cortical vs non-cortical). ASPECTS assessment was done centrally by a neuroradiologist masked to treatment group assignment.

In the primary endpoint, subjects with no follow-up mRS measurement (day 30±7/60±7/90±7) were imputed using worse possible outcome (mRS 6).

Subjects with mRS measurement on day 30±7/60±7 were imputed using the last observation carried forward approach.

7.3.3 ImpACT-24A Patient Accountability

The study was conducted between first enrolment in February 2009 and final study visit in January 2011. 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.[i]

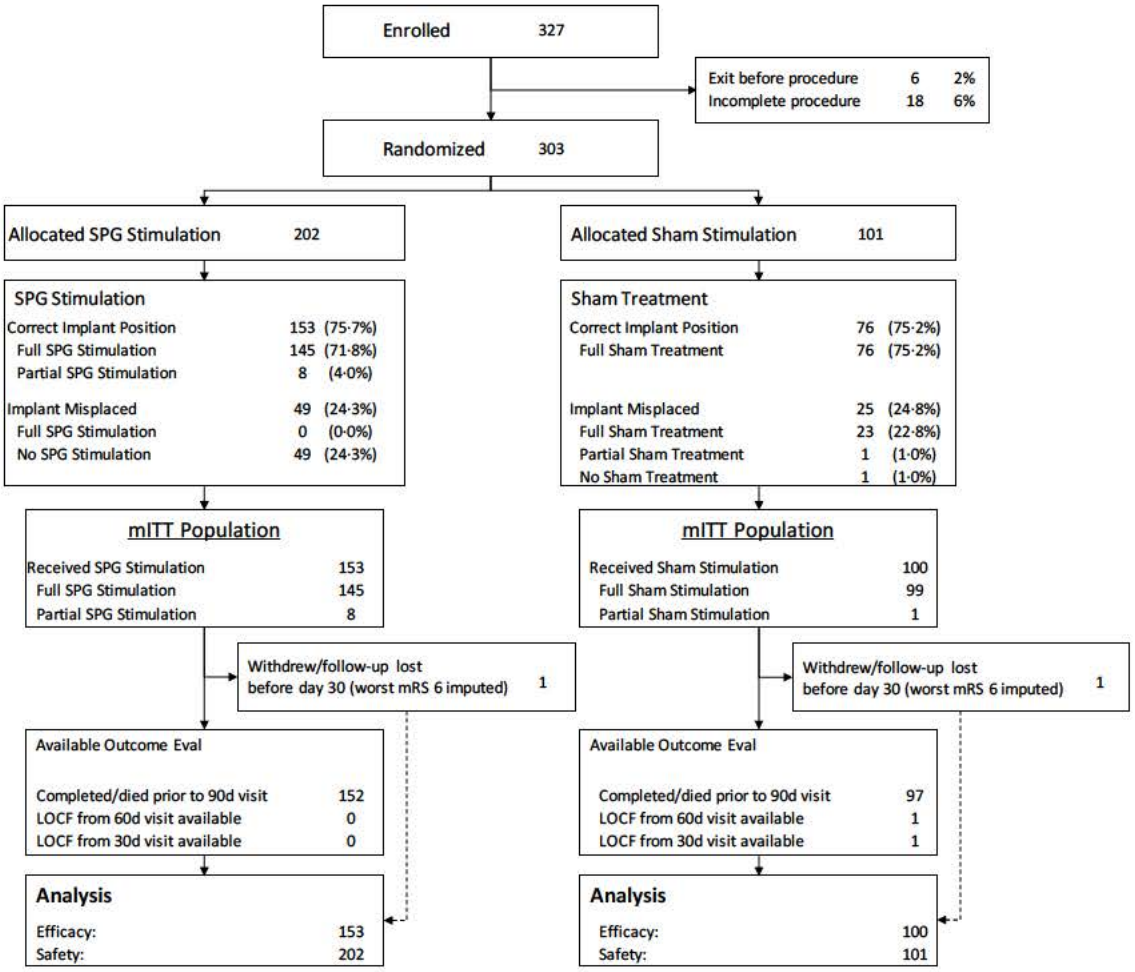

Figure 97 – CONSORT Chart

[i] Of the 6 patients who exited before the procedure, one was mistakenly randomized

7.3.4 ImpACT-24A Demographics and Baseline Characteristics

7.3.4.1 ImpACT-24A Patient Demographics

There were no differences between the SPG and sham control group with respect to age or sex.

	mITT Population		
	SPG Group	Sham Group	p-value
N	153	100	
Median age, years (IQR)	73 (64-79)	74 (64-79)	0.22
Sex (female)	82 (54%)	51 (51%)	0.69
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 34 – ImpACT-24A Demographics

7.3.4.2 ImpACT-24A Medical History and Baseline Stroke Characteristics

The medical history and baseline stroke characteristics were well-balanced between the groups.

	mITT Population		
	SPG Group	Sham Group	p-value
N	153	100	
Pre-stroke mRS = 0	90%	85%	0.21
Hypertension*	75%	74%	0.84
Diabetes*	32%	36%	0.51
Atrial Fibrillation*	26%	39%	0.03
Systolic Blood Pressure, mean (SD)	152.7 (20.8)	149.4 (26.2)	0.27
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). * Medical history data are based on automatic parsing a free-text medical history field in the eCRF			

Table 35 – ImpACT-24A Medical History

	mITT Population		
	SPG Group	Sham Group	p-value
N	153	100	
Median NIHSS (IQR)	11 (8 - 15)	11 (9 - 14)	0.50
Stroke side (left brain)	66 (43%)	52 (52%)	0.17
Median ASPECTS (IQR)	7 (5 - 10)	8 (7 - 10)	0.01
Median time from last-known-well to 1st stim, hrs (IQR)	18.3 (14.7-22.4)	18.9 (14.4-22.5)	0.70
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 36 – ImpACT-24A Baseline Stroke Severity

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.

7.3.5 ImpACT-24A Safety Results

7.3.5.1 Event Rates

There were no significant differences between the groups in any of the safety endpoints (Table 37).

	SPG Stim.	Sham	OR (95% CI)	p
Mortality	26/202 (12.9%)	16/101 (15.8%)	0.78 (0.40-1.54)	0.48
SAE	61/202 (30.2%)	36/101 (35.6%)	0.78 (0.47-1.30)	0.34
Neurological Deterioration	20/202 (9.9%)	10/101 (9.9%)	1.00 (0.45-2.22)	1.00
Symptomatic Intracranial Hemorrhage	1/202 (0.5%)	1/101 (1.0%)	0.50 (0.03-8.04)	0.54
Pneumonia SAEs	12/202 (5.9%)	10/101 (9.9%)	0.57 (0.24-1.38)	0.21

Table 37 – ImpACT-24A - safety outcomes

Event classification by SOC/PT is provided in Appendix H – ImpACT-24A AE Tables.

7.3.5.2 Stimulation-Related Events

No serious adverse events were classified by the investigators as definitely/probably related to the treatment. The following events were classified as possibly related (all cases turned out to be in the sham-control group):

PT	SPG Stim. (N=202)	Sham (N=101)
Hemorrhagic transformation stroke	-	2 (2.0%)
Brain oedema	-	1 (1.0%)
Total	-	3 (3.0%)

Table 38 – Serious Adverse Events Possibly Related to Stimulation

The following table lists frequent (>1%) non-serious stimulation-related adverse events. For a list of all events see appendix H3 – ImpACT-24A Stimulation-Related Non-Serious Adverse Events.

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%)	-
Nervous System Disorders	Headache	8 (4.0%)	1 (1.0%)
	Paresthesia	3 (1.5%)	-

Table 39 – Non-Serious Adverse Events Related to Stimulation

7.3.5.3 Implantation Events

The implantation procedure in ImpACT-24A was the same for both treatment groups (patients were randomized after implantation). Therefore, implantation-related serious adverse events are presented irrespective of group assignment.

SOC	PT	Events (%) N=303
Respiratory, thoracic and mediastinal disorders	Epistaxis	1 (0.3%)
General disorders and administration site conditions	Complication of device removal	1 (0.3%)
Total		**2 (0.7%)**

Table 40 – Implantation-Related Serious Adverse Events

The following table lists frequent (>1%) non-serious implantation-related adverse events. For a list of all events see appendix H4 – ImpACT-24A Implantation-Related Non-Serious Adverse Events

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 hemorrhage	7 (2.3%)
	Device migration	5 (1.7%)
General disorders and administration site conditions	Pain	8 (2.6%)

Table 41 – Implantation-Related Frequent (>1%) Non-Serious Adverse Events

7.3.5.4 Proportion of Failed Implantations

Implant misplacement occurred in 74 (24%) of the 303 implantations, including 49 (24%) of 202 in the SPG stimulation group and 25 (25%) of 101 in the sham-control group.

The rate of misplacement improved with the introduction of the GuideView optical navigation system after the first 143 procedures from 34% to 20% (Figure 98), and further improved after a learning period to 13% in the last 100 procedures (13/100).

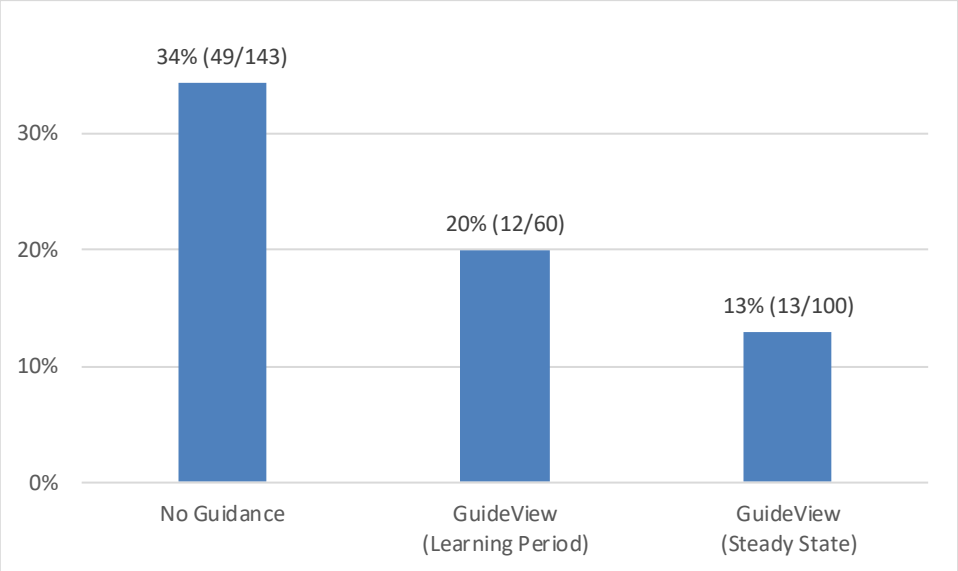

Figure 98 – Implant Misplacement by Type of Navigation Procedure (ImpACT-24A)

Despite the improvement in misplacement rate during the study, progress was slow and it was evident that additional design changes would be needed to further reduce the misplacement rate. It was therefore decided to stop recruitment before reaching the planned sample size of 660 patients.

7.3.5.5 Unrelated Serious Adverse Events

The following table shows unrelated SAE's that occurred in at least 1% of the patients (in either group). 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. For a list of all events see appendix H5 – ImpACT-24A Unrelated Serious Adverse Events

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%)
Nervous system disorders	Cerebral infarction	7 (3.5%)	1 (1.0%)
	Stroke in evolution	4 (2.0%)	2 (2.0%)
Cardiac disorders	Acute myocardial infarction	5 (2.5%)	1 (1.0%)
Vascular disorders	Pulmonary embolism	4 (2.0%)	3 (3.0%)
Surgical and medical procedures	Carotid endarterectomy	1 (0.5%)	2 (2.0%)

Table 42 – Frequent Unrelated Serious Adverse Events (>1% of the patients in either group)

7.3.5.6 Unrelated Non-Serious Adverse Events

The following table shows unrelated non-serious adverse events that occurred in at least 3% of the patients (in either group). 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. For a list of all events see appendix H6 – ImpACT-24A Unrelated Non-Serious Adverse Events

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%)
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%)
Metabolism and nutrition disorders	Hypokalemia	26 (12.9%); 30	10 (9.9%); 11
	Diabetes mellitus	3 (1.5%)	4 (4.0%)
	Hyponatremia	4 (2.0%); 5	3 (3.0%)
	Hyperglycemia	6 (3.0%); 7	-
	Hypercholesterolemia	2 (1.0%)	3 (3.0%)
Nervous system disorders	Headache	14 (6.9%)	11 (10.9%); 12
	Asymptomatic hemorrhagic transformation stroke	1 (0.5%)	3 (3.0%)
	Urinary tract infection	30 (14.9%); 36	20 (19.8%); 24

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
Renal and urinary disorders	Urinary retention	6 (3.0%)	4 (4.0%)
	Hematuria	3 (1.5%)	3 (3.0%)
General disorders and administration site conditions	Hyperthermia	29 (14.4%); 33	13 (12.9%); 14
	Pain	8 (4.0%); 9	3 (3.0%); 4
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%)
	Dyspnea	4 (2.0%)	3 (3.0%)
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%)
Cardiac disorders	Atrial fibrillation	16 (7.9%)	5 (5.0%); 7
	Tachycardia	2 (1.0%)	3 (3.0%)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	9 (4.5%)	5 (5.0%)
	Back pain	3 (1.5%)	3 (3.0%)
Skin and subcutaneous tissue disorders	Rash	-	3 (3.0%)
	Pruritus	1 (0.5%)	3 (3.0%)

Table 43 – Frequent Unrelated non-Serious Adverse Events (≥3% of the patients in either group)

7.3.6 ImpACT-24A Efficacy Results

The following table shows the results of the primary and secondary endpoint in ImpACT-24A mITT population. Although the OR numerically favors SPG, it was not statistically significant.

mITT	SPG (N=153)	Control (N=100)	Absolute Diff.	Odds Ratio	P Value
Primary Endpoint Sliding Dichotomy mRS	49.7%	40.0%	9.7%	1.48 (0.89, 2.47)	0.13
Neurologic Recovery NIHSS ≤1 or Improved ≥9	41.1%	33.7%	7.4%	1.37 (0.81, 2.33)	0.24
Improved Above Expectations Patients with aphasia	58 3%	43.8%	14.6%	1.80 (0.84, 3.88)	0.13
Stroke-Related QoL SIS-16	53.5	51.2	2.4	1.12 (0.71, 1.77)	0.63

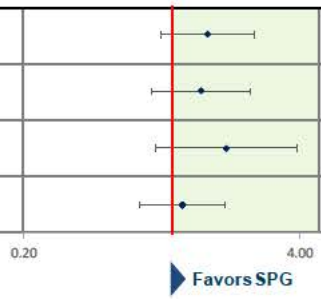

Figure 99 – ImpACT-24A – Primary and Secondary Efficacy analysis – mITT population

Importantly, a preferential treatment benefit was found in patients with CCI. As described earlier, this was the basis for defining the CCI population as a primary analysis population in ImpACT-24B.

CCI	SPG (N=50)	Control (N=37)	Absolute Diff.	Odds Ratio	P Value
Primary Endpoint Sliding Dichotomy mRS	50 0%	27.0%	23.0%	2.70 (1.08, 6.73)	0.03
Neurologic Recovery NIHSS ≤1 or Improved ≥9	46 0%	25.0%	21.0%	2.56 (1.00, 6.52)	0.05
Improved Above Expectations Patients with aphasia	64 0%	29.4%	34.6%	4.27 (1.13, 16 05)	0.03
Stroke-Related QoL SIS-16	43.6	31.9	11.7	1.75 (0.80, 3.75)	0.16

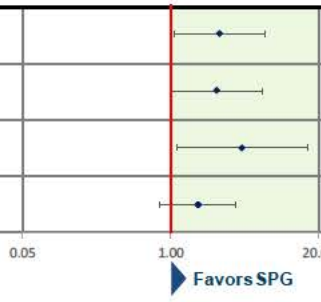

Figure 100 – ImpACT-24A – Efficacy analysis in the target CCI population (post hoc)

7.3.7 ImpACT-24A Summary

ImpACT-24A was a pilot RCT trial. The study started as a confirmatory trial with planned sample size of 660 patients but was stopped at 300 patients due to high rate of implant misplacement.[i] It was therefore underpowered to confirm efficacy.

The results of ImpACT-24A indicate that SPG stimulation using the ISS500 is safe in acute ischemic stroke patients. There was no increase in the rate of symptomatic intracranial hemorrhages in patients treated with active stimulation compared to the sham control

[i] There was also a concern, which was later ruled out, that the implant might cause some level of mechanical activation of the SPG that might mask some of the treatment effect.

group, and there is no difference between the groups in any of the pre-specified safety endpoints.

There were no serious adverse events related to the stimulation. The only two events that were classified as possibly related occurred in control patients (one case of intracranial hemorrhage and one case of brain edema).

Non-serious pain or discomfort related to the stimulation was reported in 62 patients (31%) of the 202 patients in the active stimulation group. Stimulation-related pain is avoidable by adjusting the intensity level to the patient's comfortable tolerance level, as confirmed by ImpACT-24M (see section 7.2.5.4).

Trends of potential benefit were noted and were more pronounced in patients with confirmed cortical involvement and in patients with aphasia (who are more likely to have ischemia in cortical, language areas).

Considering patient subgroups, the potential benefit of SPG stimulation up to 24 hours from stroke onset did not seem to depend on the time from onset. The effect was nominally higher in patients treated >18 hours from onset despite the fact that penumbra was not assessed in this study. Moreover, the group that benefited the most (patients with confirmed cortical ischemia) had larger infarct cores (median baseline ASPECTS score 5 in the active stimulation group). It is plausible to assume that this could result from the protective effect of SPG stimulation on the BBB (stroke disruption of the BBB peaks around 24–72 hours from onset and continues for several days).

7.4 Pooled Post Hoc Analysis (ImpACT-24A and ImpACT-24B)

7.4.1 Poolability

ImpACT-24A and ImpACT-24B had similar design, including the same treatment, follow-up period, endpoints (mRS and SIS at 90d) and the same analytic approach to primary endpoint (sliding dichotomy). The studies had the same exclusion criteria, and minor differences in inclusion criteria. Ages 18-40 were included only in ImpACT-24A but the overall median age in the two studies was similar – 71 years (IQR 63-77) in ImpACT-24B vs 73 years (IQR 64-79) in ImpACT-24A. Evidence of ischemia on baseline imaging were required only in ImpACT-24B. The sham control group in ImpACT-24A underwent implantation and sham treatment. The sham control group in ImpACT-24B underwent sham implantation (mucosa puncture) and the same sham treatment. Transmitter vibration was applied to both groups in both studies.

Treatment duration and all other treatment parameters, including the method of setting the stimulation level were identical in both studies.

Improvements in the implantation technique were implemented during both studies but none of these improvements affected the treatment.

The following tables show the similarity of demographics, medical history and baseline characteristics in the two studies:

Characteristic		**ImpACT-24B (N = 1055)**	**ImpACT-24A (N = 303)**
Age, years	Median (IQR)	71 (63 - 77)	73 (64 - 79)
Sex (% Female)	Female	50.9% (537)	50.2% (152)
Pre stroke mRS = 0	% (N)	93.1% (982)	87.1% (264)
Hypertension	% (N)	84.8% (895)	73.9% (224)
Diabetes	% (N)	25.1% (265)	31.7% (96)
Atrial Fibrillation	% (N)	25.8% (272)	30.4% (92)
Smoking	% (N)	9.7% (102)	7.6% (23)
Alcohol	% (N)	3.3% (35)	3.0% (9)
Obesity	% (N)	5.1% (54)	6.3% (19)
Systolic blood pressure, mmHg	Mean (SD)	148.7 (18.6)	150.7 (23.1)

Table 44 – Demographics and medical history – ImpACT-24B vs ImpACT-24A

Characteristic		**ImpACT-24B (N = 1055)**	**ImpACT-24A (N = 303)**
NIHSS	Median (IQR)	12 (9 – 14)	11 (9 – 15)
	Mean (SD)	11.8 (3.1)	11.8 (3.6)
Stroke side (left brain)	Left	52.8% (557)	46.5% (141)
ASPECT	Mean (SD)	7.2 (2.1)	7.3 (2.7)
TFSO to first stim., h	Median (IQR)	19.3 (15.9 – 22.2)	18.6 (14.5 – 22.2)

Table 45 – Baseline Characteristics ImpACT-24B vs ImpACT-24A

Furthermore, both studies had similar findings: the beneficial effect of SPG stimulation did not depend on the time from stroke onset[i] or infarct core size (ASPECTS), as shown in Figure 101:

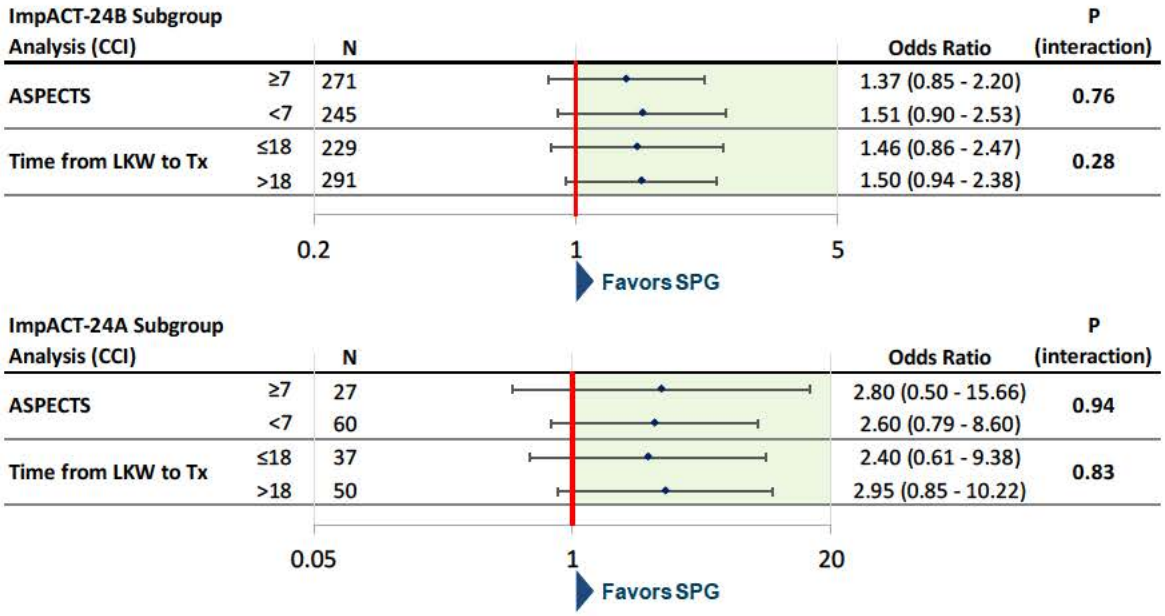

Figure 101 – Subgroup analysis by baseline ASPECTS score, ImpACT-24B and ImpACT-24A, CCI Population

Additionally, the rate of sICH was lower in the SPG stimulation group compared to the sham-control group in both trials (Figure 102).

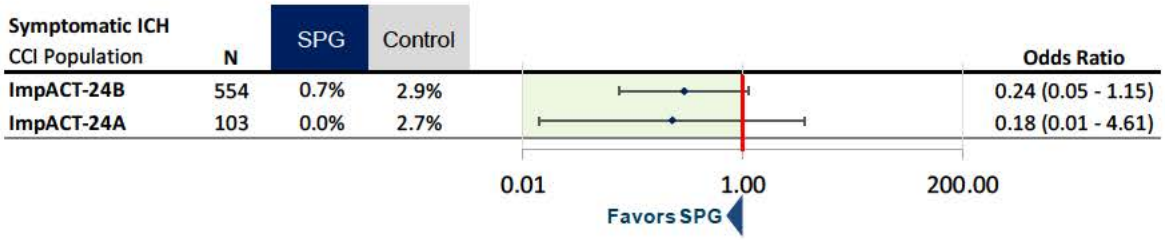

Figure 102 – Pooled rates of symptomatic ICH in SPG Stim. vs. Sham Control groups, CCI Population

These findings are consistent with pre-clinical data that shows that SPG stimulation stabilizes the BBB and with literature showing that damage to the BBB after stroke peaks at 12-72 hours after stroke (see section 4.2.2).

The pooled analysis was a patient-level one-stage meta-analysis of the primary efficacy outcome, which was improvement beyond expectations (sliding dichotomy) at 3 months on the mRS. The same primary populations (mITT and CCI) and multiplicity control (Hochberg multistep, step-up testing procedure) were used in the primary analysis of the

[i] The effect persisted up to 24 hours from onset despite the fact that small infarct core was not an inclusion criterion in the studies. In contrast, late-window EVT studies showed benefit that is independent of time, but required large volume of salvageable tissue.

pooled data as in the primary analysis of the ImpACT-24B trial. Fixed effects included in the model were treatment group and study. The model also included a random study effect.

Formal poolability testing showed homogeneity of effect across both trials (p=0.88, no difference between the trials[i]) and no significant interaction between study and treatment effect (non-significant Study x Treatment Interaction p-value).

In conclusion, the studies are similar and poolable. The pooled analysis reduces the uncertainty of the benefit, increases the sensitivity of the subgroup analysis to assess the homogeneity of treatment effect in different subgroups within the CCI population and increases the sensitivity of the safety analysis to smaller differences in SAE rates.

[i] The homogeneity of effect was assessed using a test of equal covariance between the studies

7.4.2 Pooled Safety Results

7.4.2.1 Safety Endpoints

Since the stimulation treatment protocol was the same in both the ImpACT-24A and ImpACT-24B trials, the overall safety and treatment-related risks are best evaluated by comparing the stimulation arm to the sham-control arm in the pooled dataset.

A All Pooled	SPG N=738	Control N=620	Odds Ratio (95% CI)	P Value
Mortality	13.8%	12.9%	1.08 (0.79, 1.48)	0.62
Serious Adverse Events	30.1%	29.4%	1.04 (0.82, 1.31)	0.77
Neurological Deterioration	8.3%	7.3%	1.15 (0.77, 1.72)	0.49
Pneumonia SAE	4.7%	6.1%	0.76 (0.48, 1.22)	0.26
Symptomatic ICH	0.7%	1.9%	0.35 (0.12, 0.99)	0.04

B CCI Pooled	SPG N=344	Control N=313	Odds Ratio (95% CI)	P Value
Mortality	18.3%	18.2%	1.01 (0.68, 1.50)	0.97
Serious Adverse Events	34.0%	38.0%	0.84 (0.61, 1.16)	0.28
Neurological Deterioration	7.8%	10.2%	0.75 (0.44, 1.28)	0.29
Pneumonia SAE	5.8%	8.6%	0.65 (0.36, 1.19)	0.16
Symptomatic ICH	0.6%	2.9%	0.20 (0.04, 0.92)	0.02

Figure 103 – Pooled Safety Results in the full safety analysis population (A) and in the CCI population (B)

The following figure shows the % Patients without SAE by Time from stroke onset in the full population:

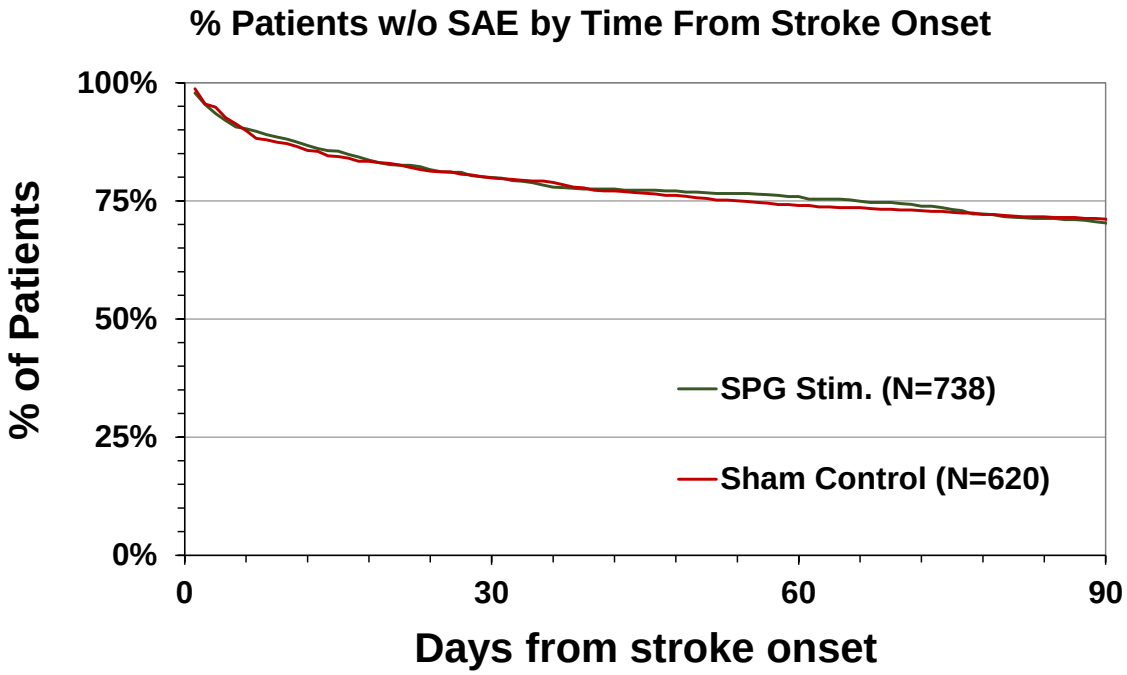

Figure 104 – % Patients without SAE by Time from stroke onset - All Patients (Pooled)

Implantation safety of the final device is assessed in section 7.6.2 and in Appendix C.

7.4.3 Pooled Efficacy Results

Figure 105 shows the pooled efficacy results of ImpACT-24A and ImpACT-24B in the CCI population. The results in the primary endpoint (sliding dichotomy) are consistent with the results of all other endpoints.

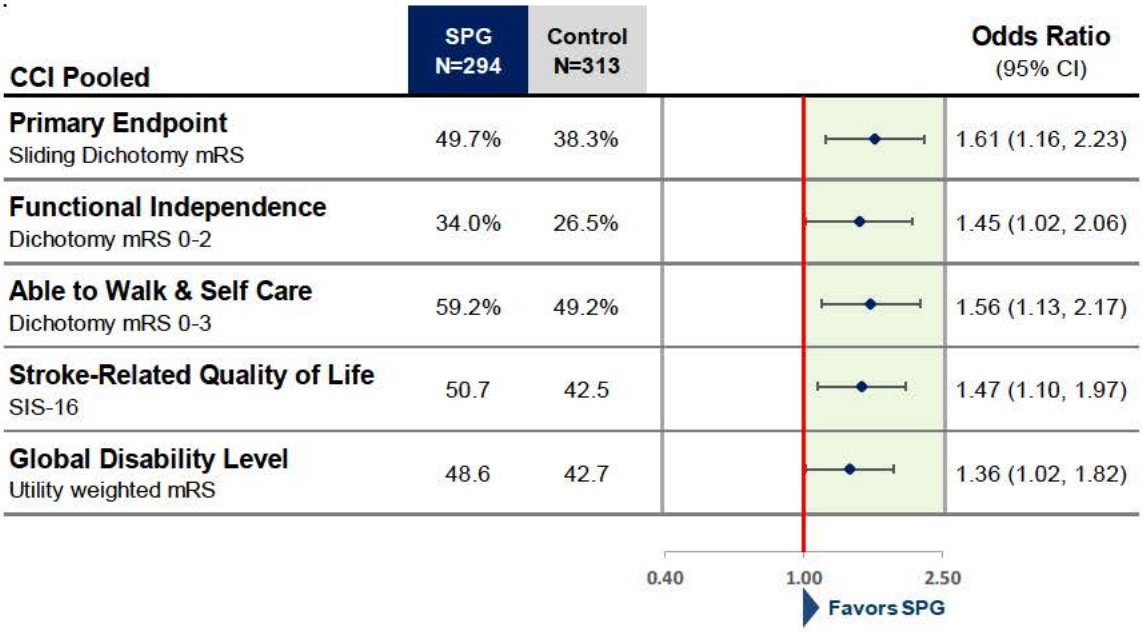

Figure 105 – Pooled efficacy analysis of randomized studies in the CCI Population

The pooled efficacy analysis supports the conclusions of the pivotal study that the treatment is safe and effective for CCI patients 8-24 hours after stroke onset.

7.4.4 Subgroup Analysis

The following figure shows the pooled subgroup analysis in the CCI population, to evaluate the heterogeneity of SPG stimulation effect (using Sliding Dichotomy, the primary efficacy endpoint).

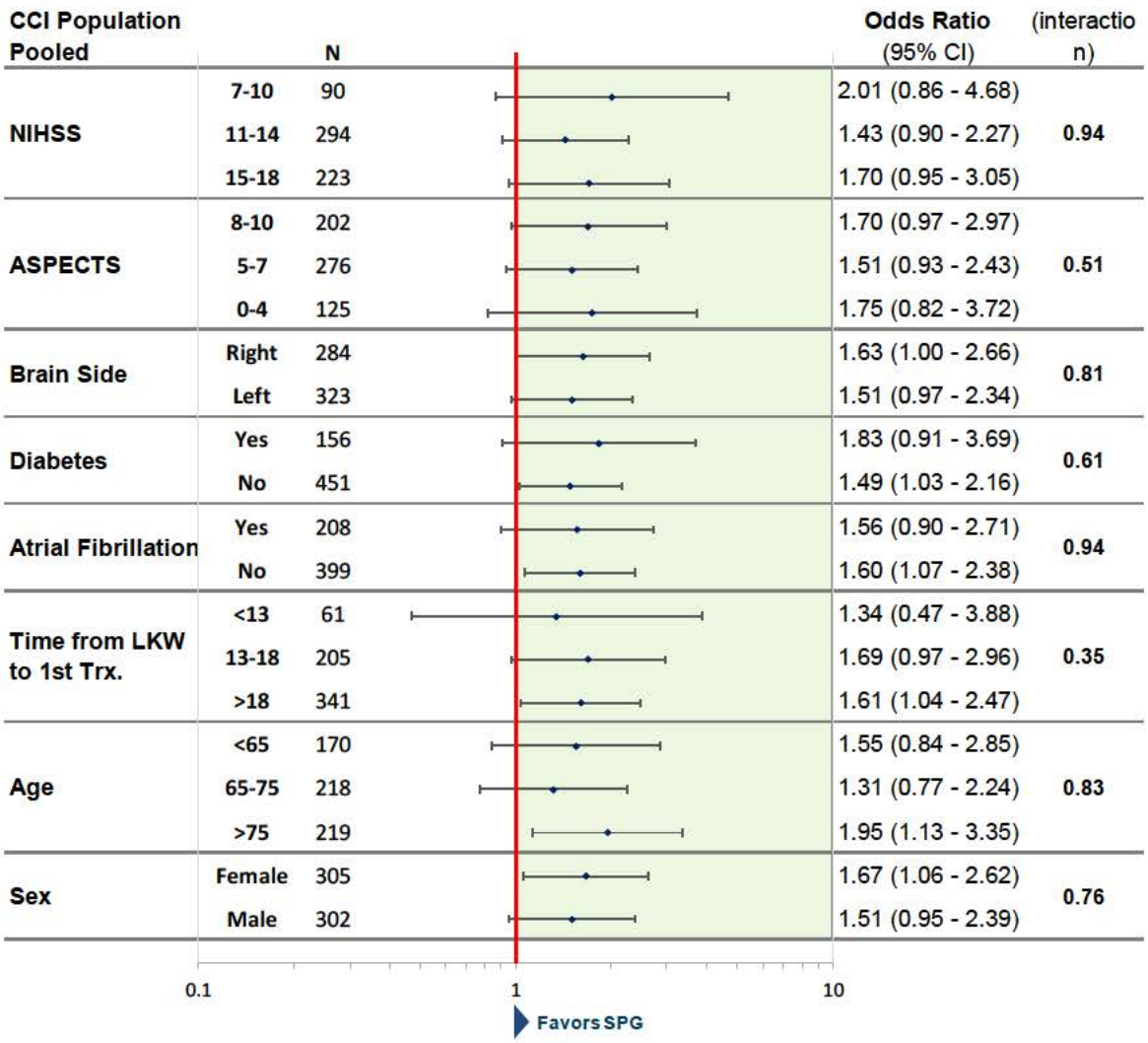

Figure 106 – Subgroup Analysis – 90-Day mRS Sliding Dichotomy

There is no heterogeneity of treatment effect with respect to any of the pre-specified covariates.[i] In particular, the pooled analysis re-affirms that the beneficial effect of SPG stimulation does not depend on the time from stroke onset or infarct core size (ASPECTS). The benefit persists up to 24-hours from onset. For discussion of the mechanism of action that may explain this late effect (without selecting patients based on penumbra/core ratio) see section 4.

[i] The interaction p-values are the significance levels of the ***covariate x treatment*** term.

7.4.5 Magnitude of the Benefit

The 9.7% absolute increase in favorable 90-day disability outcome (primary endpoint) in the CCI population in the pivotal ImpACT-24B is equivalent to number-needed-to-treat (NNT) of 10. Similar probabilities of experiencing the benefit of reduced disability were observed in all efficacy endpoints, and in the pooled analysis (Figure 105) with NNT values ranging between 9-13 in the other dichotomized efficacy outcomes.[i]

This magnitude of benefit for SPG stimulation started in 8–24 hours from stroke onset is comparable to that of IV tPA administered <3 hours from stroke onset and exceeds that of IV tPA administered 3–4.5 hours from stroke onset, both US and international guideline-based treatments.[53] It is also comparable to the magnitude of benefit of EVT in MR CLEAN,[59, 60] the largest thrombectomy trial in the <6 hour window[ii].

The magnitude of benefit of EVT in 6-24 hours in the DAWN and DEFUSE3 studies was higher (median mRS 3 vs 4, p<0.001 in the primary endpoint in DEFUSE3 and mean utility-weighted mRS 5.5 vs 3.4, posterior probability of superiority >0.999 in the primary endpoint in DAWN). Therefore, the proposed indication for use of SPG stimulation using ISS500 is limited to patients who are ineligible for EVT or have no access to it.

It is important to note, however, that the patient population in DAWN and DEFUSE3 is highly selective and very different than the CCI population in ImpACT-24B. Patients in the late EVT trials were treated earlier, and had higher NIHSS and smaller baseline infarcts (in other words, smaller core and larger penumbra) compared to ImpACT-24B:

	ImpACT-24B CCI	DAWN	DEFUSE3
Time to baseline imaging	16 (13-19)	Not published	10 (8-12)
Time to treatment	20 (16-22)	12 (10-16)	12 (9-13)
Baseline NIHSS median (IQR)	13 (12-15)	17 (13-21)	16 (10-20)
Baseline ASPECTS median (IQR)	7 (5-8)	8 (7-8)	8 (7-9)

Table 46 - ImpACT-24B CCI vs DAWN and DEFUSE3

Only 2%-3% from all AIS patients meet the DAWN and DEFUSE3 criteria. [1] Accordingly, SPG stimulation serves an unmet need by providing a treatment option for some of the patients who are ineligible for imaging-selected late thrombectomy.

[i] Alternative ways to assess the NNT with SPG stimulation yield NNT values in the range of 3.5-5.8 (see Appendix D – SPG Stimulation Number Needed to Treat).

[ii] Other EVT trials used more selective imaging criteria than MR CLEAN, and achieved lower NNT values

7.5 Usability Study: ImpACT-24M

7.5.1 ImpACT-24M Study Design

7.5.1.1 Overview

ImpACT-24B and ImpACT-24A demonstrated the safety and effectiveness of SPG stimulation for CCI patients. However, when considering the generalizability of these results to clinical use, two areas for usability improvement have been identified. The solutions have been implemented, and were validated in ImpACT-24M.

The study's main goals were to validate the simplicity and accuracy of the implantation procedure, and validate a practical method to set the stimulation level correctly in a non-blinded environment.

ImpACT-24M was a multicenter, single arm usability study, with follow-up period of 7 days. 50 patients were recruited between May-September 2018.

7.5.1.2 Inclusion/Exclusion Criteria

The inclusion criteria for the study were:

#	Criteria
1	Age: ≥ 18 years and ≤ 85 years
2	Clinical diagnosis of anterior circulation stroke
3	Baseline NIHSS ≥ 1 and ≤ 6 including hand-motor deficit
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

Table 47 – ImpACT-24M Inclusion Criteria

The low NIHSS score, and hand-motor deficit requirements were designed to select cooperative patients that will be able to perform the motor function test and to undergo blood flow measurements using CCD. Additionally, deficit in fine motor function is typical of strokes involving the cortex.

The exclusion criteria were the same as in ImpACT-24B and ImpACT-24A, including no prior intervention with IV-tPA or mechanical thrombectomy (see Appendix A – Pivotal Study Inclusion/Exclusion Criteria).

7.5.1.3 Study Flow and Follow Up

After signing the informed consent, a "bite" PRM (Figure 107) was attached to the upper teeth/gums, and the patient was scanned for the Image-Guided implantation procedure.

Figure 107 – "Bite" PRM

Following successful implantation, SPG stimulation treatment began. Stimulation was delivered for 4 hours per day on 5 consecutive days.

Unlike the previous studies, stimulation level was set at the patient's Comfortable Tolerance Level (CTL) based on non-noxious physiologic signs of SPG activation (facial tingling or lacrimation, without discomfort or pain of any kind).[i]

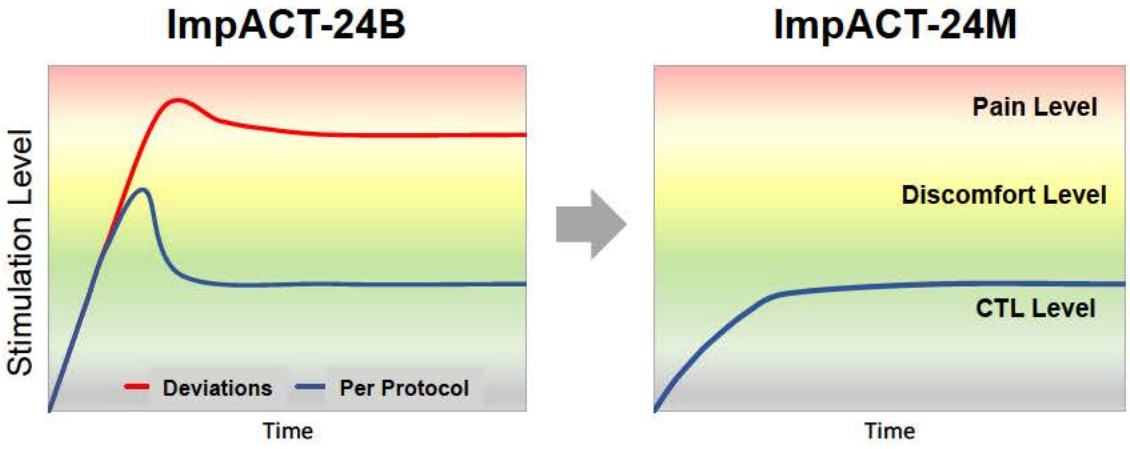

Figure 108 – Patient's Comfortable Tolerance Level (CTL) – ImpACT-24M vs ImpACT-24B

In ImpACT-24B, the intensity was initiated at a low level and gradually escalated in steps until the patient had mild discomfort. The intensity was then reduced to the CTL. In ImpACT-24M, on the other hand, non-noxious physiologic signs such as lacrimation or facial tingling were used, without reaching discomfort/pain.

[i] This approach could not be used in a blinded environment. Blinding was achieved by transmitter vibration that mimicked the sensation of SPG activation.

The following diagram summarizes the patient flow in the study:

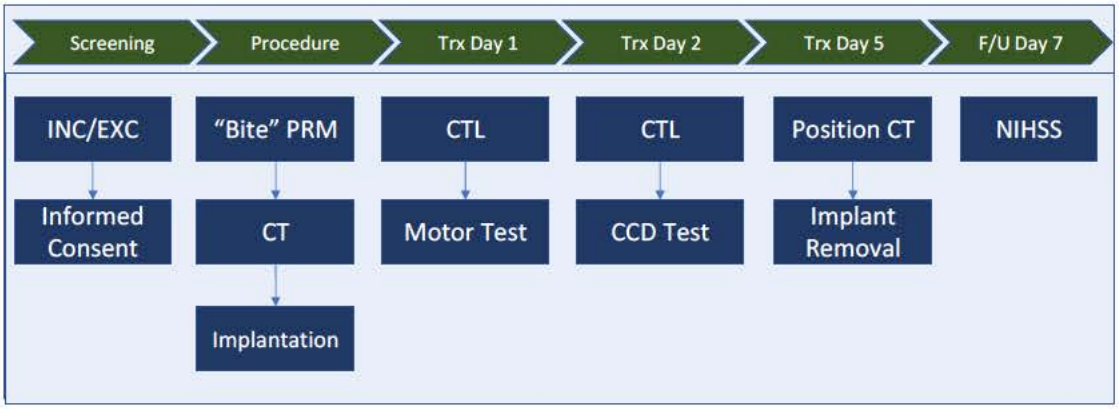

Figure 109 – ImpACT-24M Flow

Hand strength was assessed on Day 1, before and during stimulation (after 2 and 4 hours of stimulation), using quantitative measurement of hand grip strength and finger pinch strength (Baseline Hydraulic Hand Dynamometers, Fabrication Enterprises Inc, White Plains NY, USA). Hand strength was measured both in the affected hand and, for comparison, the non-affected hand.

Figure 110 – Hand Force Gauge

The effect of stimulation was assessed by measuring volumetric blood flow before and during the 2nd stimulation session (on day 2) using Common Carotid Doppler (CCD, see Figure 111).

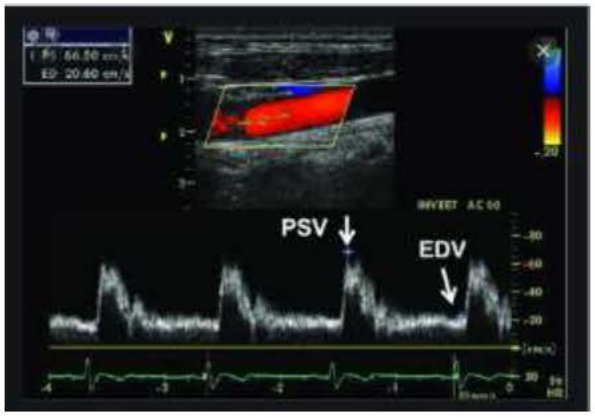

Figure 111 – Blood Flow CCD Measurements

Peak-systolic and end-diastolic absolute blood flow levels (PSF and EDF) were calculated using CCD measurements of blood velocity and vessel diameter, 1cm proximal to the carotid bulb.

Following the last treatment on Day 5, CT imaging was performed to assess the attained implant position, rated by a central positioning evaluator. After the Day 5 imaging, the implant was removed with fine forceps. Follow up time was 7 days.

7.5.1.4 Endpoints

Effectiveness endpoints:

1. Implantation – Proportion of procedures with positive indication of reaching the sphenopalatine fossa
2. Finding the CTL – Proportion of patients with unilateral lacrimation, nasal secretion, and/or facial redness (on the stimulation side)
3. Increased blood flow – Change in blood flow in CCD during stimulation compared to baseline (non-Afib patients)[i]
4. Improvement in motor symptoms – The change in grasp force and pinch force during and after stimulation.

The improvement in motor symptoms and increased blood flow (endpoints 3,4) were used as surrogates of effective SPG activation.

Safety endpoints:

1. Comparative 7-day safety data between the ISS stimulation group of this study and of the ImpACT-24B study:
    a. Incidence of Serious Adverse Events
    b. Implantation Complications
    c. Stimulation-related Adverse Events
2. 7-day mortality
3. Neurological deterioration
4. Symptomatic intracranial hemorrhage (sICH)

7.5.1.5 Statistical Methods

Change in grasp force, pinch force and blood flow (relative to baseline measurement before stimulation) are assessed as continuous variables using paired t-test and as dichotomous variables using a 20% change threshold.

[i] CCD measurements of peak systolic and end diastolic blood flow cannot be measured in patients with atrial fibrillation.

Patients enrolled with known atrial fibrillation did not undergo CCD measurements and were excluded from the blood flow analysis because of waveform variability making quantification less accurate.

Patients who were not able to cooperate with the baseline dynamometer motor strength testing (before stimulation) were excluded from the motor function analysis.

7.5.2 ImpACT-24M Demographics and Baseline Characteristics

7.5.3 Results

7.5.3.1 Patient Accountability, Demographics and Baseline Characteristics

Fifty patients were enrolled between May 2018 and final study visit in September 2018.

The following table shows the endpoint data availability:

Endpoint	Availability	Comment
Blood flow	46/50 (92%)	4 patients had known AFIB
Motor	47/50 (94%)	3 patients did not cooperate
NIHSS	50/50 (100%)	

Table 48 – ImpACT-24M Data Availability

The following table shows the main baseline characteristics:

Parameter	Value
N	50
Age, median (IQR)	66 (60-74)
Female (%)	44%
Atrial fibrillation, n (%)	4 (8%)
NIHSS, median (IQR)	5 (4-5)
Time from last-known-well to 1st stimulation, days, median (IQR)	18 (9-22)

Table 49 – ImpACT-24M Demographics and Baseline

7.5.3.2 Safety Results

Within the 7-day follow-up period, there were no mortality, neurological deterioration, symptomatic intracranial hemorrhage, or stimulation-related adverse events (including pain).

One patient had a SAE (new stroke) and one implantation-related non-serious adverse event was reported (nausea). For a list of all adverse events see Appendix M – ImpACT-24M Adverse Events. Discomfort and pain adverse events did not occur in any patient (0/50).

7.5.3.3 Implantation Results

The final implant and navigation system were used in ImpACT-24M:

Parameter	Value
N	50
Success Rate (on-target placement)	50 (100%)
Skin-to-skin time (minutes), median (IQR)	4 (3-7)

Table 50 – ImpACT-24M Implantation Results

These results confirm the accuracy and simplicity of the final implantation procedure.

7.5.3.4 Efficacy Results

CTL was successfully determined based on non-noxious physiological biomarkers of SPG activation in 96% of the patients, as shown in the following table:

Biomarker for CTL Identification	Value
Ipsilateral lacrimation and facial tingling sensation	32/50 (64%)
Facial tingling sensation only	16/50 (32%)
Total	48/50 (96%)

Table 51 – ImpACT-24M Physiologic Biomarkers of SPG Activation

Figure 112 shows the distribution of the CTL levels using the physiologic determination method in ImpACT-24M. In 92% (46/50 patients) of the patients, the CTL (which was set using physiological surrogates) was in the medium range. This "non-noxious physiologically-selected range" is the final dose range of the device. The remaining 4 outliers (8%) had no increase in blood flow or motor function.

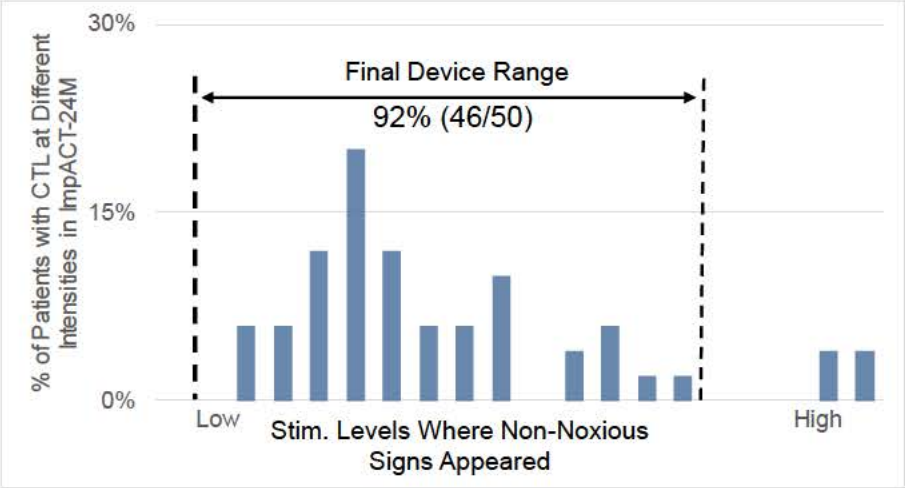

Figure 112 – Distribution of CTL Levels in ImpACT-24M (N=50)

As indicated above, discomfort and pain did not occur in any of the 50 patients in this trial.Forty-seven patients (94%) underwent grasp and pinch motor evaluation before stimulation, after 2 hours of stimulation, and after 4 hours of stimulation.[i] Figure 113 shows the change in motor function during stimulation compared to the baseline measurement before stimulation.

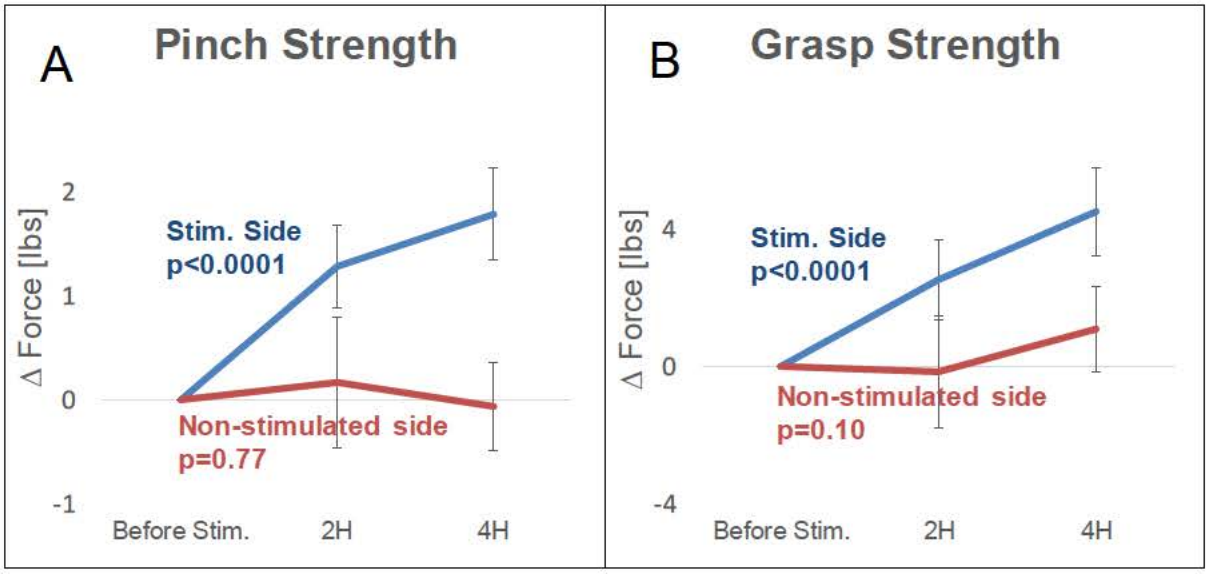

Figure 113 – Hand-strength Improvement (A) Pinch; (B) Grasp

In 40/47 patients, improvement by 20% or more was measured in at least one of the fine motor parameters (compared to the baseline).

The results are summarized in the following Table 52. The baseline measurements (before stimulation) are compared with measurements after 2 hours and 4 hours of stimulation (one in the middle of the treatment session and one at the end).

	2 Hours vs. Baseline N=47			4 Hours vs. Baseline N=47		
	Mean Increase (95% CI) [lbs]	% Change	P value (For mean increase)	Mean Increase (95% CI) [lbs]	% Change	P value (For mean increase)
Pinch force	1.3 (0.9-1.7)	30%	<0.0001	1.8 (1.3-2.2)	42%	<0.0001
Grasp force	2.5 (1.4-3.7)	15%	<0.0001	4.5 (3.2-5.8)	26%	<0.0001

Table 52 – ImpACT-24M – Increase in Motor Function (Affected Hand)

In contrast, as shown in Figure 113, in the unaffected hand, mean pinch force and mean grasp force did not increase.

[i] The remaining 3 patients were uncooperative

Forty-six patients (92%) underwent common-carotid Doppler (CCD) measurements before and during treatment at their CTL (the remaining 4 patients could not be measured due to history of atrial fibrillation). Stimulation was associated with increase in common carotid artery vessel diameter and increase in flow velocity and flow volume in the common carotid artery during both peak systole and end diastole (Figure 114, Table 53).

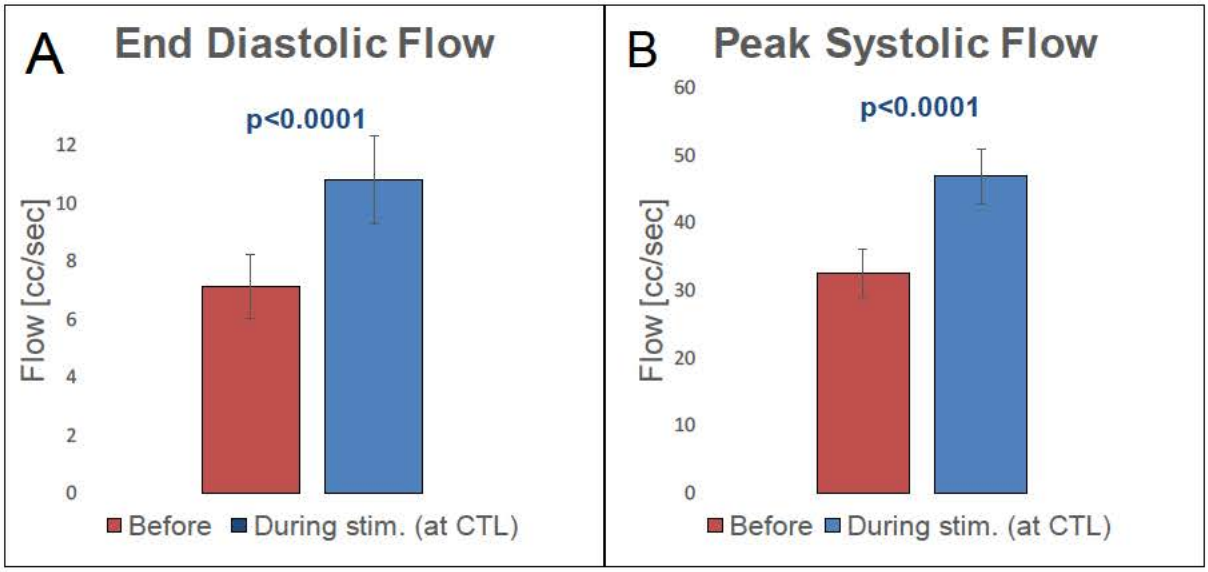

Figure 114 – Increased blood flow during stimulation (A) End Diastolic and (B) Peak Systolic

The following table shows that the diameter, peak systolic velocity and flow, and end diastolic velocity and flow, all increased with SPG stimulation compared to baseline measurements before 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 – Changes in ipsilateral common carotid artery diameter, flow velocity, and flow volume with SPG stimulation

Additionally, a significant relation was observed between the degree of improvement in blood flow augmentation and the degree of improvement in hand strength (Figure 115).[i]

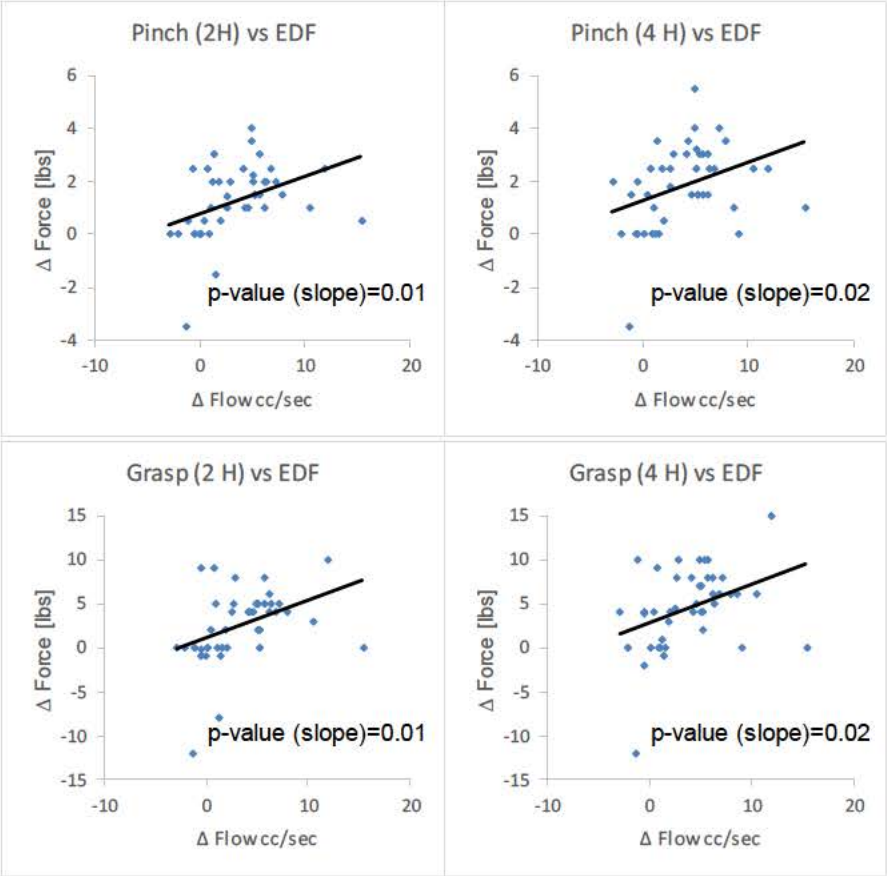

Figure 115 – Change in hand strength vs change in flow during stimulation

Another sensitivity analysis was done with the dichotomized changes in flow and force (Table 54). There was a significantly greater improvement in pinch and grasp strength at 4 hours.

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

Table 54 – Relationship between hand-strength improvement (>20%) and changes in CCA blood flow.

[i] All p-values 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. $P<0.05$ 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.

[ii] P-values were calculated using χ^2 test. Analysis was also performed using hypergeometric test (due to the small sample size) and the p-values ranged between 0.001 to 0.004.

7.5.4 Discussion and Conclusions

The ImpACT-24M study provides important evidence on the usability and mechanism of action of the ISS500 in its final PMA configuration.

7.5.4.1 Implantation Usability

This study demonstrated that the implantation is simple and accurate (zero misplacements, 4 min. skin-to-skin time). The following figure summarizes the improvement in implantation success rate and procedure over the 15 years of clinical evaluation (the blue dots represent the misplacement rate, and the grey bars represent the skin-to-skin time):

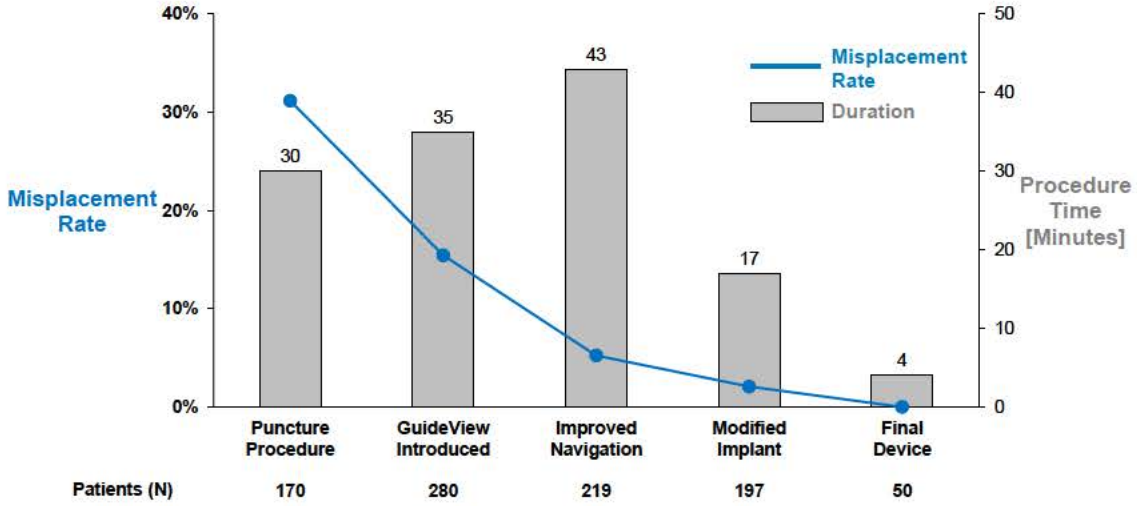

Figure 116 – Implantation Accuracy and Procedure Time

7.5.4.2 Treatment Usability

Dose-setting was based on physiological signs of SPG activation. This approach was practical (signs of SPG activation were noticed in 96% of the patients), and typically resulted in stimulation levels in the medium stimulation range. The importance of these results is discussed in section 7.6 - ImpACT-24M & ImpACT-24B – Integrated Discussion.

7.5.4.3 *Mechanism of Action*

Blood flow and fine motor function were measured during stimulation and were compared to baseline measurements before stimulation. SPG stimulation increased the mean peak systolic flow and end diastolic flow and improved fine motor function on the affected side.

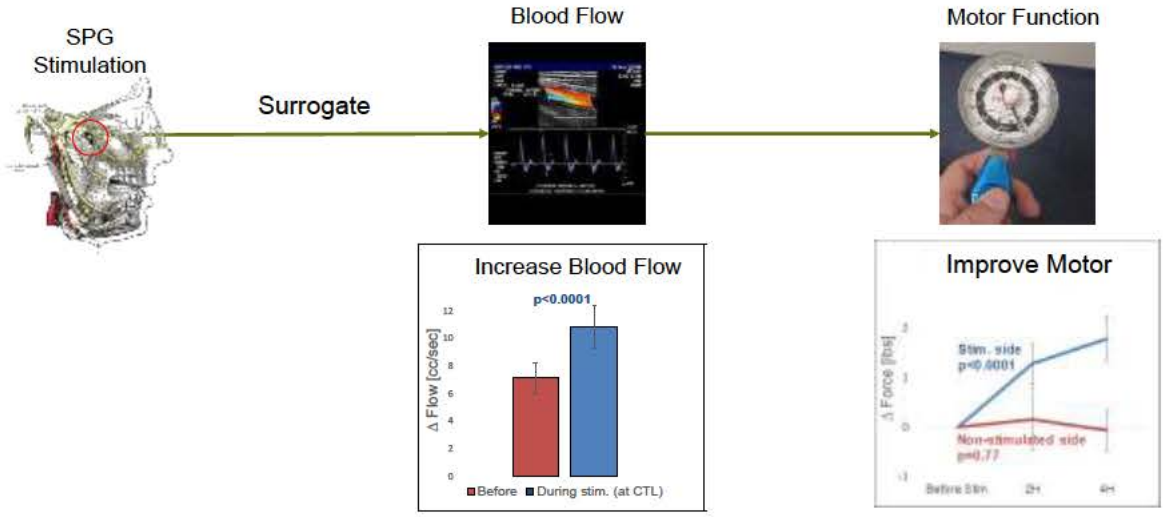

Figure 117 – SPG Stimulation Increases Blood Flow and Improves Motor Function

These results support the literature that found that patients often have salvageable tissue 24 hours after stroke onset. The data also support that blood flow to the ischemic region may be restored through the collateral circulation by SPG stimulation, without opening the occluded artery.

7.6 ImpACT-24M & ImpACT-24B – Integrated Discussion

7.6.1 Treatment

The pivotal ImpACT-24B RCT study and the single-arm usability and MOA ImpACT-24M study provide complementary information and each of these studies helps to understand the results of the other.

In the pivotal trial (ImpACT-24B), some patients were not stimulated as intended at their comfortable tolerance level (CTL), and this resulted in an inverse U-Shaped dose-response relationship between stimulation level and outcome (green line in Figure 118, for details, see section 7.2.5.4 in ImpACT-24B Safety Results).

To ensure that the CTL is not exceeded in routine clinical use, the ImpACT24-M usability study validated a practical method to set the stimulation level in an unblinded environment, using physiological signs of SPG activation (see details in section 5.2 in the Device Description).

When combining the results of the two studies[i], we see that the same stimulation range that was associated with sensation and/or lacrimation, increased blood flow and improved fine-motor function in ImpACT-24M (where the highest blue bars are concentrated), was also associated with the highest odds of favorable outcome in ImpACT-24B (the peak of the green curve), as illustrated in Figure 118.

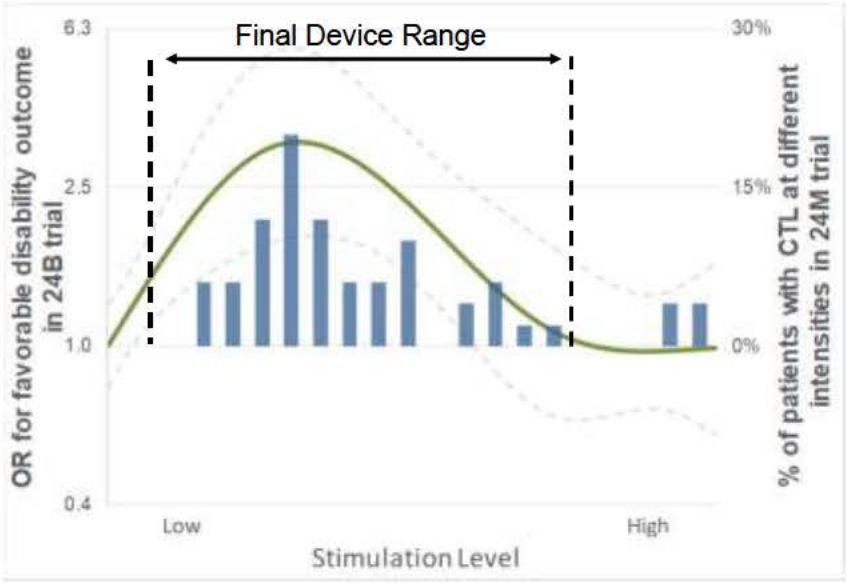

Figure 118 – Dose Response in ImpACT-24B (green, N=520) and Distribution of CTL Levels in ImpACT-24M (blue, N=50)

[i] It is important to recognize that the two studies overlapped in time - 64% of the patients in ImpACT-24M were recruited before the unblinding of the ImpACT-24B data on July 18, 2018.

In light of these findings, the final device limits the stimulation level to the physiologically selected stimulation range and ensures that all patients in clinical practice will be treated in this range.

An efficacy analysis in patients who were stimulated in final device dose range in ImpACT-24B is summarized in the following figure:

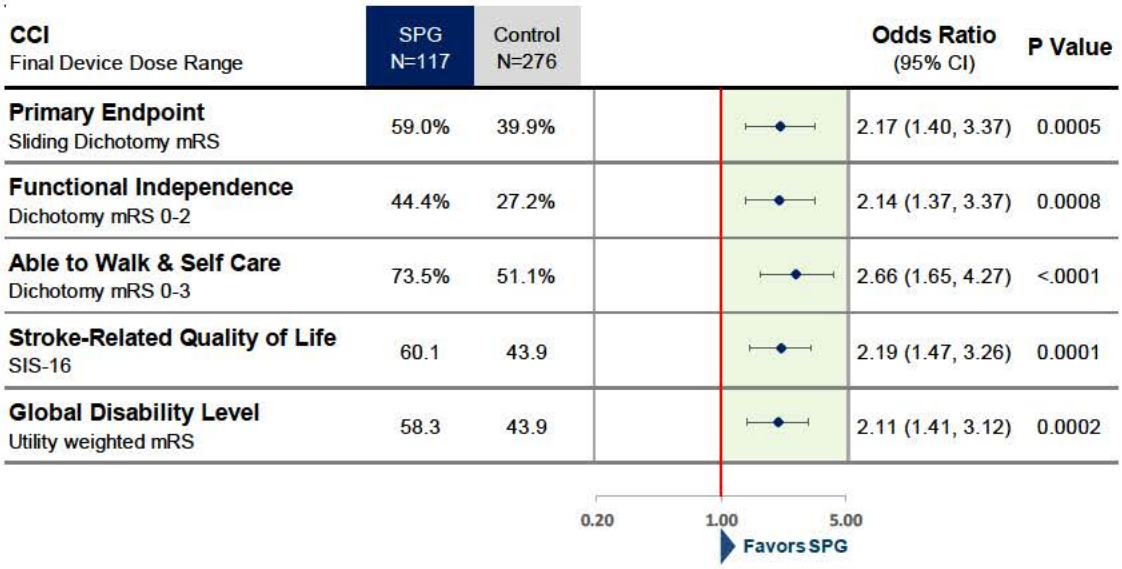

Figure 119 – SPG Stimulation in the final device dose range – CCI Population

This analysis shows a much higher treatment benefit in patients whose stimulation level was set in this range. For example, 49% of the control patients were unable to walk or care for their body after 3 months (mRS ≥4) compared to 27% in the treated arm (dichotomy 0-3 mRS).

These results suggest that the benefit of SPG stimulation in clinical practice (using the physiologic approach) may be higher than measured in the pivotal trial (where physiologic signs could not be used due to blinding limitations and higher dose was often delivered).

7.6.2 Implantation

There were no implantation-related serious adverse events or complications using the final implant and navigation system in ImpACT-24M. The following table shows that all adverse events related to the implantation in the 197 procedures using the final implant with the old navigation system in ImpACT-24B appear to be directly related to the longer implantation procedure duration.

AE Preferred Term (PT)	ImpACT-24B % of Procedures (N=197)	ImpACT-24M % of Procedures (N=50)
Agitation	5 (2.5%)	0
Hypertension	3 (1.5%)	0
Implant site pain	2 (1.0%)	0
Anxiety	1 (0.5%)	0
Nausea	1 (0.5%)	1 (2%)

Table 55 – Adverse Events Related to Implantation using the Final Implant in ImpACT-24B

Only one non-serious event occurred in the short procedures in ImpACT-24M (skin-to-skin time <5 minutes).

Additionally, there were two adverse events related to removal of the final device in ImpACT-24B. In both cases, the implant was removed successfully without complications. Analysis of the implant removal events (see Appendix C1 - Contributing factors to complications and their mitigations) concluded that there is no unacceptable risk associated with the removal procedure.

Appendix C assesses all risks that could be related to the implantation, implant removal, or device misplacement. The conclusion of this analysis and the clinical data is that the implantation is safe and there are no unacceptable risks in the implantation.

7.7 The Effect in US Patients

The US sample size in ImpACT-24B is small and the effect did not follow a consistent trend (was smaller in the US in some endpoints compared to the OUS population and was higher in others). Following FDA's request, additional analyses were performed to support the applicability of the results to the US population.

These additional analyses are divided into 3 parts:

1. ImpACT-24B US vs OUS analysis, accounting for effects of the small sample size
2. Additional relevant analysis of the ImpACT-24B results
3. Pooled analysis

All the results support the same conclusion that the benefit of SPG stimulation is not region-specific and the benefit in patients with confirmed cortical involvement is consistent in both US and OUS.

7.7.1 ImpACT-24B – Adjusted Analysis - US vs OUS

The following table present the subgroup analysis in the ImpACT-24B CCI population:

CCI	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
mRS 0–2	42.1% (8/19)	33.3% (4/12)	1.45 (0.32-6.56)	34.2% (77/225)	26.9% (71/264)	1.41 (0.96-2.08)	0.97
mRS 0–3	68.4% (13/19)	66.7% (8/12)	1.08 (0.23-5.06)	61.8% (139/225)	50.4% (133/264)	1.59 (1.11-2.28)	0.63
	SPG stim Mean±SD	**Sham stim Mean±SD**	**Diff. (95% CI)**	**SPG stim Mean±SD**	**Sham stim Mean±SD**	**Diff. (95% CI)**	
SIS	65.6 (36.8)	56.3 (39.5)	9.4 (-18.0-36.8)	51.1 (38.6)	43.3 (38.0)	7.8 (0.9-14.6)	0.91
uw-mRS	58.3 (32.2)	53.5 (36.0)	4.8 (-19.2-28.8)	49.3 (35.9)	43.5 (35.6)	5.9 (-0.5-12.2)	0.94

Table 56 – Unadjusted Efficacy Results by US/OUS – ImpACT-24B CCI Population

Comparison of the baseline characteristics of the ImpACT-24B treated and sham-control groups in the US, shows imbalance in several clinically important baseline characteristics:

			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)
Pooled	N		25	21
	Sex (% Female)	Female	12 (48.0%)	14 (66.7%)
	Stroke side (left brain)	Left	15 (60.0%)	10 (47.6%)
	Atrial Fibrillation	%	1 (4.0%)	7 (33.3%)
	Smoking	%	5 (20.0%)	2 (9.5%)

Table 57 – Imbalanced Covariates – US CCI Population (ImpACT-24B and Pooled Cohorts)

To account for this imbalance, the adjusted treatment effect in all endpoints in the US and OUS populations is provided below:

ImpACT-24B Covariate Adjusted Efficacy Analysis (CCI) for US (N=31) vs OUS (N=489)		
Endpoint	Region	OR [95% CI]
Sliding Dichotomy	OUS	1.46 [0.98,2.18]
	US	1.62 [0.30,8.63]
Dich. 0-2	OUS	1.39 [0.88,2.19]
	US	2.55 [0.38,17.35]
Dich. 0-3	OUS	1.57 [1.02,2.43]
	US	1.74 [0.23,13.14]
Endpoint	Region	Diff [95% CI]
SIS	OUS	4.90 [-0.88,10.68]
	US	19.35 [-4.32,43.03]
Utility weighted mRS	OUS	3.24 [-2.09,8.56]
	US	13.01 [-8.65,34.67]

Table 58 – ImpACT-24B Adjusted Efficacy Analysis US/OUS

As shown above, the smaller effect in the US in ImpACT-24B was caused by covariate imbalance due to the small sample size. Once the imbalance is accounted for using adjusted

analysis, the effect in the ImpACT-24B US CCI population is consistent with the effect in the CCI population outside the US in all endpoints with a consistent trend of a slightly larger effect in the US compared to OUS.

7.7.2 ImpACT-24B – US vs OUS Dose Response Analysis

Background: The SPG stimulation intensity is associated with patient outcome in the CCI population in an inverse U-shaped dose response relationship. Patients who received stimulation at the "non-noxious physiologic range" (the final stimulation range of the device) had a significantly higher rate of favorable outcome compared to patients who were treated at higher stimulation levels (for details, see section 7.6.1).

The following table compares the primary outcomes by stimulation level in US and OUS patients in the CCI population:

Stimulation Level	US	OUS
Inside the Final Device Range	58.3% (7/12)	59.0% (62/105)
Outside the Final Device Range	42.9% (3/7)	40.8% (49/120)

Table 59 – ImpACT-24B US vs OUS Sliding Dichotomy Success Rate by Stimulation Level

Despite the small sample size, the US data shows the same trend of better outcome in the physiologic range and similar success rates in the SPG group in both ranges. The dose-response relationship is a strong indication of a true biological effect (in US as well as OUS patients).

7.7.3 Pooled Post Hoc Analysis – US vs OUS

To increase the sample size of the adjusted analysis, the analysis was repeated using the pooled CCI population. The pooled results (treatment effect in all endpoints in the pooled US and OUS populations) are detailed in Table 60:

Pooled CCI Covariate Adjusted Efficacy Analysis for US (N=46) vs OUS (N=561)		
Endpoint	Region	OR [95% CI]
Sliding Dichotomy	OUS	1.59 [1.09,2.33]
	US	2.84 [0.72,11.10]
Dich. 0-2	OUS	1.44 [0.94,2.21]
	US	3.34 [0.65,17.32]
Dich. 0-3	OUS	1.50 [0.99,2.27]
	US	2.09 [0.45,9.71]

Pooled CCI Covariate Adjusted Efficacy Analysis for US (N=46) vs OUS (N=561)		
Endpoint	Region	OR [95% CI]
Endpoint	Region	Diff [95% CI]
SIS-16	OUS	6.04 [0.64,11.44]
	US	10.53 [-7.90,28.97]
Utility weighted mRS	OUS	3.80 [-1.15,8.76]
	US	6.34 [-10.44, 23.12]

Table 60 – Adjusted Pooled Efficacy Analysis US/OUS (ImpACT-24B and 24A) – CIR rev. 3 Table 41

The same consistent trend that was observed in ImpACT-24B is also evident in the pooled analysis – the results in the US CCI population are consistent with the results of the OUS CCI population and the point estimates of the effects are higher in the US.

7.7.4 The Effect in US Patients – Summary

FDA noted that the effect in some of the endpoints in the US CCI population is lower than in the rest of the world and requested additional analyses to support the applicability of the study results to US patients.

The analysis of US data included:

a. Covariate-adjusted analysis of the pivotal study data (ImpACT-24B).
b. Additional analyses of the effect in the US based on ImpACT-24B data.
c. Pooled analysis

The small sample size in the US led to sensitivity of the efficacy results to imbalance in baseline covariates between the treated and control groups.

The adjusted analysis that accounts for these imbalances shows consistent benefit in US CCI patients that is comparable and even numerically higher than in OUS CCI patients. This trend repeats itself in all the endpoints.

The additional analyses all support the same conclusion, that the treatment benefit is applicable to the US population, and the US-only results are similar to the results of the OUS patients.

It should also be noted that patients in all study sites received Standard of Care in accordance with 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 antiplatelets, management of secondary stroke, dyslipidemia, hypertension, diabetes and counseling regarding smoking cessation.

8 Clinical Perspective

If approved, SPG stimulation will fulfill the unmet need, by expanding the treatment window for patients with confirmed cortical involvement (CCI) who do not meet the strict criteria for late EVT, as illustrated in Figure 120. It is estimated that ~10% of US ischemic stroke patients will be eligible for SPG stimulation.

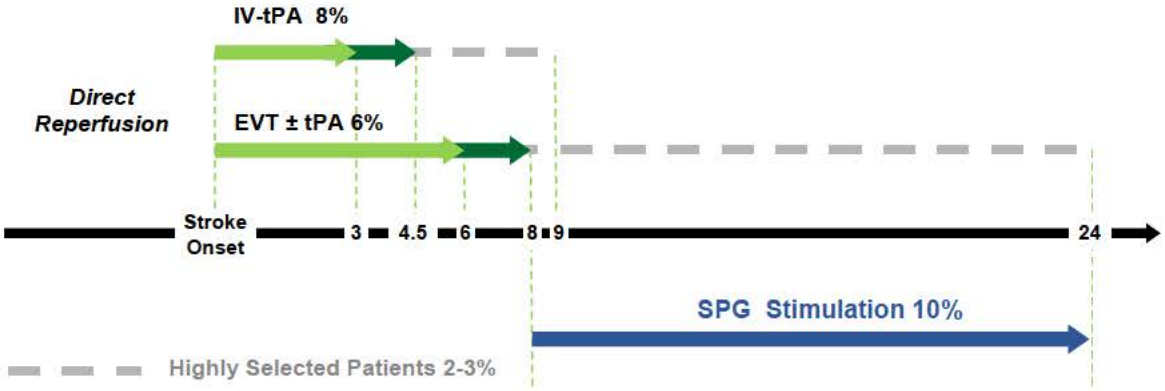

Figure 120 – The extended therapeutic window

The final implantation system does not require complex infrastructure. It may be placed either in the neurology department or near the CT (in the emergency department or in radiology), allowing the implantation to be performed by qualified medical doctor (MD) in large comprehensive stroke centers and front-line hospitals.

As with any novel technology, the transition from the clinical trial environment to the real-world clinical practice has to be managed carefully. In this section we discuss the main challenges identified in the clinical trials and the measures taken to support the transition to widespread clinical use.

Implantation

The implantation procedure evolved during the clinical trials. Study learnings were implemented in the final design and simplified the procedure. Initially, the procedure time often exceeded one hour due to difficulties in finding the canal opening and the need to dilate the canal for the fragile implant.

The modified implant no longer requires canal preparation, and the final navigation system guides the implanter directly to the canal, resulting in a short bedside procedure not much different than a simple dental procedure.

Therefore, implantation safety data from ImpACT-24B represent a worst-case scenario, and the improvements in the device which were evaluated in ImpACT-24M reduce the level of uncertainty regarding implantation safety in widespread use.

Implantation shall be done by trained physicians that underwent hands-on training that includes simulated implantation (see details in Appendix E – Training Program Overview). Following training, the first 5 procedures of every implanter shall be guided remotely by company's specialists (Real Time Support team), and 3 additional procedures shall be reviewed remotely to assess the implanter's performance and ensure qualification.

The post market approval study (see overview in Appendix F – Plans for Post Approval Study) will collect and monitor procedure duration and accuracy data. This will enable close monitoring of the procedures in the field to ensure they do not deviate from the observed performance in the ImpACT-24M trial.

Stimulation Level (CTL)

Another challenge in the randomized clinical trials was setting the correct stimulation level for treatment. In ImpACT-24B, stimulation level was set too high in 50% of patients, exceeding the non-noxious physiologic range where treatment benefit was highest.

The final system limits the stimulation level so it cannot exceed this range. As a result, the efficacy in clinical practice is expected to be higher than in the ImpACT-24B trial, as estimated by efficacy analysis in the final device range (Figure 119 in section 7.6.1). Health care professionals will be trained to use physiologic signs of SPG stimulation to set the stimulation level for each patient. This approach (which could not be used in randomized settings) was validated in the ImpACT-24M usability study.

The post market approval registry will collect stimulation level data and the identification of physiological markers (which are recorded in the device log file).

CCI Patients Identification

CCI patients are identified based on a neurological examination (NIHSS) and ASPECTS scoring on a non-contrast CT/MR. Both NIHSS and non-contrast CT/MR are performed routinely as part of the initial evaluation of stroke patients in clinical practice.

The sensitivity of NCCT to detect ischemic changes improves with time from stroke onset. The 8- to 24-hour time window of SPG stimulation allows imaging to be performed when ischemic changes are more evident and ASPECTS scoring becomes more accurate. Additionally, in some hospital networks image interpretation is done via teleradiology by experienced neuroradiologists that are available 24/7 and further reduce the variability of ASPECTS scoring.

The DAWN late thrombectomy trial showed that the NIHSS ≥10 criterion increases the probability that the patient has a large territorial stroke that involve the cortex, and also increases the likelihood that salvageable tissue still exists.

Together, the two criteria reduce the likelihood that non-cortical strokes will be mistakenly treated with SPG stimulation.

For more information on patient selection in the clinical studies and how it compares with the device labeling see Appendix I – Patient Selection.

9 Risk Benefit Summary

CDRH is charged with determining whether the data demonstrate a reasonable assurance of safety and effectiveness. A plain language version of the regulatory definitions of those terms is that when used properly, the probable benefits to health outweigh the probable risks, there is an absence of unreasonable risk, and that there are clinically significant results in a significant portion of the target population.

A careful analysis of benefit and risk information is critical to the understanding of any dataset, and this one is no exception. As described in the benefit-risk worksheet in Appendix J – Benefit-Risk Assessment– the same format as is described in the guidance, the first question is whether there is any evidence of clinical benefit, without consideration for the uncertainty that may be associated with it. Without benefit, we recognize that there can be no favorable outcome as any risk outweighs a lack of benefit. However, our data do demonstrate a clinically meaningful benefit.

Having established benefit, we can discuss whether the uncertainty associated with those benefits is reasonable or not. Like all trials, there is some uncertainty associated with our evidence. However, as described in this document, it is not so high as to call into question whether the results can be believed.

Having determined that there is a clinically meaningful benefit with a reasonable amount of uncertainty, we can then establish that the probable benefits to health outweigh the probable risks, which for this intervention are relatively low.

When evaluating the safety, the pooled dataset of the two similar randomized studies increases the sensitivity to detect small differences in SAE rates (see poolability method and rationale in section 7.4.1). SAE and mortality rates were nominally higher in the treated group in ImpACT-24B and lower in ImpACT-24A and the pooled safety data show that SPG stimulation does not increase the risks of mortality, serious adverse events, and common stroke complications.

A lower rate of symptomatic intracranial hemorrhages (sICH) in the treated arm was observed in both studies. Patients in the sham-control arm had 5 times higher odds of experiencing an adverse symptomatic intracranial hemorrhage compared to treated patients.

The implantation procedure evolved during the clinical trials and study learnings were implemented in the implant design and navigation system to simplify the procedure.

Although the implantation safety data from ImpACT-24A and ImpACT-24B reflect the longer procedure, no significant risks were identified (including no increase in aspiration SAEs compared to sham control).

The final implantation technique was evaluated in 50 patients in ImpACT-24M, with no implantation SAEs and no failed implantations. It was performed under local anesthesia, and the median skin-to-skin time was 4 minutes.

The uncertainty of the benefit is assessed based on the cumulative evidence, including pre-clinical and the two RCT studies:

- In both randomized studies, treatment benefit did not depend on baseline core size or on the time from stroke onset, consistent with the device MOA and preclinical results
- In both studies, the rate of sICH was lower in the SPG stimulation group compared to control, consistent with the BBB protection effect in preclinical studies
- No heterogeneity of treatment effect between the two studies (p=0.88)

In the analysis of pooled individual participant-level data, combining data from the ImpACT-24A and the ImpACT-24B trials, the proportion of patients who improved beyond expectations at 90 days was 49.7% versus 38.3% (1.61, 1.16–2.23) in the CCI population. The ImpACT-24B pivotal trial was a prospective, multi-center, multinational, randomized, sham control, double-blind, adjunctive to standard of care, parallel arm study, and is, to our knowledge, the largest device trial in acute ischemic stroke patients.

The absolute risk reduction (ARR) of 9.8% in the primary CCI population is clinically meaningful, higher than the 1.5% MCID in dichotomized endpoints in stroke [12], the 3% MCID for continuous utility-weighted endpoints [13] and the 7% ARR that was pre-specified in the protocol as the minimum desirable effect.

The statistical uncertainty of this clinically meaningful treatment benefit is reduced by:

- Consistent benefit in all secondary endpoints (lower disability and improved quality of life)
- The benefit persists in the long term follow up at 180 and 360 days
- Strong dose response relationship in ImpACT-24B and same optimal dose range in ImpACT-24M (the final device dose range)
- Robust treatment effect in the pivotal study in patients stimulated within the final device dose range

Considering the totality of evidence above, the relative consistency of benefit across all endpoints and both studies, as well as the dose response and clear mechanism of action, help mitigate the extent of uncertainty regarding the clinically meaningful benefits and

risks, consistent with the FDA guidance on Consideration of Uncertainty in Making Benefit-Risk Determinations.

The final device incorporates study learnings, improving safety and effectiveness even further.

In conclusion, although the primary endpoint in the pivotal trial missed the formal multiplicity-adjusted p-value threshold (0.0258 vs 0.025), the totality of evidence reduces the uncertainty and leads to conclude that the probable clinically meaningful benefits of reduced post-stroke disability and improved quality of life in the target CCI population outweigh the low risks of the procedure and the treatment.

This innovative first of a kind technology addresses the unmet need for a treatment that is simple to administer and is safe and effective in an 8- to 24-hour window in patients who are ineligible for or have no access to alternative therapies.

Appendix A – Pivotal Study Inclusion/Exclusion Criteria

The following tables lists the study inclusion and exclusion criteria.

Inclusion Criteria

#	Criteria
1	Age: ≥ 40 years and ≤ 80 years for male and 85 for female subjects
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	Imaging findings demonstrating signs of ischemia in the anterior circulation, consistent with the clinical diagnosis
4	Baseline NIHSS ≥ 7 and ≤ 18 within 2 hours prior to implantation
5	Ability to initiate treatment within 8-24 hours from stroke onset
6	Signed informed consent from patient him/herself or legally authorized representative if applicable

Table 61 – Inclusion Criteria

Exclusion Criteria

#	Criteria
1	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).
2	Massive stroke, defined as acute parenchymal lesion with effacement of cerebral sulci in over 2/3 of the MCA territory.
3	Acute stroke due to lacunar infarct as defined by a clinical syndrome (pure motor hemiparesis, ataxic hemiparesis, sensorimotor stroke, dysarthria-clumsy hand syndrome), unless brain imaging demonstrates a relevant lesion > 1.5 cm in size.
4	Clinical signs and symptoms or evidence for a relevant lesion by neuro-imaging 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.
5	Minor stroke with non-disabling deficit or rapidly improving neurological symptoms.
6	Clinical signs and symptoms or imaging evidence of bilateral stroke.
7	Treated with IV-tPA, IA-tPA or neurothrombectomy devices for the current stroke.

#	Criteria
8	NIHSS level of consciousness score ≥ 2.
9	Previous stroke in the last 6 months or previous stroke with existing sequelae or with mRS > 0 for any reason.
10	Pre-existing disability; Pre-existing Modified Rankin Score >1, even if not Stroke-related.
11	Patients with bleeding propensity and/or one of the following: INR > 1.8, prolonged activated partial thromboplastin time (aPTT) ≥ 45 sec., platelets count < 75×109/L.
12	Known cerebral arteriovenous malformation, cerebral aneurysm.
13	Seizure at onset
14	Blood glucose concentration < 60 mg/dL.
15	Clinical suspicion of septic embolus.
16	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.
17	Serious systemic infection.
18	Women known to be pregnant or having a positive or indeterminate pregnancy test.
19	Patients with other implanted neural stimulator/ electronic devices (pacemakers).
20	History of SPG ablation ipsilateral to the stroke side.
21	Any condition in the oral cavity that prevents implantation of the INS, such as patient is intubated, orthodontics or non-hygienic condition.
22	Life expectancy < 1 year from causes other than stroke.
23	Participating in any other therapeutic investigational trial within the last 30 days.
24	Known sensitivity to any medications to be used during study.
25	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.
26	Subjects who, in the judgment of the investigator, are likely to be non- compliant or uncooperative during the study

Table 62 – Exclusion Criteria

Appendix B – Safety of Increasing Blood Flow in Stroke Patients

B1 - The Risk of Hemorrhage

Unlike other reperfusion therapies such as Endovascular Thrombectomy (EVT) or IV-tPA, SPG stimulation does not open the occluded artery but rather increases flow through the collateral circulation (without increasing blood pressure), as illustrated in Figure 121.

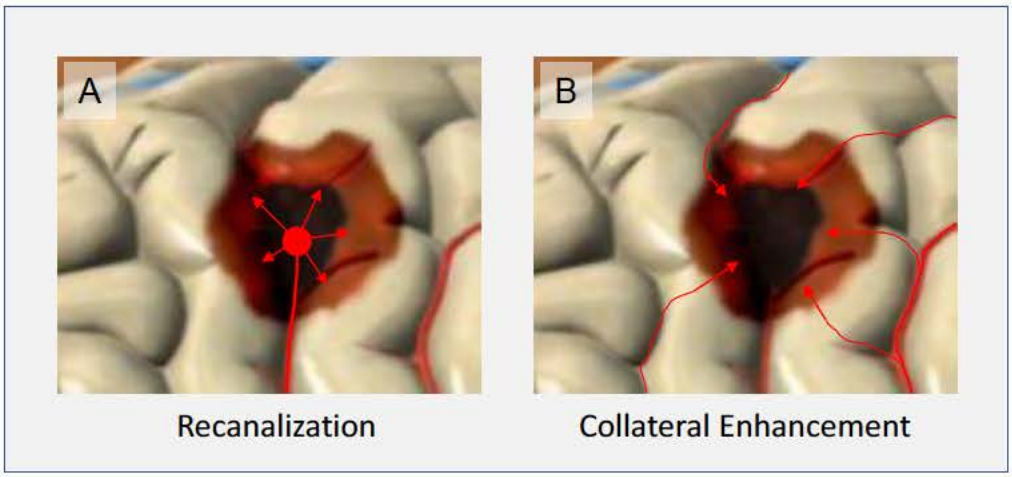

Figure 121 – Mechanism of Action Comparison

Still, the concern that increasing flow might increase the risk of symptomatic intracranial hemorrhages (sICH) was one of the early concerns that was assessed in pre-clinical settings. The results showed not only that SPG stimulation does not increase the risk of sICH, but also that it has a stabilizing effect on the blood-brain barrier (BBB), as shown in the following figure:

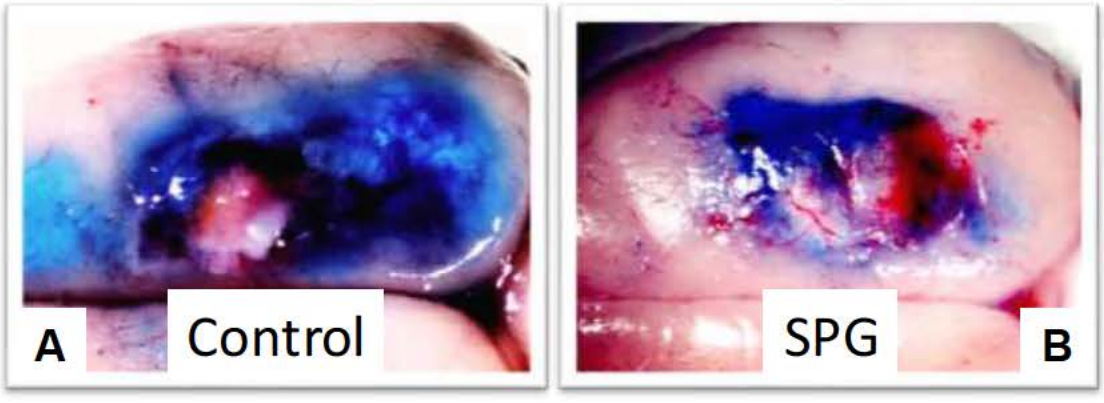

Figure 122 – BBB Stabilization

The mechanism by which SPG stimulation increases flow, preserves the BBB and improves outcome has been studied pre-clinically and is summarized in section 4.2 (SPG Stimulation Mechanisms of Action).

Based on the pre-clinical results, the BBB stabilization effect was expected to reduce the rate of sICH in the clinical trials.

Indeed, the same phenomena of lower sICH rate in the treated arm was observed in the two RCT clinical trials (ImpACT-24B and ImpACT-24A) and the results reached statistical significance in the pooled analysis:

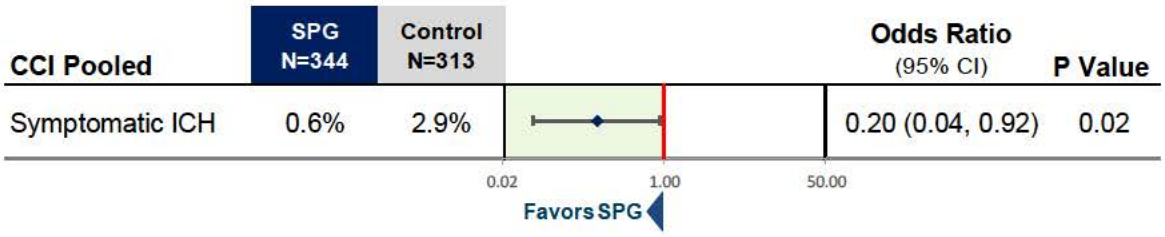

Figure 123 – sICH (Pooled) - SPG Stim. vs Sham Control

B2 - Potential Risks of Increased Blood Flow – Targeted Analysis

Although good collateral flow is associated with good outcome in stroke [3, 10] and the rate of sICH was lower in the SPG stimulation group compared to the sham control group, FDA raised a concern regarding the safety of increasing collateral blood flow, and requested that we assess how the dose response and increased CBF affect safety.

Direct measurements of increased blood flow in a feasibility study (before the IDE studies), showed increased in blood flow during stimulation at the comfortable tolerance level (CTL).

The ImpACT-24M usability study also showed significant increase in blood flow at the CTL. The CTL was identified in this study, as in the final device, using non-noxious physiologic signs of SPG activation (lacrimation and tingling sensation), without reaching a level of discomfort or pain (see details of how stimulation level was set in the different studies in section 7.5.1.3).

Flow was measured directly in the common carotid artery (using Doppler), and verification that blood flow is increased in the brain was performed by correlating the increased blood flow and with improvement in neurologic deficit during stimulation. The study showed a direct relationship between stimulation (at the level that was set based on physiological signs) and flow, and most importantly, it showed a clear link between increased flow and functional improvement (see section 7.5.3.4 – ImpACT-24M Efficacy Results).

No side effects that could be related to increased flow were reported in any of the patients in ImpACT-24M (including intracranial hemorrhage, reperfusion injury, and hypertension).

The stimulation range in which most patients had lacrimation and tingling sensation overlaps the range which was identified in the most effective in the dose response analysis in ImpACT-24B. This range was set as the final device stimulation range.

The safety analysis below aims to identify the patients in ImpACT-24B with the highest likelihood of flow increase and to look for the potential adverse effects of increased flow in this targeted group, compared to the Control group.

In most patients in ImpACT-24M (46/50), the physiological signs of SPG activation were identified at medium stimulation levels (the "Non-Noxious Physiologic Range"), which is the dose range of the final device.

The targeted analysis compared the patients in ImpACT-24B whose stimulation level was in the final device range with the control group (who all received zero stimulation), the rationale being that patients in this group have the highest likelihood of increased blood flow, so any possible adverse effects of increased blood flow will be most evident in this group.

The analysis included the following potential adverse effects of increased blood flow:

1. Core infarct growth (the change in ASPECTS score from baseline to day 5)
2. sICH
3. Hypertension, Hypertensive Crisis, Hypertensive Heart Disease and Pulmonary Hypertension adverse events (there were no serious adverse events of these types)
4. Neurological deterioration (a typical symptom of reperfusion injury)

The results:

	SPG Stim.	Sham	OR (95% CI)	p
sICH	0.9%	2.9%	0.29 (0.04 - 2.34)	0.30
Hypertension AE	3.4%	4.7%	0.71 (0.23-2.24)	0.56
Neuro. Deterioration	7.7%	9.4%	0.8 (0.36 - 1.77)	0.58

	SPG Stim.	Sham	Diff.	p
Core growth (lower is better)	1.0	1.5	-0.5 (-1.0--0.0)	0.04

Table 63 – Potential Side Effects in the Optimal Stimulation Range

The results show no increase in any of the potential risks due to the stimulation, even in the range were flow increase to ischemic tissue is likely to be the highest. Some of the risks are even reduced due to the benefit of the treatment.

In conclusion, CBF increase by SPG stimulation does not increase the risks of sICH, hypertension or reperfusion injury and even reduces these risks. These results are consistent with the mechanism of action and the preclinical results and may be explained by the fact that the stimulation does not open the occluded artery but rather increases flow through collateral vessels.

B3 - The Risk of a "Steal" Effect

Another risk that was considered was that increasing blood flow to healthy tissue might reduce blood flow to ischemic tissue (a "Steal" effect).

The following figure shows the increased blood flow in a pre-clinical stroke model.

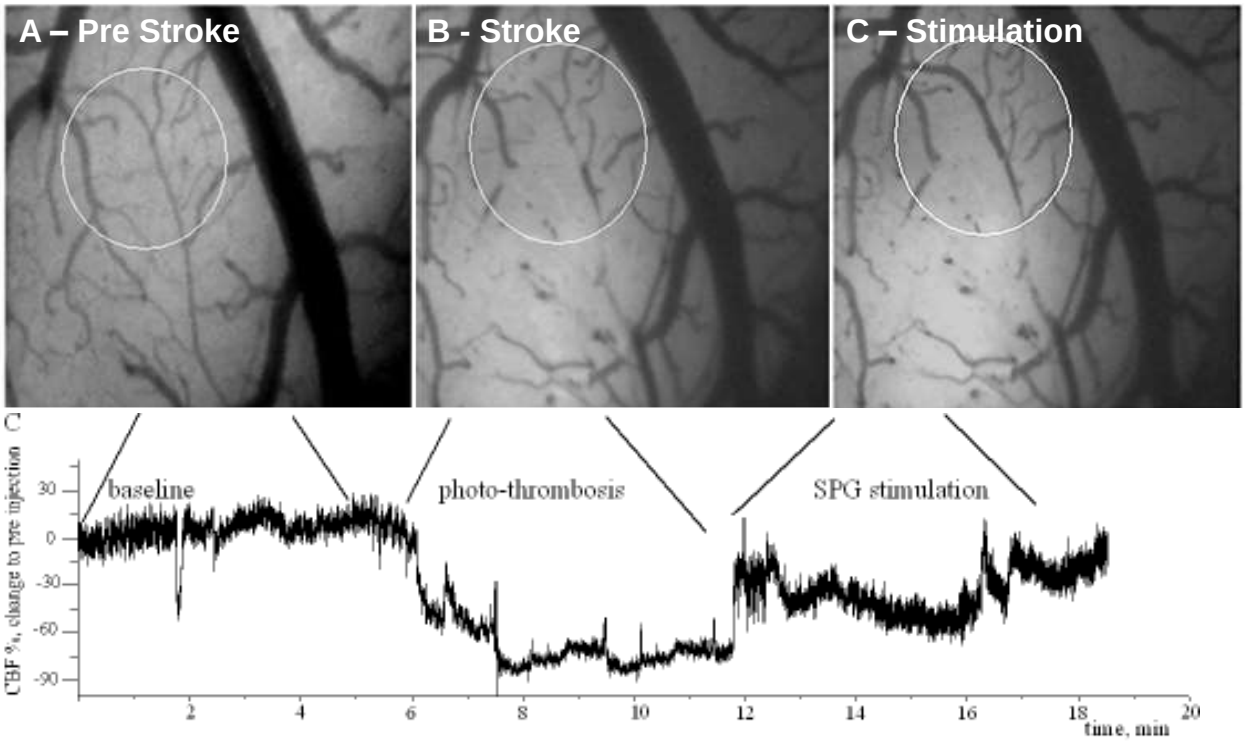

Figure 124 – Collateral Flow Augmentation

Figure 124 shows an increase (not reduction) in collateral flow to the ischemic area. The bottom part of Figure 124 shows an absolute increase in CBF to the hemisphere during stimulation, confirming that collateral flow augmentation by SPG stimulation is not causing a reduction of blood flow to the ischemic regions (no steal effect). This is consistent with the results of ImpACT-24M, which showed increased blood flow and improvement in motor function at the same time.

B4 - The Risks of Increasing Flow to Infarcted Tissue

Considering that all CCI patients had established core in baseline non-contrast CT, the median time to the first stimulation session was 19 hours, and the treatment continued for 5 days (4 hours per day), practically all patients in the trial had at least some of the brain lesion evolve from ischemia to infarction before or during treatment.

It is important to note that not only that collateral flow augmentation in patients with established infarct does not increase the risk of hemorrhage, pre-clinical data showed that SPG stimulation reduced the levels of lactate inside the core 18 hours after stroke, and improved metabolism 8 days after stroke compared to control animals (see details in section 4.2 - SPG Stimulation Mechanisms of Action). This reduction in the levels of toxicity and improved metabolism may explain some of the benefit of late SPG stimulation in patients with established core, such as CCI patients, and may explain the lower hemorrhage rate in the treated arm of the clinical studies.

In conclusion, clinical as well as pre-clinical data support that there is no risk of reduction of flow to the ischemic regions due to SPG stimulation and no risk of performing stimulation as the brain lesion evolves from ischemia to infarction.

Appendix C – Implantation Risks – Detailed Analysis

C1 - Contributing factors to complications and their mitigations

The following factors might contribute to complications or device misplacement:

1. 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.
   With the emphasis on performing suction in the training and documentation, no cases of pneumonia were reported using the final implant, and the total rate of pneumonia SAE events in ImpACT-24B was lower in the treated arm than in the control arm (note that pneumonia is a common side effect in the first few days after stroke, and none of the pneumonia SAE cases was classified by the investigators as related to the implantation).
   As the procedure became shorter (<5 minutes with the final device), the risk of aspiration was reduced even further and suction is only required for a short period of time.

2. Airway obstruction – Stroke is known to cause swallowing problems in some CCI patients, and patients with swallowing problems are at risk of aspiration. The implant injection procedure, however, does not increase the risk of airway obstruction (including obstructive sleep apnea syndrome) for the following reasons:
   a. As shown in Figure 57 above, the canal opening is anterior to the hard-soft palate border, and the puncture site is anterior to the canal opening.
   b. The procedure does not involve any manipulation of the posterior oropharynx, soft palate or tonsillar pillars whose manipulation might exacerbate patient's underlying obstructive sleep apnea syndrome.
   c. The implanter always has direct visualization of the patient's posterior oropharynx and could easily visualize any potential obstruction in the airway in the unlikely event that would occur.
   d. The procedure is performed under local anesthesia and does not require sedation.
   e. The procedure skin-to-skin time is typically less than 5 minutes (and never exceeds 15 minutes)
   f. Suction is performed throughout the procedure by a dedicated person, and patency of the airway is always maintained
   g. Bleeding is minimal (1-3 mm puncture) and can easily be stopped by applying local pressure.
   h. The patient is undergoing continuous monitoring during the procedure, including heart, oxygen levels and blood pressure.

Although breathing difficulties are not a common syndrome of anterior stroke (cardiorespiratory functions are controlled by brain stem reflex mechanisms), we have seen implantation candidates in the trial with breathing difficulties. Such patients had an airway cannula, and their breathing was not affected by the procedure.

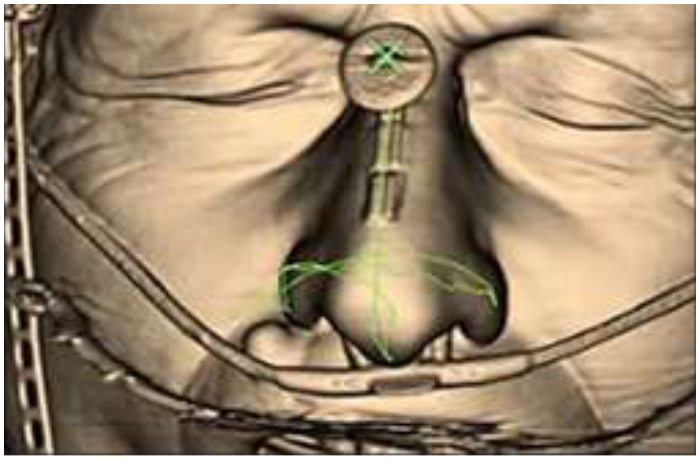

Figure 125 – Airway Canula Placed before Implantation

In summary, the implantation procedure does not increase the risk of airway obstruction. Nevertheless, the user documentation instructs the implanter how to identify patients at risk of airway obstruction and instructions how to manage such patients during implantation.

3. Use errors

   Several use errors occurred during the trial that could complicate the procedure. Most of these use errors were addressed by the final implant and navigation system, but a few things still depend on the implanter:

   a. 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 implant might be misplaced, and the patient will not be treated.

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

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

The conclusion of the risk analysis is that there is no unacceptable risk in the implantation procedure, including in case of device fault or use error.

C2 - Risks assessment – non-alert/unconscious patients

Some level of patient cooperation is required during the procedure preparations (opening the mouth for the dental impression application). Therefore, the device labeling instructs the implanter to verify that the patient is cooperative ahead of time. If the patient would not open the mouth, implantation preparations cannot start and no harm is done to the patient (preparing the dental impression is the first step, before the CT).

C3 - Risks Associated with SPG Injury

The risk of damage to the SPG was assessed over 15 years ago in cadavers, before the first implantations in human patients. After implanting the cadavers, a sagittal cut was made and the SPG was examined to assess the impact of the electrodes on the tissue. The SPG is a soft, flexible tissue (like "Jelly") and the cadavers study showed that when the smooth, 1.3mm dome-shaped electrode reaches the SPG, the SPG is "shifted" within the much larger fossa volume. The implant tip contact with the ganglion appears atraumatic and has not been associated with any ganglion damage.

Electrical damage to the SPG has also been ruled out. Between 2000-2004, before BrainsGate decided to focus on treatment of acute ischemic stroke, various stimulation protocols were studied, using a broad range of stimulation parameters (including much stronger and weaker stimulation compared to the stroke protocol). No SPG damage occurred in this broad stimulation range.

The conclusion of all the pre-clinical tests and cadaver studies was that the INS500 implantation and the stimulation of the SPG are not associated with SPG damage.

C4 - Risks Associated with Implant Misplacement

Although there were no misplacements using the final system, one cannot rule out this possibility and this section analyzes all misplacement risks.

The following few paragraphs describe the implantation procedure in general and implant misplacements in particular and analyze the effects of implant misplacement (including assessment of the risks of corneal anesthesia and anesthesia dolorosa).

Implantation background

The implantation procedure is used to insert the INS into the greater palatine canal by means of a small puncture in the upper mucosa.

The puncture area is clearly visible to the implanter and is well defined (1cm from the last molar). The maximal reasonable error by the implanter, even if extreme GuideView navigation errors occur, is within the area marked with a dashed yellow line in Figure 126 below. This area is visible in the patient's mouth and readily identifiable without the assistance of the navigation system.

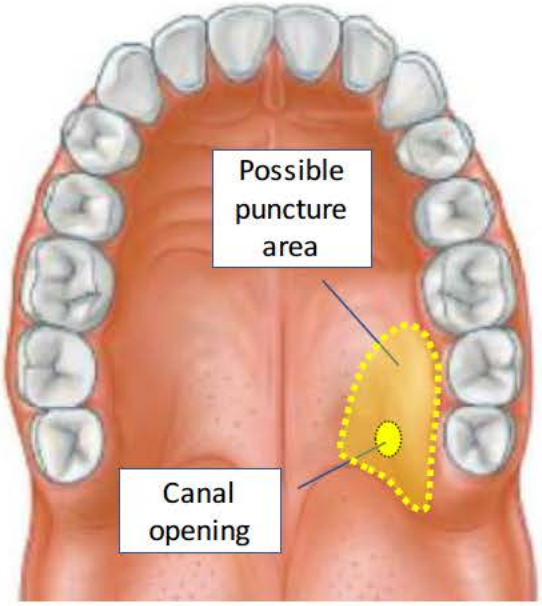

Figure 126 – Maximal Puncture Area Error

In case of misplacement, navigation errors may lead the implantation tools and the implant to one of the following anatomies:

a. Nasal Cavity
b. Maxillary sinus
c. Nasopharynx

It is important to note that even when the device was implanted without a navigation system (in ImpACT-24A), all misplacements were in the 3 anatomies listed above.

Figure 127 illustrates a closeup view of the puncture area in a patient's mouth. The yellow circle marks the canal opening and the three highlighted regions mark the puncture areas that might lead to misplacement in the anatomies listed above:

- Region A might lead to the nasal cavity
- Region B might lead to the maxillary sinus
- Region C might lead to the nasopharynx

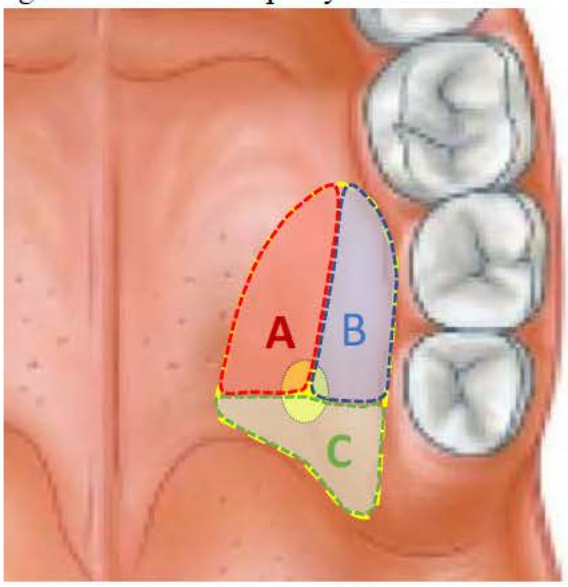

Figure 127 – Potential Misplacement Areas

The same 3 possible "misplacement anatomies" are shown from above in the following illustration:

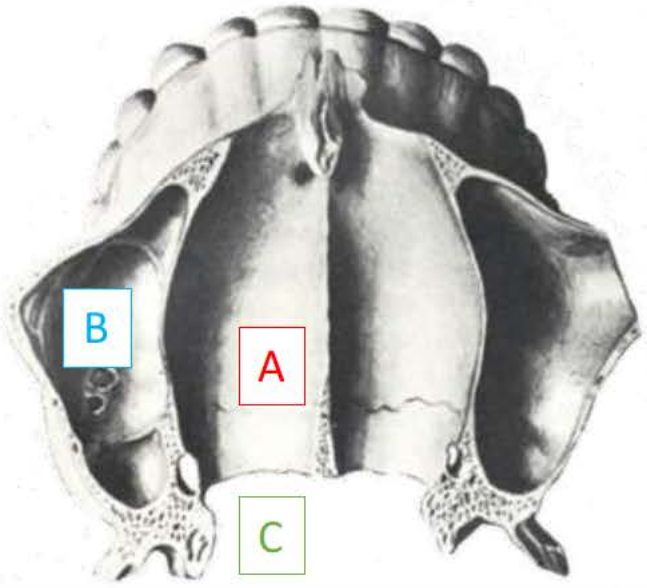

Figure 128 – Potential Misplacement Areas – View from Above

Two tools are used during implantation:

1. Puncture tool – used for the initial puncture through the mucosa and for clearing the proximal 8mm of the canal
2. Introducer – used to navigate the implant to the canal opening and to inject the implant into the canal

The Puncture tool's wide "shoulders" do not allow penetration deeper than 8mm from the hard palate. The Introducer is capable of injecting the implant to a maximal distance of only 30.5mm from the hard palate, and in any case, the flexible structure of the implant and the 400-gram force limitation mechanism prevent the implant from penetrating bony structures.

Review of the anatomies listed in A through C above shows that there are no nerves or other sensitive organs in these areas that might be injured during implantation/stimulation and pose a risk to the patient.

In summary, implant misplacement might lead the implant and implantation tools to the nasopharynx, the maxillary sinus or the nasal cavity, none of which contains nerve bundles or major arteries. Accordingly, there is no navigation system failure mode or tool failure that might lead to any severe adverse event.

C5 - Implantation Risks - Summary

The implantation technique evolved over the years, and the implant was redesigned to mitigate risks that could lead to adverse events. This section summarizes the potential implantation risks of the commercial product.

50 procedures were performed in ImpACT-24M using the market version of the implant and navigation software. Additional 197 procedures were performed in ImpACT-24B using the final implant and a previous version of the navigation system.

The final implantation is a bedside procedure, typically performed by neurologists, does not require special infrastructure, and is suitable to all hospitals, including small hospitals that currently do not have endovascular thrombectomy capability and refer stroke patients to larger centers (if such centers exist nearby).

The following table 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 64 – Implantation Complications Rate

The one implantation-related SAE using the modified implant and old implantation system was a moderate-severity Complication of Device Removal which was recovered without sequela within one day. An oral surgeon successfully removed the implant via the maxillary sinus.

The above Table 64 shows that procedure duration with the final system was significantly reduced to 4 minutes skin-to-skin time (IQR 3 – 7 minutes) with zero misplacements, compared to 20-40 minutes in the pivotal ImpACT-24B study. It is important to note that the rate of Pneumonia was not increased even by the longer procedure (in ImpACT-24B), and the risk of aspiration in the final 5-minute procedure is even lower.

Procedure duration is not the only factor that contributed to the reduced complications rate. The final implant has a rigid-flexible neck that allows it to pass through narrow and curved canals with no resistance[i] and without having to dilate the canal using rigid trocars.[ii]

The only required preparation for the final device is an initial puncture of the mucosa and clearing the first 8mm of the canal, which are accessible in all patients, using the Puncture Tool. As a result, no difficulty in injecting the implant was reported in any of the 247 procedures using this implant.

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.

[i] The force required to slide the implant into the canal is less than 400gr.

[ii] The use of rigid trocars was one of the main reasons for misplacements, prolonged procedures, and complications with the old implant.

The result of these improvements is **zero misplacements** and **zero adverse events** related to the implantation/removal in the 50 procedures using the final implant and final navigation system.

Although there were no complications in the 50 procedures using the final system, we cannot rule out the possibility of rare cases of misplacement and therefore we analyzed the potential consequences of misplacements to patient safety (see Appendix C4 - Risks Associated with Implant Misplacement). The conclusion is that there is no unacceptable risk related to the implantation or implant removal even in case of misplacement.

Appendix D – SPG Stimulation Number Needed to Treat

The 9.7% absolute increase in favorable 90-day disability outcome in the primary CCI population in the pivotal study is equivalent to number-needed-to-treat (NNT) of 10. Similar probabilities of experiencing benefit were observed in all efficacy endpoints (Figure 13) with NNT values ranging between 9-13 in the other dichotomized efficacy outcomes.

An alternative way to delineate the probability of experiencing better global disability outcome with SPG stimulation is using the distribution of 3-month mRS disability levels in the SPG-stimulated and sham-stimulated treatment groups, without dichotomization.

The advantage of this approach is that it shows the attained disability outcomes (rather than just those that were favorable outcomes based on patient's baseline prognostic features).

Figure 129 shows the distribution of 3-month mRS levels in the pivotal ImpACT-24B in CCI patients (the intended population of the device):

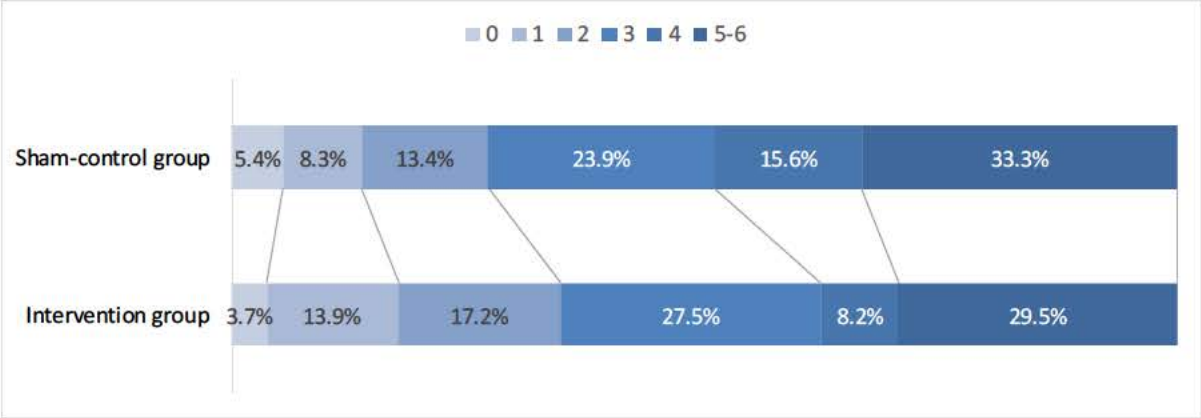

Figure 129 – mRS Distribution in the CCI population (ImpACT-24B, N=520)

Applying the automated, algorithmic joint outcome table NNT derivation technique to these distributions, the number needed to treat for 1 patient to have a better outcome with SPG- than sham-stimulation by 1 or more levels on the 3-month mRS is 5.8.

NNT can also be calculated using the assumption that the benefit of SPG stimulation when started 8-24 hours from stroke onset is of one mRS level, a clinically meaningful transitions (see section 3.1.3).

The following Table 65 summarizes all the transitions in the intervention group compared to the sham-control group:

mRS Transition	% of patients in ImpACT-24B[i]
0 ← 1	2%
1 ← 2	6%
2 ← 3	8%
3 ← 4	11%
4 ← 5,6	4%

Table 65 – Probability of Experiencing Benefit

Based on this analysis, 28% of the patients experienced a one-level improvement in disability (NNT 3.5) and 2% experienced a one-level increase from mRS 0 (no symptoms) to mRS 1 (minor symptoms with no significant disability), a number-needed-to-harm of 50.

[i] Negative value indicates transition to the higher disability level

Appendix E – Training Program Overview

The training program is comprised of two modules:

1. Implantation training
2. Treatment delivery training

Implantation Training

During ImpACT-24A and ImpACT-24B, BrainsGate developed its implantation training methodology in parallel to the evolution of the implantation system. Implanters' feedback was that training was beneficial and well represented their experience in the actual procedures, therefore we propose to implement the same training methods in the market.

The medical facility will identify the implantation team (implanters and assistants) that shall meet the following criteria:

1. Implanters must be medical doctors (MD)
2. Either the implanter or assistant must be a stroke specialist
3. Both team members must have high availability to perform implantations

Training is required for both team members.

Implanter Training will include:

(a) A 2-hour theory session

The theory session will cover the canal and surrounding anatomy, review of implantation CTs, familiarity with the navigation system and implantation safety.

(b) A 5-hour hands-on training using a head model with replaceable palates and canals

In the hands-on training, the implanters will practice the basic implantation (bite preparation, registration quality control and the use of the puncture tool and introducer), as well as how to avoid common mistakes and how to detect and overcome registration errors.

(c) Remote guidance

The first 5 procedures after the frontal training will be performed under remote guidance by a BrainsGate implantation specialist.

Implanter Qualification:

Implanter shall perform procedures remotely monitored by BrainsGate's implantation specialists. Successful completion of 3 monitored procedures without guidance shall qualify the implanter to perform implantations without remote supervision.

Assistant Training:

The assistant shall participate in the frontal session and focus on patient monitoring and suction.

Treatment Delivery Training

An online session for a healthcare professional (typically in the neurology or emergency department), focusing on:

- Overview of the treatment session phases
- Identifying the correct stimulation level (CTL)
- Correct transmitter positioning
- Additional topics (indication for use, precautions and warnings, familiarity with the Treatment system and its use)

Passing an online test is a condition for treatment delivery qualification.

Appendix F – Plans for Post Approval Study

BrainsGate intends to conduct a post market study to assess the system's performance in widespread use.

Post market data will be collected from multiple sources:

1) Automatic data collection

   The ISS500 system automatically collects data on each procedure, including:

   a. GuideView registration accuracy data (expected accuracy: <2mm)

   b. Implantation simplicity, measured as skin-to-skin time (expected: <5 min.)

   c. Stimulation level – the treatment system automatically collects information about the physiologic markers that were used to set the stimulation level, and the level at which they appeared.

2) Registry Data collection

   Sites participating in the registry will be required to report to BrainsGate data on each procedure they perform (up to total of 1000 procedures). These include:

   a. Failed implantation cases

      The goal is to investigate cases of failed implantation and to monitor if implantation performance is related to the type of medical facility and its volume of stroke patients (large-volume comprehensive stroke centers vs. small frontline hospitals).

   b. Clinical outcome

      Sites will report the following data:

      - Day-90 disability using the modified Rankin Score (mRS)
      - Baseline demographics (age, sex, stroke hemisphere side, time from stroke onset to treatment, and medical history of atrial fibrillation and diabetes)
      - Cases of patients treated outside the IFU criteria

c. Device related complications

To identify device-related complications under wide-spread use and rare events.

d. Safety related incidents, including:

- Cases of sICH at 5 days
- Cases of device related Serious Adverse Events (SAEs)
- Cases of headache
- Cases of hypokalemia (low potassium levels in the blood)

3) Customer reports

Analysis of customer reports (customer complaints or AE reports) will complement the information collected by the registry on device related complications and failed implantations.

Appendix G – ImpACT-24B (Pivotal Study) Additional Tables

G1 – Baseline Characteristics of non-mITT Patients

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, as detailed in the following tables:

	mITT	Non-mITT
N	1000	78
Median age, years (IQR)	70 (63 - 77)	73 (62 - 79)
Sex (female)	509 (50.9%)	37 (48.1%)

Figure 130 – mITT vs non-mITT - Patient Demographics

	mITT	Non-mITT
N	1000	78
Pre-stroke mRS = 0	930 (93.0%)	69 (92.0%)
Hypertension	857 (85.7%)	48 (61.5%)
Diabetes	256 (25.6%)	15 (19.2%)
Atrial Fibrillation	254 (25.4%)	24 (30.8%)
Smoking	94 (9.4%)	10 (12.8%)
Alcohol	31 (3.1%)	4 (5.1%)
Obesity	51 (5.1%)	5 (6.4%)
Systolic Blood Pressure, mean (SD)	148.4 (18.4)	153.3 (18.9)
Diastolic Blood Pressure, mean (SD)	82.8 (11.6)	85.5 (10.5)
Heart Rate, mean (SD)	78.0 (13.5)	79.3 (12.5)
INR, mean (SD)	1.1 (0.1)	1.1 (0.2)
aPTT, mean (SD)	28.8 (6.8)	27.9 (6.9)

Figure 131 – mITT vs non-mITT – Medical History

	mITT	Non-mITT
N	1000	78
Median NIHSS (IQR)	12 (9 - 14)	12 (9 - 15)
Stroke side (left brain)	532 (53.2%)	38 (49.4%)
Median ASPECTS (IQR)	7 (6 – 9)	7 (5 - 8)
Median time from last-known-well to 1st stim, hrs (IQR)	19.3 (15.8 - 22.2)	19.4 (16.7 - 21.5)
Median time from last-known-well to rand., hrs (IQR)	16.6 (13.5 - 20.0)	14.9 (12.2 - 19.0)

Figure 132 – mITT vs non-mITT – Baseline Stroke Characteristics

G2 – Mortality by SOC/PT

The table below details the SOC and PT classification of all fatal events.

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
Nervous system disorders	Stroke in evolution	6 (1.1%)	10 (1.9%)
	Cerebral infarction	9 (1.7%)	7 (1.3%)
	Hemorrhagic transformation stroke	5 (0.9%)	3 (0.6%)
	Brain stem stroke	3 (0.6%)	-
	Brain oedema	1 (0.2%)	-
Cardiac disorders	Cardiac arrest	6 (1.1%)	5 (1.0%)
	Cardio-respiratory arrest	4 (0.7%)	5 (1.0%)
	Cardiac failure	4 (0.7%)	-
	Acute myocardial infarction	2 (0.4%)	1 (0.2%)
	Cardiovascular insufficiency	2 (0.4%)	-
	Cardiac failure congestive	1 (0.2%)	-
	Myocardial infarction	1 (0.2%)	-
Respiratory, thoracic and mediastinal disorders	Respiratory failure	3 (0.6%)	4 (0.8%)
	Pneumonia	3 (0.6%)	3 (0.6%)
	Bronchopneumonia	2 (0.4%)	2 (0.4%)
	Pneumonia aspiration	1 (0.2%)	2 (0.4%)
	Aspiration	2 (0.4%)	-
	Pulmonary embolism	2 (0.4%)	1 (0.2%)
	Pulmonary oedema	-	1 (0.2%)
	Lung neoplasm malignant	-	1 (0.2%)
	Lower respiratory tract infection	-	1 (0.2%)
	Respiratory arrest	-	1 (0.2%)
	Influenza	1 (0.2%)	-
General disorders and administration site conditions	Death	9 (1.7%)	8 (1.5%)
Infections and infestations	Sepsis	4 (0.7%)	3 (0.6%)
	Septic shock	-	2 (0.4%)
	Staphylococcal sepsis	1 (0.2%)	-
Gastrointestinal disorders	Intestinal ischemia	2 (0.4%)	1 (0.2%)
	Peritonitis	1 (0.2%)	1 (0.2%)
	Upper gastrointestinal hemorrhage	-	1 (0.2%)
Injury, poisoning and procedural complications	Post procedural complication	-	1 (0.2%)
Renal and urinary disorders	Urosepsis	1 (0.2%)	-

Table 66 – Mortality by SOC/PT - ImpACT-24B Safety Analysis Set (all patients)

G3 – SAE by SOC/PT

The table below details the SOC and PT classification of all serious adverse events. 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 = 536)	Sham (N = 519)
Nervous system disorders	Cerebral infarction	25 (4.7%)	16 (3.1%); 17
	Stroke in evolution	19 (3.5%)	20 (3.9%)
	Hemorrhagic transformation stroke	8 (1.5%)	11 (2.1%)
	Brain oedema	5 (0.9%)	2 (0.4%)
	Transient ischemic attack	4 (0.7%)	2 (0.4%)
	Seizure	4 (0.7%); 5	2 (0.4%)
	Brain stem stroke	3 (0.6%)	-
	Hemorrhage intracranial	-	2 (0.4%)
	Epilepsy	1 (0.2%)	2 (0.4%)
	Cerebral artery occlusion	2 (0.4%)	-
	Vertebrobasilar insufficiency	-	1 (0.2%)
	Brain neoplasm	-	1 (0.2%)
	Subdural hematoma	-	1 (0.2%); 2
	Neurological decompensation	1 (0.2%)	1 (0.2%)
	Cerebellar infarction	-	1 (0.2%)
	Sedation	1 (0.2%)	-
	Neurological symptom	1 (0.2%)	-
	Presyncope	1 (0.2%)	-
Respiratory, thoracic and mediastinal disorders	Pneumonia	12 (2.2%); 14	12 (2.3%); 13
	Respiratory failure	5 (0.9%)	5 (1.0%)
	Pulmonary embolism	4 (0.7%)	4 (0.8%)
	Lower respiratory tract infection	-	3 (0.6%)
	Bronchopneumonia	2 (0.4%)	2 (0.4%)
	Lung neoplasm malignant	1 (0.2%)	2 (0.4%)
	Pneumonia aspiration	1 (0.2%)	2 (0.4%)
	Aspiration	2 (0.4%)	1 (0.2%)
	Pulmonary oedema	-	1 (0.2%)
	Bronchitis	1 (0.2%)	1 (0.2%)
	Respiratory arrest	-	1 (0.2%)
	Respiratory tract infection	-	1 (0.2%)
	Upper respiratory tract infection	1 (0.2%)	-
	Influenza	1 (0.2%)	-
Cardiac disorders	Cardiac arrest	7 (1.3%)	5 (1.0%)
	Cardio-respiratory arrest	4 (0.7%)	5 (1.0%)
	Atrial fibrillation	5 (0.9%)	-

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
	Cardiac failure	4 (0.7%)	2 (0.4%)
	Cardiac failure congestive	3 (0.6%)	1 (0.2%)
	Acute myocardial infarction	2 (0.4%)	2 (0.4%)
	Cardiovascular insufficiency	2 (0.4%)	-
	Nodal arrhythmia	-	1 (0.2%)
	Coronary artery disease	-	1 (0.2%)
	Atrioventricular block	-	1 (0.2%)
	Angina pectoris	1 (0.2%)	-
	Silent myocardial infarction	1 (0.2%)	-
	Myocardial infarction	1 (0.2%)	-
	Intracardiac thrombus	1 (0.2%)	-
Gastrointestinal disorders	Clostridium colitis	1 (0.2%)	6 (1.2%); 7
	Intestinal ischemia	2 (0.4%)	2 (0.4%)
	Upper gastrointestinal hemorrhage	-	2 (0.4%)
	Appendicitis	1 (0.2%)	1 (0.2%)
	Hematochezia	1 (0.2%)	1 (0.2%)
	Peritonitis	1 (0.2%)	1 (0.2%)
	Gastroenteritis	1 (0.2%)	-
	Gastrointestinal infection	1 (0.2%)	-
	Diarrhea	1 (0.2%); 2	-
	Vomiting	1 (0.2%)	-
	Gastrointestinal hemorrhage	1 (0.2%)	-
General disorders and administration site conditions	Death	9 (1.7%)	8 (1.5%)
	Complication of device removal	2 (0.4%)	-
	Chest pain	-	1 (0.2%)
	Adverse drug reaction	-	1 (0.2%)
	Pyrexia	1 (0.2%)	-
	Device breakage	1 (0.2%)	-
Renal and urinary disorders	Acute kidney injury	1 (0.2%)	4 (0.8%)
	Urinary tract infection	3 (0.6%)	4 (0.8%)
	Urosepsis	3 (0.6%)	2 (0.4%)
	Urinary retention	1 (0.2%)	1 (0.2%)
	Renal failure	-	1 (0.2%)
Vascular disorders	Hypotension	4 (0.7%)	-
	Arterial occlusive disease	3 (0.6%)	2 (0.4%)
	Hematoma	-	2 (0.4%)
	Deep vein thrombosis	2 (0.4%)	1 (0.2%)
	Arteriosclerosis	-	1 (0.2%)
	Vascular pseudoaneurysm ruptured	-	1 (0.2%)
	Pulmonary embolism	-	1 (0.2%)
	Venous thrombosis	1 (0.2%)	-
	Hypovolemic shock	1 (0.2%)	-

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
Infections and infestations	Sepsis	7 (1.3%)	3 (0.6%)
	Septic shock	1 (0.2%)	2 (0.4%)
	Tuberculosis	-	1 (0.2%)
	Infections and infestations	-	1 (0.2%)
	Staphylococcal sepsis	1 (0.2%)	-
	Bacteremia	1 (0.2%)	-
Psychiatric disorders	Depression	-	2 (0.4%)
	Post stroke depression	-	1 (0.2%)
	Agitation	-	1 (0.2%)
	Adjustment disorder	1 (0.2%); 2	-
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	-	1 (0.2%)
	Femur fracture	1 (0.2%)	1 (0.2%)
	Arthralgia	1 (0.2%)	-
Hepatobiliary disorders	Cholecystitis	2 (0.4%)	1 (0.2%)
Blood and lymphatic system disorders	Anemia	-	1 (0.2%)
	Splenic abscess	1 (0.2%)	-
Injury, poisoning and procedural complications	Post procedural complication	-	1 (0.2%)
	Toxicity to various agents	1 (0.2%)	-
Investigations	Oxygen saturation decreased	1 (0.2%)	-
	White blood cell count increased	1 (0.2%)	-
Endocrine disorders	Diabetic ketoacidosis	1 (0.2%)	-
Metabolism and nutrition disorders	Hypoglycemia	1 (0.2%)	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Gallbladder cancer metastatic	1 (0.2%)	-
Skin and subcutaneous tissue disorders	Cellulitis	1 (0.2%)	-
Surgical and medical procedures	Carotid angioplasty	1 (0.2%)	-

Table 67 – SAEs by SOC/PT - ImpACT-24B Safety Analysis Set (all patients)

G4 – Stimulation-Related Non-Serious Adverse Events

The table below details the SOC and PT classification of all non-serious stimulation-related adverse events. 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 = 536)	Sham (N = 519)
Injury, poisoning and procedural complications	Application site pain	84 (15.7%); 110	4 (0.8%)
	Implant site pain	34 (6.3%); 45	-
	Medical device site discomfort	1 (0.2%)	-
	Implant site hemorrhage	1 (0.2%)	-
	Implant site bleeding	1 (0.2%)	-
Eye disorders	Lacrimation increased	71 (13.2%); 74	3 (0.6%); 4
	Lacrimation	4 (0.7%)	-
	Eye pain	-	1 (0.2%)
	Conjunctivitis	1 (0.2%)	-
Nervous system disorders	Headache	19 (3.5%); 21	4 (0.8%); 6
	Hemorrhagic transformation stroke	4 (0.7%)	1 (0.2%)
	Brain oedema	2 (0.4%)	-
	Seizure	-	1 (0.2%)
	Depressed level of consciousness	1 (0.2%)	-
	Myoclonus	1 (0.2%)	-
General disorders and administration site conditions	Medical device discomfort	5 (0.9%); 6	6 (1.2%)
	Pyrexia	5 (0.9%)	5 (1.0%)
Psychiatric disorders	Agitation	5 (0.9%)	1 (0.2%)
	Anxiety	4 (0.7%)	-
	Confusional state	1 (0.2%)	-
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	3 (0.6%)	-
	Pulmonary hypertension	-	1 (0.2%)
	Cough	-	1 (0.2%)
	Pneumonia	1 (0.2%)	-
	Nasal congestion	1 (0.2%); 2	-
	Epistaxis	1 (0.2%)	-
Musculoskeletal and connective tissue disorders	Pain in extremity	1 (0.2%)	1 (0.2%)
	Pain in jaw	-	1 (0.2%)
	Muscle spasms	1 (0.2%)	-
Vascular disorders	Hypertension	2 (0.4%)	-
	Hematoma	-	1 (0.2%)
	Hypotension	1 (0.2%)	-
Blood and lymphatic system disorders	Anemia	-	1 (0.2%)
	Leukocytosis	-	1 (0.2%)
Cardiac disorders	Tachycardia	1 (0.2%); 2	-

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
Gastrointestinal disorders	Nausea	-	1 (0.2%)
Renal and urinary disorders	Hematuria	-	1 (0.2%)

Table 68 – Non-serious Stimulation-Related AEs by SOC/PT - ImpACT-24B Safety Analysis Set (all patients)

G5 – Implantation-Related Non-Serious Adverse Events

The table below details the SOC and PT classification of all non-serious adverse events related to the implantation or implant removal. 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	Old Implant (N=339)	Final Implant (N=197)
Injury, poisoning and procedural complications	Implant site pain	32 (9.4%); 36	2 (1.0%)
	Implant site hemorrhage	13 (3.8%); 16	-
	Application site pain	7 (2.1%)	-
	Implant site nerve injury	5 (1.5%)	-
	Implant site erythema	4 (1.2%)	-
	Post procedural infection	2 (0.6%)	-
	Medical device site discomfort	1 (0.3%)	-
General disorders and administration site conditions	Complication of device removal	8 (2.4%)	1 (0.5%)
	Pyrexia	4 (1.2%); 5	-
	Device breakage	4 (1.2%)	-
	Device deployment issue	3 (0.9%)	-
	Device dislocation	2 (0.6%)	-
Psychiatric disorders	Agitation	10 (2.9%)	5 (2.5%)
	Anxiety	2 (0.6%)	1 (0.5%)
	Restlessness	1 (0.3%)	-
Gastrointestinal disorders	Vomiting	4 (1.2%)	-
	Nausea	2 (0.6%)	1 (0.5%)
	Oral fungal infection	1 (0.3%)	-
Respiratory, thoracic and mediastinal disorders	Pneumonia aspiration	2 (0.6%)	-
	Sinusitis	1 (0.3%)	-
	Pneumonia	1 (0.3%)	-
	Respiratory failure	1 (0.3%)	-
	Apnea	1 (0.3%)	-
	Bronchopneumonia	1 (0.3%)	-
Nervous system disorders	Headache	4 (1.2%)	-
	Depressed level of consciousness	1 (0.3%)	-
Vascular disorders	Hypertension	-	3 (1.5%)
	Hypotension	1 (0.3%)	-
	Hypertensive crisis	1 (0.3%)	-

SOC	PT	Old Implant (N=339)	Final Implant (N=197)
Eye disorders	Lacrimation increased	-	2 (1.0%)
Investigations	Oxygen saturation decreased	1 (0.3%)	-
	C-reactive protein increased	1 (0.3%)	-
Musculoskeletal and connective tissue disorders	Soft tissue injury	-	-
	Back pain	1 (0.3%)	-
Cardiac disorders	Tachycardia	1 (0.3%)	-
Immune system disorders	Drug hypersensitivity	1 (0.3%)	-
Infections and infestations	Infection	1 (0.3%)	-
Total		125 (36.9%); 133	15 (7.6%)

Table 69 – Non-serious AEs Related to Implantation/Removal by SOC/PT and Implant model

G6 – Unrelated Serious Adverse Events

The table below details the SOC and PT classification of all serious adverse events that were classified as unrelated to the device or 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 = 536)	Sham (N = 519)
Nervous system disorders	Cerebral infarction	25 (4.7%)	16 (3.1%); 17
	Stroke in evolution	18 (3.4%)	19 (3.7%)
	Hemorrhagic transformation stroke	7 (1.3%)	10 (1.9%)
	Brain oedema	5 (0.9%)	2 (0.4%)
	Transient ischemic attack	4 (0.7%)	2 (0.4%)
	Seizure	4 (0.7%); 5	2 (0.4%)
	Brain stem stroke	3 (0.6%)	-
	Hemorrhage intracranial	-	2 (0.4%)
	Epilepsy	-	2 (0.4%)
	Cerebral artery occlusion	2 (0.4%)	-
	Vertebrobasilar insufficiency	-	1 (0.2%)
	Brain neoplasm	-	1 (0.2%)
	Subdural hematoma	-	1 (0.2%); 2
	Neurological decompensation	1 (0.2%)	1 (0.2%)
	Cerebellar infarction	-	1 (0.2%)
	Sedation	1 (0.2%)	-
	Neurological symptom	1 (0.2%)	-
	Presyncope	1 (0.2%)	-
Respiratory, thoracic and mediastinal disorders	Pneumonia	12 (2.2%); 14	12 (2.3%); 13
	Respiratory failure	5 (0.9%)	5 (1.0%)
	Pulmonary embolism	4 (0.7%)	4 (0.8%)
	Lower respiratory tract infection	-	3 (0.6%)

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
	Bronchopneumonia	2 (0.4%)	2 (0.4%)
	Lung neoplasm malignant	1 (0.2%)	2 (0.4%)
	Pneumonia aspiration	1 (0.2%)	2 (0.4%)
	Aspiration	2 (0.4%)	1 (0.2%)
	Pulmonary oedema	-	1 (0.2%)
	Bronchitis	1 (0.2%)	1 (0.2%)
	Respiratory arrest	-	1 (0.2%)
	Respiratory tract infection	-	1 (0.2%)
	Upper respiratory tract infection	1 (0.2%)	-
	Influenza	1 (0.2%)	-
Cardiac disorders	Cardiac arrest	7 (1.3%)	5 (1.0%)
	Cardio-respiratory arrest	4 (0.7%)	5 (1.0%)
	Atrial fibrillation	5 (0.9%)	-
	Cardiac failure	4 (0.7%)	2 (0.4%)
	Cardiac failure congestive	3 (0.6%)	1 (0.2%)
	Acute myocardial infarction	2 (0.4%)	2 (0.4%)
	Cardiovascular insufficiency	2 (0.4%)	-
	Nodal arrhythmia	-	1 (0.2%)
	Coronary artery disease	-	1 (0.2%)
	Atrioventricular block	-	1 (0.2%)
	Angina pectoris	1 (0.2%)	-
	Silent myocardial infarction	1 (0.2%)	-
	Myocardial infarction	1 (0.2%)	-
	Intracardiac thrombus	1 (0.2%)	-
Gastrointestinal disorders	Clostridium colitis	1 (0.2%)	6 (1.2%); 7
	Intestinal ischemia	2 (0.4%)	2 (0.4%)
	Upper gastrointestinal hemorrhage	-	2 (0.4%)
	Appendicitis	1 (0.2%)	1 (0.2%)
	Hematochezia	1 (0.2%)	1 (0.2%)
	Peritonitis	1 (0.2%)	1 (0.2%)
	Gastroenteritis	1 (0.2%)	-
	Gastrointestinal infection	1 (0.2%)	-
	Diarrhea	1 (0.2%); 2	-
	Vomiting	1 (0.2%)	-
	Gastrointestinal hemorrhage	1 (0.2%)	-
General disorders and administration site conditions	Death	9 (1.7%)	8 (1.5%)
	Chest pain	-	1 (0.2%)
	Adverse drug reaction	-	1 (0.2%)
	Pyrexia	1 (0.2%)	-
Renal and urinary disorders	Acute kidney injury	1 (0.2%)	4 (0.8%)
	Urinary tract infection	3 (0.6%)	4 (0.8%)
	Urosepsis	3 (0.6%)	2 (0.4%)

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
	Urinary retention	1 (0.2%)	1 (0.2%)
	Renal failure	-	1 (0.2%)
Vascular disorders	Hypotension	4 (0.7%)	-
	Arterial occlusive disease	3 (0.6%)	2 (0.4%)
	Hematoma	-	2 (0.4%)
	Deep vein thrombosis	2 (0.4%)	1 (0.2%)
	Arteriosclerosis	-	1 (0.2%)
	Vascular pseudoaneurysm ruptured	-	1 (0.2%)
	Pulmonary embolism	-	1 (0.2%)
	Venous thrombosis	1 (0.2%)	-
	Hypovolemic shock	1 (0.2%)	-
Infections and infestations	Sepsis	7 (1.3%)	3 (0.6%)
	Septic shock	1 (0.2%)	2 (0.4%)
	Tuberculosis	-	1 (0.2%)
	Infections and infestations	-	1 (0.2%)
	Staphylococcal sepsis	1 (0.2%)	-
	Bacteremia	1 (0.2%)	-
Psychiatric disorders	Depression	-	2 (0.4%)
	Post stroke depression	-	1 (0.2%)
	Agitation	-	1 (0.2%)
	Adjustment disorder	1 (0.2%); 2	-
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	-	1 (0.2%)
	Femur fracture	1 (0.2%)	1 (0.2%)
	Arthralgia	1 (0.2%)	-
Hepatobiliary disorders	Cholecystitis	2 (0.4%)	1 (0.2%)
Blood and lymphatic system disorders	Anemia	-	1 (0.2%)
	Splenic abscess	1 (0.2%)	-
Injury, poisoning and procedural complications	Post procedural complication	-	1 (0.2%)
	Toxicity to various agents	1 (0.2%)	-
Investigations	Oxygen saturation decreased	1 (0.2%)	-
	White blood cell count increased	1 (0.2%)	-
Endocrine disorders	Diabetic ketoacidosis	1 (0.2%)	-
Metabolism and nutrition disorders	Hypoglycemia	1 (0.2%)	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Gallbladder cancer metastatic	1 (0.2%)	-
Skin and subcutaneous tissue disorders	Cellulitis	1 (0.2%)	-

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
Surgical and medical procedures	Carotid angioplasty	1 (0.2%)	-

Table 70 – SAEs Unrelated to the device by SOC/PT

G7 – Unrelated Non-serious Adverse Events

The table below details the SOC and PT classification of all non-serious adverse events that were classified as unrelated to the device or 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 = 536)	Sham (N = 519)
Psychiatric disorders	Insomnia	39 (7.3%)	53 (10.2%); 56
	Depression	49 (9.1%)	36 (6.9%)
	Agitation	44 (8.2%); 46	34 (6.6%); 35
	Anxiety	24 (4.5%); 25	24 (4.6%); 25
	Post stroke depression	6 (1.1%)	9 (1.7%)
	Confusional state	7 (1.3%)	5 (1.0%)
	Restlessness	4 (0.7%)	3 (0.6%)
	Sleep disorder	3 (0.6%)	3 (0.6%)
	Delirium	3 (0.6%)	3 (0.6%)
	Depressed mood	2 (0.4%)	2 (0.4%)
	Hallucination	2 (0.4%)	2 (0.4%)
	Nervousness	2 (0.4%)	1 (0.2%)
	Dementia	-	1 (0.2%)
	Mania	-	1 (0.2%)
	Psychiatric disorders	-	1 (0.2%)
	Mental disorder due to a general medical condition	1 (0.2%)	1 (0.2%)
	Crying	1 (0.2%)	-
	Stress	1 (0.2%)	-
	Panic attack	1 (0.2%)	-
Gastrointestinal disorders	Constipation	57 (10.6%); 59	61 (11.8%); 65
	Diarrhea	23 (4.3%); 24	21 (4.0%); 23
	Nausea	15 (2.8%)	14 (2.7%); 16
	Vomiting	13 (2.4%); 15	12 (2.3%); 13
	Oral candidiasis	4 (0.7%)	7 (1.3%)
	Clostridium colitis	6 (1.1%)	7 (1.3%)
	Gastritis	7 (1.3%)	4 (0.8%)
	Dysphagia	4 (0.7%)	4 (0.8%)
	Abdominal discomfort	2 (0.4%)	3 (0.6%)
	Abdominal pain	1 (0.2%)	3 (0.6%)

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
	Oropharyngeal pain	1 (0.2%)	3 (0.6%)
	Hemorrhoids	3 (0.6%)	1 (0.2%)
	Hiccups	2 (0.4%)	2 (0.4%)
	Gingivitis	-	2 (0.4%)
	Dyspepsia	1 (0.2%)	2 (0.4%)
	Gastrointestinal hemorrhage	-	2 (0.4%)
	Abdominal pain upper	2 (0.4%)	1 (0.2%)
	Mouth ulceration	2 (0.4%)	1 (0.2%)
	Duodenal ulcer	2 (0.4%)	-
	Gastroenteritis	2 (0.4%)	-
	Hematochezia	-	1 (0.2%)
	Salivary hypersecretion	1 (0.2%)	1 (0.2%)
	Upper gastrointestinal hemorrhage	1 (0.2%)	1 (0.2%)
	Tooth infection	1 (0.2%)	1 (0.2%)
	Toothache	1 (0.2%)	1 (0.2%)
	Proctitis	-	1 (0.2%)
	Rectal ulcer	-	1 (0.2%)
	Oral fungal infection	-	1 (0.2%)
	Loose tooth	-	1 (0.2%)
	Diarrhea infectious	-	1 (0.2%)
	Umbilical hernia	-	1 (0.2%)
	Hiatus hernia	-	1 (0.2%)
	Oral disorder	-	1 (0.2%)
	Melaena	-	1 (0.2%)
	Rectal cancer	1 (0.2%)	-
	Glossodynia	1 (0.2%)	-
	Enteritis	1 (0.2%)	-
	Epigastric discomfort	1 (0.2%)	-
	Malabsorption	1 (0.2%)	-
Nervous system disorders	Headache	66 (12.3%); 78	70 (13.5%); 76
	Hemorrhagic transformation stroke	14 (2.6%)	19 (3.7%)
	Stroke in evolution	14 (2.6%)	6 (1.2%)
	Brain oedema	6 (1.1%)	9 (1.7%)
	Seizure	8 (1.5%)	7 (1.3%)
	Cerebral infarction	3 (0.6%)	4 (0.8%)
	Presyncope	4 (0.7%)	-
	Muscle spasticity	3 (0.6%)	3 (0.6%)
	Epilepsy	3 (0.6%); 5	-
	Neuralgia	3 (0.6%)	2 (0.4%)

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
	Neuropathy peripheral	3 (0.6%)	1 (0.2%)
	Cognitive disorder	2 (0.4%)	2 (0.4%)
	Subarachnoid hemorrhage	-	2 (0.4%)
	Syncope	2 (0.4%)	2 (0.4%)
	Neurological symptom	-	2 (0.4%)
	Hypoaesthesia	-	2 (0.4%)
	Cerebral artery occlusion	2 (0.4%)	1 (0.2%)
	Depressed level of consciousness	2 (0.4%)	1 (0.2%)
	Central pain syndrome	2 (0.4%)	1 (0.2%)
	Paresthesia	1 (0.2%)	1 (0.2%)
	Neurological decompensation	1 (0.2%)	1 (0.2%)
	Paresthesia oral	-	1 (0.2%)
	Convulsion	-	1 (0.2%)
	Encephalopathy	-	1 (0.2%)
	Memory impairment	1 (0.2%)	1 (0.2%)
	Anxiety	-	1 (0.2%)
	Dysarthria	-	1 (0.2%)
	Hemiparesis	1 (0.2%)	-
	Vertigo positional	1 (0.2%)	-
	Dysphonia	1 (0.2%)	-
	Complex regional pain syndrome	1 (0.2%)	-
	Hyperaesthesia	1 (0.2%)	-
	Balance disorder	1 (0.2%)	-
	Dysgeusia	1 (0.2%)	-
Renal and urinary disorders	Urinary tract infection	89 (16.6%); 103	96 (18.5%); 114
	Hematuria	8 (1.5%)	14 (2.7%); 15
	Renal failure	4 (0.7%)	12 (2.3%)
	Urinary retention	9 (1.7%)	9 (1.7%)
	Incontinence	1 (0.2%)	5 (1.0%)
	Oliguria	4 (0.7%); 5	2 (0.4%)
	Acute kidney injury	4 (0.7%)	3 (0.6%)
	Dysuria	2 (0.4%)	2 (0.4%)
	Nephropathy	-	2 (0.4%)
	Bacteriuria	2 (0.4%)	-
	Hypertonic bladder	1 (0.2%)	1 (0.2%)
	Renal cancer	-	1 (0.2%)

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
	Nephrolithiasis	-	1 (0.2%)
	Nocturia	1 (0.2%)	-
	Renal ischemia	1 (0.2%)	-
	Proteinuria	1 (0.2%)	-
Metabolism and nutrition disorders	Hypokalaemia	46 (8.6%); 51	24 (4.6%)
	Vitamin b12 deficiency	15 (2.8%); 16	13 (2.5%)
	Hyperlipidaemia	8 (1.5%)	12 (2.3%)
	Hypercholesterolaemia	10 (1.9%)	7 (1.3%)
	Hyperglycaemia	6 (1.1%)	3 (0.6%)
	Hypomagnesaemia	6 (1.1%)	2 (0.4%)
	Hyponatraemia	5 (0.9%)	4 (0.8%)
	Hypernatraemia	3 (0.6%)	4 (0.8%)
	Hyperkalaemia	3 (0.6%)	4 (0.8%)
	Hypoproteinaemia	4 (0.7%); 5	2 (0.4%)
	Hypoalbuminaemia	3 (0.6%)	1 (0.2%)
	Dehydration	2 (0.4%)	2 (0.4%)
	Hypoglycemia	1 (0.2%)	2 (0.4%)
	Decreased appetite	2 (0.4%)	1 (0.2%)
	Dyslipidaemia	2 (0.4%)	1 (0.2%)
	Hypervolaemia	-	1 (0.2%)
	Hyperuricaemia	1 (0.2%)	1 (0.2%)
	Hypertriglyceridaemia	-	1 (0.2%)
	Hypochloraemia	-	1 (0.2%)
	Hyperphosphataemia	-	1 (0.2%)
	Folate deficiency	-	1 (0.2%)
	Hypocalcaemia	1 (0.2%)	1 (0.2%)
	Hypophosphataemia	1 (0.2%)	1 (0.2%)
	Underweight	-	1 (0.2%)
	Hyperbilirubinaemia	1 (0.2%)	-
	Glucose tolerance impaired	1 (0.2%)	-
	Hypolipidaemia	1 (0.2%)	-
General disorders and administration site conditions	Pyrexia	63 (11.8%); 70	58 (11.2%); 64
	Pain	9 (1.7%)	9 (1.7%)
	Oedema peripheral	8 (1.5%)	5 (1.0%)
	Chest pain	4 (0.7%)	6 (1.2%)
	Infusion site infection	3 (0.6%)	1 (0.2%)
	Adverse drug reaction	-	2 (0.4%)
	Injection site haematoma	1 (0.2%)	1 (0.2%)
	Medical device complication	-	1 (0.2%)
	Adverse event	1 (0.2%)	1 (0.2%)
	Drug interaction	-	1 (0.2%)

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
	Drug effect prolonged	1 (0.2%)	-
	Asthenia	1 (0.2%)	-
	Wound secretion	1 (0.2%)	-
	Chest discomfort	1 (0.2%)	-
	Inflammation	1 (0.2%)	-
	Device dislocation	1 (0.2%)	-
Respiratory, thoracic and mediastinal disorders	Bronchitis	20 (3.7%)	9 (1.7%)
	Pneumonia	17 (3.2%)	15 (2.9%)
	Lower respiratory tract infection	5 (0.9%)	8 (1.5%)
	Epistaxis	4 (0.7%)	7 (1.3%)
	Nasopharyngitis	7 (1.3%)	2 (0.4%)
	Bronchopneumonia	6 (1.1%)	1 (0.2%); 2
	Respiratory tract infection	5 (0.9%)	1 (0.2%)
	Dyspnoea	5 (0.9%)	1 (0.2%)
	Sinusitis	5 (0.9%)	1 (0.2%)
	Cough	4 (0.7%)	4 (0.8%)
	Pleural effusion	4 (0.7%)	1 (0.2%)
	Pulmonary oedema	4 (0.7%)	2 (0.4%)
	Bronchospasm	1 (0.2%)	3 (0.6%)
	Upper respiratory tract infection	3 (0.6%)	3 (0.6%)
	Hypoxia	3 (0.6%)	-
	Respiratory failure	3 (0.6%)	-
	Pneumonia aspiration	1 (0.2%)	2 (0.4%)
	Sleep apnoea syndrome	1 (0.2%)	2 (0.4%)
	Aspiration	-	2 (0.4%)
	Productive cough	-	2 (0.4%)
	Chronic obstructive pulmonary disease	1 (0.2%)	2 (0.4%)
	Atelectasis	1 (0.2%)	2 (0.4%)
	Nasal congestion	2 (0.4%)	-
	Pulmonary embolism	1 (0.2%)	1 (0.2%)
	Wheezing	-	1 (0.2%)
	Tachypnea	-	1 (0.2%)
	Sputum discoloured	-	1 (0.2%)
	Pulmonary congestion	1 (0.2%)	1 (0.2%)
	Rhinitis	1 (0.2%)	-
	Respiratory distress	1 (0.2%)	-
	Lung neoplasm malignant	1 (0.2%)	-
Cardiac disorders	Atrial fibrillation	31 (5.8%)	25 (4.8%); 26
	Tachycardia	12 (2.2%)	8 (1.5%)

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
	Cardiac failure	8 (1.5%)	3 (0.6%)
	Bradycardia	4 (0.7%)	4 (0.8%)
	Cardiac failure congestive	4 (0.7%); 5	3 (0.6%)
	Tachyarrhythmia	1 (0.2%)	3 (0.6%)
	Arrhythmia	1 (0.2%)	2 (0.4%)
	Atrial flutter	1 (0.2%)	2 (0.4%)
	Intracardiac thrombus	1 (0.2%)	2 (0.4%)
	Coronary artery disease	2 (0.4%)	-
	Hypertensive heart disease	1 (0.2%)	1 (0.2%)
	Silent myocardial infarction	1 (0.2%)	1 (0.2%)
	Cardiac arrest	-	1 (0.2%)
	Aortic valve stenosis	-	1 (0.2%)
	Cardiac disorders	-	1 (0.2%); 2
	Ventricular extrasystoles	-	1 (0.2%)
	Nodal arrhythmia	1 (0.2%)	-
	Hypertrophic cardiomyopathy	1 (0.2%)	-
	Angina pectoris	1 (0.2%)	-
	Mitral valve disease	1 (0.2%)	-
	Supraventricular tachyarrhythmia	1 (0.2%)	-
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	18 (3.4%); 19	15 (2.9%); 16
	Back pain	5 (0.9%)	16 (3.1%)
	Pain in extremity	9 (1.7%); 10	6 (1.2%); 7
	Arthralgia	7 (1.3%)	7 (1.3%)
	Gout	5 (0.9%); 7	2 (0.4%)
	Muscle spasms	1 (0.2%)	4 (0.8%)
	Musculoskeletal chest pain	4 (0.7%)	2 (0.4%)
	Joint dislocation	2 (0.4%)	2 (0.4%)
	Myalgia	2 (0.4%)	1 (0.2%)
	Arthritis	2 (0.4%)	1 (0.2%)
	Tendonitis	2 (0.4%)	-
	Soft tissue injury	-	1 (0.2%)
	Ankle fracture	-	1 (0.2%)
	Dupuytren's contracture	-	1 (0.2%)
	Gouty arthritis	1 (0.2%)	1 (0.2%); 2
	Muscle spasticity	-	1 (0.2%)
	Pain in jaw	-	1 (0.2%)
	Osteoarthritis	1 (0.2%)	-
	Cervical spinal stenosis	1 (0.2%)	-
	Sarcopenia	1 (0.2%)	-
Vascular disorders	Hypertension	22 (4.1%); 23	18 (3.5%); 19

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
	Hypotension	12 (2.2%)	12 (2.3%); 14
	Carotid artery stenosis	10 (1.9%); 11	4 (0.8%)
	Hypertensive crisis	3 (0.6%)	5 (1.0%)
	Arteriosclerosis	5 (0.9%)	3 (0.6%)
	Deep vein thrombosis	3 (0.6%)	4 (0.8%)
	Dizziness	3 (0.6%)	4 (0.8%)
	Thrombophlebitis superficial	1 (0.2%)	3 (0.6%)
	Orthostatic hypotension	3 (0.6%)	-
	Peripheral vascular disorder	1 (0.2%)	1 (0.2%)
	Aneurysm	1 (0.2%)	1 (0.2%)
	Hematoma	-	1 (0.2%)
	Peripheral embolism	1 (0.2%)	-
Skin and subcutaneous tissue disorders	Rash	8 (1.5%)	5 (1.0%)
	Decubitus ulcer	8 (1.5%)	5 (1.0%)
	Dermatitis	5 (0.9%)	-
	Pruritus	1 (0.2%)	3 (0.6%)
	Skin disorder	1 (0.2%)	3 (0.6%)
	Erythema	3 (0.6%)	3 (0.6%)
	Tinea cruris	2 (0.4%)	3 (0.6%)
	Hyperhidrosis	3 (0.6%)	1 (0.2%)
	Dermatitis allergic	-	2 (0.4%)
	Skin ulcer	1 (0.2%)	1 (0.2%)
	Laceration	-	1 (0.2%)
	Rash pruritic	1 (0.2%)	1 (0.2%)
	Herpes simplex	1 (0.2%)	1 (0.2%)
	Infusion site cellulitis	-	1 (0.2%)
	Eczema	-	1 (0.2%)
	Contusion	1 (0.2%)	1 (0.2%)
	Folliculitis	-	1 (0.2%)
	Skin candida	-	1 (0.2%)
	Acarodermatitis	1 (0.2%)	-
	Granuloma	1 (0.2%)	-
	Tinea pedis	1 (0.2%)	-
	Dry skin	1 (0.2%)	-
	Cellulitis	1 (0.2%)	-
	Purpura	1 (0.2%)	-
	Herpes zoster	1 (0.2%)	-
Blood and lymphatic system disorders	Anemia	21 (3.9%)	11 (2.1%)
	Anemia macrocytic	-	1 (0.2%)
	Thrombocytopenia	1 (0.2%)	1 (0.2%)

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
	Leukocytosis	1 (0.2%)	1 (0.2%)
	Splenic infarction	1 (0.2%)	-
	Disseminated intravascular coagulation	1 (0.2%)	-
	Lymphoma	1 (0.2%)	-
Eye disorders	Conjunctivitis	12 (2.2%)	9 (1.7%)
	Lacrimation increased	5 (0.9%)	-
	Eye pain	-	2 (0.4%)
	Eye infection	1 (0.2%)	2 (0.4%)
	Dry eye	1 (0.2%)	2 (0.4%)
	Conjunctival oedema	-	1 (0.2%)
	Cataract	-	1 (0.2%)
	Eye injury	-	1 (0.2%)
	Glaucoma	1 (0.2%)	1 (0.2%); 2
Investigations	Liver function test abnormal	4 (0.7%)	2 (0.4%)
	C-reactive protein increased	3 (0.6%)	2 (0.4%)
	Inflammatory marker increased	1 (0.2%)	2 (0.4%); 3
	White blood cell count increased	-	2 (0.4%)
	International normalized ratio increased	2 (0.4%)	-
	Blood lactate dehydrogenase increased	1 (0.2%)	1 (0.2%)
	Blood osmolarity decreased	1 (0.2%)	1 (0.2%)
	Urine leukocyte esterase positive	-	1 (0.2%)
	Endoscopy gastrointestinal abnormal	1 (0.2%)	1 (0.2%)
	Anticoagulation drug level above therapeutic	1 (0.2%)	1 (0.2%)
	Tumour marker increased	1 (0.2%)	-
	Haemoglobin decreased	1 (0.2%)	-
	Antibiotic resistant staphylococcus test	1 (0.2%)	-
	Oxygen saturation decreased	1 (0.2%)	-
Injury, poisoning and procedural complications	Fall	10 (1.9%); 11	8 (1.5%)
	Implant site pain	3 (0.6%)	-
	Application site pain	1 (0.2%)	1 (0.2%)
	Postoperative wound infection	-	1 (0.2%)

SOC	PT	SPG Stim. (N = 536)	Sham (N = 519)
	Catheter site infection	-	1 (0.2%)
	Post-traumatic pain	-	1 (0.2%)
	Toxic encephalopathy	1 (0.2%)	-
	Bronchial injury	1 (0.2%)	-
Endocrine disorders	Diabetes mellitus	6 (1.1%)	9 (1.7%)
	Hyperthyroidism	2 (0.4%)	2 (0.4%)
	Hypothyroidism	1 (0.2%)	2 (0.4%)
	Euthyroid sick syndrome	-	1 (0.2%)
	Goitre	1 (0.2%)	-
	Adrenal adenoma	1 (0.2%)	-
Hepatobiliary disorders	Liver disorder	2 (0.4%)	5 (1.0%)
	Hypoalbuminaemia	1 (0.2%)	1 (0.2%)
	Hyperammonaemia	1 (0.2%)	-
	Hepatic infarction	1 (0.2%)	-
	Cholecystitis	1 (0.2%)	-
	Cholelithiasis	1 (0.2%)	-
	Hepatitis	1 (0.2%)	-
Immune system disorders	Hypersensitivity	3 (0.6%)	2 (0.4%)
	Drug eruption	1 (0.2%)	2 (0.4%)
	Drug hypersensitivity	1 (0.2%)	1 (0.2%)
	Drug allergy	1 (0.2%)	-
Reproductive system and breast disorders	Vaginal infection	1 (0.2%)	2 (0.4%)
	Benign prostatic hyperplasia	2 (0.4%)	1 (0.2%)
	Prostatomegaly	-	1 (0.2%)
	Breast mass	-	1 (0.2%)
	Breast cancer	-	1 (0.2%)
	Vulval ulceration	1 (0.2%)	-
	Ovarian cyst	1 (0.2%)	-
Infections and infestations	Infection	2 (0.4%)	-
	Bacteremia	2 (0.4%)	1 (0.2%)
	Localised infection	2 (0.4%)	-
	Staphylococcal sepsis	1 (0.2%)	-
	Staphylococcal infection	1 (0.2%)	-
Ear and labyrinth disorders	Middle ear inflammation	3 (0.6%)	1 (0.2%)
	Vertigo	1 (0.2%)	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastatic neoplasm	-	1 (0.2%)
	Cerebellar haemangioma	1 (0.2%)	-
Congenital, familial and genetic disorders	Atrial septal defect	1 (0.2%)	-

Table 71 – Non-serious AEs Unrelated to the device by SOC/PT

Appendix H – ImpACT-24A AE Tables

H1 – ImpACT-24A Mortality by SOC/PT

The following table details the SOC and PT classification of all fatal events in ImpACT-24A.

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
Nervous system disorders	Stroke in evolution	4 (2.0%)	1 (1.0%)
	Cerebral infarction	4 (2.0%)	1 (1.0%)
	Brain stem stroke	-	1 (1.0%)
	Hemorrhagic transformation stroke	1 (0.5%)	-
	Brain oedema	1 (0.5%)	-
	Intracranial pressure increased	1 (0.5%)	-
Respiratory, thoracic and mediastinal disorders	Respiratory failure	-	5 (5.0%)
	Pneumonia	2 (1.0%)	3 (3.0%)
	Pneumonia aspiration	2 (1.0%)	1 (1.0%)
Cardiac disorders	Acute myocardial infarction	4 (2.0%)	1 (1.0%)
	Cardio-respiratory arrest	2 (1.0%)	-
Vascular disorders	Gastrointestinal hemorrhage	-	1 (1.0%)
	Cardiovascular insufficiency	-	1 (1.0%)
	Pulmonary embolism	-	1 (1.0%)
	Haematemesis	1 (0.5%)	-
	Hypovolemic shock	1 (0.5%)	-
General disorders and administration site conditions	Sudden death	1 (0.5%)	-
	Death	1 (0.5%)	-
Hepatobiliary disorders	Hepatic failure	1 (0.5%)	-

Table 72 – Mortality by SOC/PT (ImpACT-24A)

H2 – ImpACT-24A SAE by SOC/PT

The following table details the SOC and PT classification of all SAEs in ImpACT-24A.

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
Nervous system disorders	Cerebral infarction	7 (3.5%)	1 (1.0%)
	Stroke in evolution	4 (2.0%)	2 (2.0%)
	Hemorrhagic transformation stroke	2 (1.0%)	2 (2.0%)
	Brain oedema	1 (0.5%)	2 (2.0%)
	Status epilepticus	-	1 (1.0%)
	Transient ischemic attack	1 (0.5%)	1 (1.0%)
	Neurological symptom	-	1 (1.0%)
	Intracranial pressure increased	2 (1.0%)	-
	Brain stem stroke	-	1 (1.0%)

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
	Cerebellar infarction	1 (0.5%)	-
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%)	-
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%)
	Epistaxis	-	1 (1.0%); 2
	Gastrointestinal hemorrhage	-	1 (1.0%)
	Cardiovascular insufficiency	-	1 (1.0%)
	Hematoma muscle	-	1 (1.0%)
	Haematemesis	1 (0.5%)	-
	Hypovolemic shock	1 (0.5%)	-
Gastrointestinal disorders	Gastroenteritis	-	1 (1.0%)
	Gastrointestinal obstruction	-	1 (1.0%)
	Diarrhea infectious	1 (0.5%)	-
	Gastric varices hemorrhage	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	Complication of device removal	-	1 (1.0%)
	Feeding tube complication	1 (0.5%)	-
	Drug toxicity	1 (0.5%)	-
	Vascular procedure complication	1 (0.5%)	-
	Fall	1 (0.5%)	-

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
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 normalized 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 73 – SAEs by SOC/PT (ImpACT-24A)

H3 – 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%)
	Paresthesia	3 (1.5%)	-
	Subarachnoid hemorrhage	-	1 (1.0%)
	Neurological symptom	-	1 (1.0%)
	Localized 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 74 – Stimulation-Related Non-serious AEs by SOC/PT (ImpACT-24A)

H4 – ImpACT-24A Implantation-Related 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 hemorrhage	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 75 – Implantation-Related Non-serious AEs by SOC/PT (ImpACT-24A)

H5 – 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 ischemic attack	1 (0.5%)	1 (1.0%)
	Hemorrhagic 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 hemorrhage	-	1 (1.0%)
	Cardiovascular insufficiency	-	1 (1.0%)
	Hematoma muscle	-	1 (1.0%)
	Haematemesis	1 (0.5%)	-

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
	Hypovolemic shock	1 (0.5%)	-
Gastrointestinal disorders	Gastroenteritis	-	1 (1.0%)
	Gastrointestinal obstruction	-	1 (1.0%)
	Diarrhea infectious	1 (0.5%)	-
	Gastric varices hemorrhage	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 normalized 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 76 – Unrelated Serious AEs by SOC/PT (ImpACT-24A)

H6 – 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%)
	Diarrhea	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 hemorrhage	-	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%)	-
	Hematochezia	1 (0.5%)	-
	Gingival infection	1 (0.5%)	-
	Gingival ulceration	1 (0.5%)	-
	Mouth ulceration	1 (0.5%)	-
	Gastrointestinal hemorrhage	1 (0.5%)	-
	Gingival pain	1 (0.5%)	-
	Glossodynia	1 (0.5%)	-

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
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%)
	Hypoglycemia	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%)	-

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
	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%)	-
	Hemorrhagic 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%)

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
	Hematuria	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 localized	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%)	-

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
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%)	-
	Hypovolemic shock	-	1 (1.0%)
	Hematoma	-	1 (1.0%)
	Thrombophlebitis superficial	1 (0.5%)	-
	Portal hypertension	1 (0.5%)	-
	Venous thrombosis	1 (0.5%)	-
	Myocardial ischemia	1 (0.5%)	-
	Peripheral embolism	1 (0.5%)	-
	Gastrointestinal hemorrhage	1 (0.5%)	-
	Contusion	1 (0.5%)	-
	Hemorrhoids	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%)

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
	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%)

SOC	PT	SPG Stim. (N=202)	Sham (N=101)
	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	Anemia	1 (0.5%)	2 (2.0%)
	Anemia macrocytic	-	1 (1.0%)
	Leukocytosis	-	1 (1.0%)
	Lymphoma	1 (0.5%)	-
Endocrine disorders	Hypoglycemia	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 77 – Unrelated Non-serious AEs by SOC/PT (ImpACT-24A)

Appendix I – Patient Selection

This section discusses the exclusion criteria in the pivotal study in the context of the device labeling.

The IFU is based on the main inclusion and exclusion criteria:

- Acute ischemic stroke in the anterior circulation
- Confirmed cortical involvement (defined as NIHSS≥10 and at ischemic changes in at least one of the cortical ASPECTS regions, M1-M6 and insular cortex)
- Ineligibility for or no access to IV-tPA and EVT
- Treatment initiation between 8-24 of last known well

Hemorrhagic strokes, of any kind, are listed as contra indications.

The device labeling includes a Caution messages that informs the physician that the treatment was not evaluated in patients with high bleeding propensity (INR>1.8, aPTT≥45 sec. or platelet count < 75×10^9/L), women known to be pregnant, and patients with other implanted neural stimulators or electronic devices such as pacemakers.

The device labeling also guides the physician how to identify patients who are not suitable for implantation and how to identify patients at risk of airway obstruction.

The remaining inclusion/exclusion criteria listed below, aimed to reduce the chances that the study would succeed or fail solely due to imbalanced enrollment of patients with very good prognosis (even if untreated), patient with poor prognosis (even if receiving beneficial treatment) and patients with rare conditions or deficits due in part to non-stroke conditions. Such patients were considered "non-informative" and were not included in the trial, including:

1) Young patients (<40 years old)
2) Neuro-imaging evidence of significant abnormality (e.g. tumor, abscess)
3) Known cerebral arteriovenous malformation
4) Cerebral aneurysm
5) Clinical signs and symptoms or imaging evidence of bilateral stroke
6) NIHSS level of consciousness score ≥ 2.
7) Previous stroke in the last 6 months or previous stroke with existing sequelae or with mRS > 0 for any reason.
8) Pre-existing disability (pre-existing mRS >1, even if not Stroke-related)
9) Seizure at onset
10) Blood glucose concentration < 60 mg/dL.

11) Clinical suspicion of septic embolus
12) Uncontrolled hypertension.
13) Serious systemic infection
14) Life expectancy < 1 year from causes other than stroke.

The study also excluded patients with NIHSS>18, women older than 85 years old, men older than 80 years old and patients with massive stroke. However, 58 patients with massive stroke (defined as stroke involving >2/3 of the middle cerebral artery territory) were recruited in ImpACT-24A and ImpACT-24B and were included in the safety and efficacy analyses. Although these patients have worse prognosis compared to patients with smaller strokes, the absolute risk reduction in this population was 10%, not different than in the rest of the CCI population. The subgroup analysis indicates no interaction between baseline infarct size, age or NIHSS and treatment benefit. Therefore, it is reasonable to assume that the treatment is safe and effective in CCI patients outside the 40-80/85 age range or with NIHSS >18 or with massive stroke. The decision is left for the physician's judgement on a case-by-case basis.

Appendix J – Benefit-Risk Assessment

Assessment of Benefit

Q1. Evidence of Clinical Benefit

☒ *A favorable change in at least 1 clinical assessment that is equal to or greater than seen in the control group*

The rates of favorable outcomes in the primary and all secondary endpoints in the CCI population were higher than in the sham control group, including 90-day disability level using the mRS scale (sliding dichotomy, 0-2 vs 3-6 and 0-3 vs 4-6), Quality of life (SIS-16 patient-reported outcome) at day-90 and RIKS at 180 and 360 days, as well as the per-protocol analysis.

☒ *A favorable change in at least 1 clinical assessment that meets a predetermined performance goal*

The predetermined performance goal was an absolute risk reduction of 7%. All dichotomized endpoints in the CCI population showed benefit that was greater or equal this threshold.

☒ *A favorable change in at least 1 clinical assessment that meets or surpasses a minimally important clinical difference*

The minimally important clinical difference is 1.5% [12]

☒ *A favorable change in at least 1 clinical assessment that is equal to or greater than changes seen with other available modalities for the disease or condition*

The magnitude of benefit of SPG stimulation started in 8–24 hours from stroke onset (pooled OR 1.61, 95% CI 1.16-2.23) is comparable to that of IV tPA administered <3 hours from stroke onset (OR 1.7, 95% CI 1.2-2.6) and exceeds that of IV tPA administered 3–4.5 hours from stroke onset (OR 1.34, 95% CI 1.02-1.76).[53] It is also comparable to the magnitude of benefit of EVT in MR CLEAN (OR 1.66, 95% CI 1.21-2.28), the largest thrombectomy trial in the <6 hour window. The late-window EVT trials (DAWN and DEFUSE3) used more selective imaging criteria. The IFU is limited to patients who are ineligible or have no access to EVT.

☒ *A favorable change in at least 1 clinical assessment that would be meaningful to patients considering the severity, chronicity, etc., of the condition, taking into consideration patient-reported outcomes and health-related quality of life*

One-point improvement in mRS and 10-point improvement in SIS-16 are clinically meaningful. Transitions from higher disability levels are valued more than transitions from lower levels (see section 3.1.3).

☒ *Other(s):*

NNT for favorable outcome ranges between 9-13 (10 for the primary outcome) and odds-ratio point estimates range between 1.43-1.58. In patients who received stimulation at the optimal low-medium intensity range the NNT was 5.

The rate of symptomatic ICH (a known complication of stroke) was 5x lower in the SPG stimulation group compared to sham control.

The benefits of reduced disability and improved quality of life persisted for 90 days, 180 days and one year.

Q1: Is there any evidence of clinical benefit?

☒ YES → Continue to Question 2
☐ NO → Move to Question 9

Q2. Extent of Uncertainty for the Benefits

☐ *Inconsistent or conflicting results between studies*
Two large RCTs provided consistent results

☒ *Wide confidence intervals surrounding the point estimate(s) and/or odds ratio(s)*

The primary endpoint in the CCI population was borderline (0.0258 compared to 0.025, the multiplicity adjusted threshold).

☒ *Study design or results lead to lack of generalizability for the intended use population or specific clinical subpopulations*

The CCI population is identified using a combination of clinical assessment (NIHSS) and radiologic assessment (ASPECTS). In the study, ASPECTS were assessed by central readers. Both NIHSS and ASPECTS are already used according to guidance to select patients for stroke therapies. See discussion of the generalizability of the results in section 8.

☐ *High subject or specimen loss-to-follow-up at critical assessment point(s)*

8 patients in the mITT cohort were lost to follow up (0.8%), including 3/481 in the treated group (0.6%) and 5/519 in the control group (1.0%).

☐ *Large amount of missing data at critical assessment time(s) +/- imputation*

There were no missing mRS data other than in patients lost to follow up.

☒ *Others Factor Increasing Uncertainty:*

- Implantation failures and mITT analysis.

☒ *Others Factor Reducing Uncertainty:*

- The rate of misplacements using the final system (in ImpACT-24M) was zero.
- Patients entering the mITT and patients not entering the mITT were similar in baseline characteristics.
- Consistent results in secondary analyses – the primary mRS endpoint was analyzed in different ways. The results of the primary sliding dichotomy analysis were consistent with the results of the secondary fixed dichotomies. The p-value using sliding dichotomy was lower than that of dichotomy 0-2 and higher than that of dichotomy 0-3.
- Dose response – Strong dose response relationship in ImpACT-24B, with maximum benefit in the low-medium dose range (typical of neurostimulation) and same optimal dose range in ImpACT-24M, reducing the uncertainty of benefit. The dose-response relationship repeated in all endpoints, with and without covariate adjustment, and with both models of the implant.
- U-shaped dose–responses for stimulation intensity are a common feature of electrical stimulation applied to neuronal systems, reflecting tuning of neurobiological systems to respond maximally at low–midrange levels. [15, 16]
- Stimulation levels – In ImpACT-24B, stimulation level was set too high in 50% of patients (due to blinding constraints), exceeding the non-noxious physiologic range where treatment benefit was highest. The final system limits the stimulation level so it cannot exceed this range. As a result, the efficacy in clinical practice is expected to be higher than in the ImpACT-24B trial, as estimated by efficacy analysis in the final device range (NNT 4-6 for the various endpoints).
- Consistent results in the two randomized studies – In both studies, treatment benefit did not depend on baseline core size or on the time from stroke onset, consistent with the device MOA and preclinical results. In both studies, the rate of sICH was lower in the SPG stimulation group compared to control, consistent with the BBB protection effect in preclinical studies. No heterogeneity of treatment effect between the two studies (p=0.88).
- Consistent benefit was shown in all endpoints in the pooled analysis, sliding dichotomy odds ratio of 1.61 (95% CI 1.16-2.23)
- Prediction of which patients will benefit – It was anticipated, based on the mechanism of action, that patients with cortical involvement will benefit the most,

and this population was defined as a primary analysis population in the pivotal ImpACT-24B trial. The entire benefit analysis is focused on this population.

Q2: What is the extent of uncertainty for the benefits?

☐ Low → Continue to Question 3
☒ Med → Continue to Question 3
☐ High → Continue to Question 3

Summary of the Assessment of Benefit

The ImpACT-24B pivotal trial was a prospective, multi-center, multinational, randomized, sham control, double-blind, adjunctive to standard of care, parallel arm study, and is, to our knowledge, the largest device trial in acute ischemic stroke patients.

The study results show a clinically meaningful treatment effect in the CCI population. The absolute risk reduction (ARR) of 9.8% is higher than the 1.5% MCID threshold and higher than the 7% ARR that was pre-specified in the protocol as the minimum desirable effect.

Uncertainty factors include:

- Borderline p-value for the primary endpoint (0.0258 vs the multiplicity-adjusted threshold of 0.025)
- The use of primary mITT analysis
- The use of central radiologist to identify CCI patients

On the other hand, factors reducing the uncertainty include:

- The rate of misplacements using the final system (in ImpACT-24M) was zero.
- Consistent benefit in all secondary endpoints (lower disability and improved quality of life). For example, 49% of the patients in the control arm in ImpACT-24B were unable to walk or care for their body on day 90 (mRS ≥4) compared to 37% in the treated arm.
- The benefit persists in the long term follow up at 180 and 360 days
- Strong dose response relationship in ImpACT-24B and same optimal dose range in ImpACT-24M (the final device dose range)
- Robust treatment effect in the pivotal study in patients stimulated within the final device dose range

- Similarity of findings between ImpACT-24B and ImpACT-24A and no heterogeneity of treatment effect between the studies
- Consistent benefit in in all endpoints in the individual patient data meta-analysis, sliding dichotomy odds ratio of 1.61 (95% CI 1.16-2.23)

Assessment of Risk

Q3. Are Known/Probable Risks More than Minimal?

☒ *Adverse events (AEs) or outcomes related to the device itself*

SAE and mortality rates were nominally higher in the treated group in ImpACT-24B and lower in ImpACT-24A and the pooled safety data show that SPG stimulation does not increase the risks of mortality, serious adverse events, and common stroke complications.

No serious adverse events were classified as probably related to treatment.

Headache non-serious adverse events, which occurred in 3.5% of the patients, may be a side-effect of SPG activation. All headache cases resolved without sequela (median time to resolution within the same day, IQR 0-3 days).

Pain adverse events were non serious and are avoidable (not expected to occur with the final device, see section 7.2.5.4).

The risk of implantation failure was mitigated by the final device and validated in ImpACT-24M.

☒ *Other*

Several potential risks have been identified such as the risk of aspiration, airway obstruction, and implant misplacement due to use error. These risks were mitigated by training and labeling and did not occur in the study.

Q3: Are known/probable risks more than minimal?

☐ YES → Continue to Question 4
☒ NO → Move to Question 4

Q4. What is the Extent of Uncertainty for the Risks?

☐ *Insufficient patient numbers to detect serious events*

Treatment risks: 634 patients received at least one treatment dose in the pooled SPG stimulation group in ImpACT-24A and ImpACT-24B. The upper 95% confidence limit of the rate of risk occurrence based on this sample size is 0.5%.

Implantation risks: The final implant was implanted in 247 patients in ImpACT-24B and ImpACT-24M. The upper 95% confidence limit of the rate of risk occurrence based on this sample size is 1.2%.

☐ *Insufficient duration of follow-up to detect delayed/late events*

The primary endpoint follow up period of 90 days. Patient reported outcomes were collected at 180 and 360 days by phone interviews and the results were consistent with the clinician assessment at day 90.

☐ *Inconsistent or conflicting results between studies*

Both RCT trials showed no safety concerns. Both trials showed reduced rate of symptomatic intracranial hemorrhage.

☒ *None*

No significant harmful events. Complication of device removal might occur in ~0.5% of the procedures, and is addressed by a simple surgical procedure by an ear, nose and throat specialist or a maxillofacial surgeon.

The treatment safety of the device was assessed in >1400 patients (including >1300 in two randomized trials). 247 patients were implanted with the final version of the implant.

Q4: What is the Extent of Uncertainty for the Risks?

☒ Low → Continue to Question 5
☐ Med → Continue to Question 5
☐ High → Continue to Question 5

Summary of the Assessment of Risk:

The pooled[i] safety data show that SPG stimulation does not increase the risks of mortality, serious adverse events, and common stroke complications.

A lower rate of symptomatic intracranial hemorrhages (sICH) in the treated arm was observed in both studies. Patients in the sham-control arm had 5 times higher odds of

[i] ImpACT-24A and ImpACT-24B had similar design, including the same treatment, follow-up period, endpoints. The studies had the same exclusion criteria, and minor differences in inclusion criteria. Treatment duration and all other treatment parameters, including the method of setting the stimulation level were identical in both studies. Improvements in the implantation technique were implemented during both studies but none of these improvements affected the treatment.

experiencing an adverse symptomatic intracranial hemorrhage compared to treated patients.

The implantation procedure evolved during the clinical trials and study learnings were implemented in the implant design and navigation system to simplify the procedure. Although the implantation safety data from ImpACT-24A and ImpACT-24B reflect the longer procedure, no significant risks were identified (including no increase in aspiration SAEs compared to sham control). The final implantation technique (the updated PRM) was evaluated in 50 patients in ImpACT-24M, with no implantation SAEs and no failed implantations. It was performed under local anesthesia, and the median skin-to-skin time was 4 minutes (the final implant was used in additional 197 procedures in ImpACT-24B).

Q5: Assessment of Benefit-Risk

Q5: Do the Benefits outweigh the Risks, considering the assessment of Benefit and Risk and the extent of uncertainty identified above?

☒ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☐ Unable to conclude that benefits outweigh the risks – further discussion and consideration of relevant factors is appropriate – Continue to Q6

Summary of the Assessment of Benefit-Risk

SAE and mortality rates were nominally higher in the treated group in ImpACT-24B and lower in ImpACT-24A and the pooled safety data show that SPG stimulation does not increase the risks of mortality, serious adverse events, and common stroke complications.

A lower rate of symptomatic intracranial hemorrhages (sICH) in the treated arm was observed in both studies. Patients in the sham-control arm had 5 times higher odds of experiencing an adverse symptomatic intracranial hemorrhage compared to treated patients.

The implantation procedure evolved during the clinical trials and study learnings were implemented in the implant design and navigation system to simplify the procedure.

Although the implantation safety data from ImpACT-24A and ImpACT-24B reflect the longer procedure, no significant risks were identified (including no increase in aspiration SAEs compared to sham control).

The final implantation technique was evaluated in 50 patients in ImpACT-24M, with no implantation SAEs and no failed implantations. It was performed under local anesthesia, and the median skin-to-skin time was 4 minutes.

The ISS500 provides a clinically meaningful benefit of reduced post-stroke disability and improved quality of life in the target CCI population.

The uncertainty in the primary analysis of treatment benefit is reduced by the cumulative evidence, including pre-clinical and the two RCT studies:

- In both randomized studies, treatment benefit did not depend on baseline core size or on the time from stroke onset, consistent with the device MOA and preclinical results
- In both studies, the rate of sICH was lower in the SPG stimulation group compared to control, consistent with the BBB protection effect in preclinical studies
- No heterogeneity of treatment effect between the two studies (p=0.88)
- Consistent benefit in all endpoints in the pooled analysis of the two RCTs

The absolute risk reduction (ARR) of 9.8% in the primary CCI population is clinically meaningful, and higher than the pre-specified 7% minimal ARR.

The uncertainty of this clinically meaningful benefit is further reduced by:

- Consistent benefit in all secondary endpoints
- The benefit persists in the long term follow up at 180 and 360 days
- Strong dose response relationship in ImpACT-24B and same optimal dose range in ImpACT-24M (the final device dose range)
- Robust treatment effect in the pivotal study in patients stimulated within the final device dose range

Considering the totality of evidence above, the relative consistency of benefit across all endpoints and both studies, as well as the dose response and clear mechanism of action, help mitigate the extent of uncertainty regarding the clinically meaningful benefits and risks.

The final device incorporates study learnings, improving safety and effectiveness even further.

This innovative first of a kind technology addresses the unmet need for a treatment that is simple to administer and is safe and effective in an 8- to 24-hour window in patients who are ineligible for or have no access to alternative therapies.

Additional Considerations

Q6. Do the Benefits outweigh the Risks, when considering the following additional considerations?

☒ *Available qualitative or quantitative PPI on the relative desirability or acceptability to patients of outcomes or other attributes that differ among alternative health interventions*

Patients value reduced disability and improved quality of life after stroke. A study quantifying the patient-centered value of the benefit of each transition between mRS disability levels showed that all one-step transitions in the mRS disability scale are valued by patients and families (when mRS 5/6 are grouped to a single worst-outcome level). The study combined data from time-tradeoff (patient/caregiver-centered) and person-tradeoff (clinician-centered) studies.[23, 24, 25] According to this assessment, all one-step mRS transitions have health utility values that range from 0.09 to 0.33, all exceeding the minimally clinically important difference (MCID) of 0.03 for health utility.[13]

According to published data, 89% of patients accept the risks of IV-tPA in 0-3 hours from onset and 83% accept the higher hemorrhage risk at 3-4.5 hours from onset. SPG stimulation does not increase the risk of hemorrhage (or other significant risks) and the benefit is comparable.

☒ *Understanding that the device represents novel technology for which the current device technology is different*

SPG stimulation is a novel mechanism of action that increases blood flow to the affected hemisphere of the brain by augmenting collateral blood-flow. This is in contrast to direct reperfusion therapies, which rely on opening the occluded vessel

☒ *The device fills an unmet medical need or niche for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease/conditions*

Acute ischemic strokes are devastating events that can result in lifetime of disability and reduced quality of life. Available therapies (IV-tPA and EVT) are limited by time from onset and/or the penumbra and core volumes, and by limited availability of EVT due to expensive infrastructure and expertise.

There is a significant unmet need for a safe and effective therapy for patients who arrive at the hospital 8 to 24 hours after their ischemic stroke and only 2%-3% are eligible for other treatment alternatives in this time window. According to published data, over 30% of the stroke patients in large centers have large/medium vessel occlusion and are currently ineligible for IV-tPA and EVT (see Figure 36). It is estimated that half of them will be eligible for SPG stimulation.

☒ *The device avoids serious harms associated with currently available therapies for the disease or condition*

Symptomatic ICH is a known complication of stroke, and this risk is increased with the use of IV-tPA and EVT. SPG stimulation was shown to avoid this harm.

☒ *The adverse events associated with use of the device are reversible*

The adverse events associated with the device (headache and pain) were reversible.

Q6: Do the Benefits outweigh the Risks, when taking into account additional relevant considerations?

☒ Yes – the benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination
☐ Unable to conclude that benefits outweigh the risks – further discussion and consideration of relevant factors is appropriate – Continue to Q7

Appendix K – Summary of MOA Evidence

The following summary table was published as Table 1 in the supplemental data of reference 6.

Study	Number and type of subjects	Timing of SPG-Stim	Outcome measure	Magnitude of Effect
SPG-Stim application Preclinical Studies				
Toda et al 2000(25)	Healthy Beagle dogs of both sexes	After baselineand during DSA	Arterial Diameter Measurement based on DSA	Frequency dependent (max with10Hz) vasodilation of ipsilateral middle cerebral and posterior communicating arteries (21.1 ± 20.4% and 10.5 ±4.2%) disappearedafter 5 min of SPG-Stim Frequency dependent (max with 5Hz)vasodilation of ipsilateral middle cerebral and posterior communicating arteries with petrosal nerve stim
Toda et al 2000(26)	26 healthy Japanese monkeys of both sexes	After baselineand during DSA	Arterial Diameter Measurement based on DSA	Significant vasodilation of ipsilateral middle and anterior cerebral arteries by15-20%
Seylaz etal 1988(24)	6 healthy male Wistar rats	After baselineand during CBF monitoring	CBF and tissue O2 and CO2 measurements with mass spectroscopy via gas-sampling cannula	Significant increase (~50%) in ipsilateral CBF and milder increase incontralateral CBF, increase (~20%) in ipsilateral tissue PO2
Goadsbyet al 1990(20)	23 healthy cats	After baselineand during CBF monitoring	Regional CBF using the freely diffusible tracer and regional cerebral glucose utilization	Significant increase (up to 45%) in ipsilateral CBF and contralateral CBFonly in restricted areas (frontal and parietal cortex), no change in regionalcerebral glucose utilization
Goadsbyet al 1996(21)	4 healthy cats	After baselineand during CBF monitoring	Cerebral cortical perfusion measurement using laser Doppler flowmetry (LDF)	Significant increase (up to 57%) inipsilateral CBF
Yarnsitsky et al 2004(27)	6 female mongrel dogs SAH models	Day 7 post-SAH	Arterial Diameter Measurement based on DSA	Significant increase in ipsilateral arterial diameter during the secondseries of stimulation (13-32%)
Ayajiki etal 2005(19)	28 healthy male Wistar rats	After baselineand during CBF monitoring	Cerebral cortical perfusion measurement using laser Doppler flowmetry (LDF)	Significant increase (23, 40, and 37%)in ipsilateral CBF
Henningeret al 2007(22)	21 Adult Sprague-Dawley Male Rats, non-MCAO and pMCAO models	60 min post-pMCAO, 0 and 15 minafter baselineMRI in non- MCAO models	**pMCAO models:** Histological (infarct volume corrected for cerebral edema) andBehavioral Assessment at 24 hours post- MCAO, Radiographic (ADC and ASL perfusion) at 30, 60, 90, 120, 150, 180 min post-MCAO **Non-MCAO models:** Radiographic (ADC and ASL perfusion) at baseline, then 0, 5, 10, 15, 20, 25, 30, 60, 90, 120, 150, 180 minutes	**pMCAO models:** Improvement in neurological score, significantly reduced final infarct volume, significantly preserved DWI/PWI mismatch, Mild increased CBF in bothcore and penumbra **Non-MCAO models:** ~25% increasein bilateral hemispheric CBF (mainlyACA) during stim

Study	Number and type of subjects	Timing of SPG-Stim	Outcome measure	Magnitude of Effect
Levi et al 2012 (23)	Healthy and focal photothrombotic models male Sprague - Dawley rats	5 - 15 min and 24hr after pMCAO During and after CBF monitoring and angiography in non-MCAO models	**pMCAO models:** Cerebral cortical perfusion measurement using laser Doppler flowmetry (LDF) Arterial Diameter Measurement based on fluorescent angiography, Blood-brain barrier integrity calculation using Albumin binding dye Evans blue in pMCAO models, Histological (infarct volume corrected for cerebral edema), **Non-MCAO models:** Cerebral cortical perfusion measurement using LDF Arterial Diameter Measurement based on fluorescent angiography	**pMCAO models:** Significant increasein CBF, vasodilation, reduction in BBB damage, and significant smaller infarct volume following SPG-Stim infocal model both 15 min and 24 hour after photo thrombosis of MCA **Non-MCAO models:** Significant increase in ipsilateral CBF (>100%)and vasodilation (10-30%) in non- MCAO
Bar-Shir et al 2010 (72)	25 Male Wistar rats tMCAO models	18±2hr after tMCAO and immediatelyafter MRI scan	Measurement of NAA, DWI lesion volume, behavioral test,	More pronounced recovery w/ higher NAA level 28 days post-MCAO, significantly smaller infarct volume 28days after SPG-Stim
SPG-Stim application Human Studies				
Bornstein et al 2019	303 AIS patients (median 73y/o),	11hr (IQR 9-15hr) from LKW time	Improvement beyond expectation on 3-month mRS, functional independence, Bodily self-care or better (mRS <3),	For primary endpoint of favorable global disability outcome: in the mITTpopulation, SPG-stim 49.7% vs sham
ImpACT 24A (1)	202 in intervention group (153 received minimum of 1 stimulation session) vs 101 in sham group		Stroke related quality of life, Disability related quality of life.	40%, (OR 1.48, P=0.13; in the CCI population, SPG-Stim 50% vs sham 27%, OR 2.7, P=0.03.
Bornstein et et al 2019 ImpACT 24B (2)	1078 AIS patients (40-80 years old) 481 in intervention group vs 519 in sham group	19.9hr (IQR 16 - 22.6 hr) from LKW time	Improvement beyond expectation on 3-month mRS, functional independence, Bodily self-care or better (mRS <3), Stroke related quality of life, Disability related quality of life.	For primary endpoint of favorable global disability outcome: in the mITTpopulation, SPG-Stim 49% vs sham 45%, OR 1.14, P=0.31); in the CCI population SPG-Stim 50% vs sham 40 %, OR 1.48, P=0.0258.
Saver et al 2019 ImpACT-M (33)	50 AIS patients (median 66y/o)	18h (IQR 9 - 20) from LKW time	Measuring volumetric blood flow in the ipsilateral common carotid artery by ultrasound, grasp and pinch strength in the affected hand before and during stimulation, and by change in NIIH Stroke Scale from day 1 to 7.	SPG-Stim significantly increased common carotid artery diameter by 11% (p<0.0001), peak systolic and enddiastolic blood flow by 44%, (p<0.0001) and 52% (p<0.0001), improved pinch strength by 42% (p<0.0001), and grasp strength by 26%(p<0.0001). Degree of NIHSS recovery by day 7 was greater than in matched historic controls, median 75% vs 50%, p=0.0003.

Table 78 – preclinical and human studies testing SPG stimulation in cerebral ischemia

Appendix L – Estimated Number of Eligible US Patients

Of the approximately 700,000 annual acute ischemic stroke patients in the US[i], less than 15% receive any recanalization therapy for a variety of reasons (such as mild strokes and late arrival). [61]

To assess the number of patients who will be eligible for SPG stimulation according to the proposed IFU, the following factors shall be considered:

1. The proportion of patients who are treated in primary stroke centers (PSC) vs comprehensive stroke centers (CSC).
2. The proportion of patients treated with recanalization therapies in both hospital types.
3. EVT procedure growth, inter-hospital transfers, and futile transfers.
4. The rate of moderate-severe anterior-circulation AIS and the rate of recanalization treatment in this group

A study comparing stroke care in PSC vs CSC between 2013-2015 [61], which reviewed the data from 1,181 US hospitals participating in the "Get with the Guidelines" program, showed that ~80% of all stroke patients were treated at PSC, where EVT availability is limited, and published the recanalization procedure volumes by hospital type (see Table 79).

The following table summarizes the number of US patients treated with recanalization therapies:

	PSC	CSC	Total
% of AIS patients	80%	20%	100%
Overall # of patients	560,000	140,000	700,000
tPA Rate	10.3%	14.3%	
# of Patients receiving tPA (2013-2015)	57,680	20,020	77,700
EVT Rate	1.0%	4.1%	
# of Patients receiving EVT (2013-2015)	5,600	5,740	11,340
Total # of Recanalization Procedures	63,280	25,760	89,040

Table 79 - Recanalization Therapies - US Procedure Volume

However, since these data were collected, CSCs have become more widely spread in the US, so that more patients have access to CSCs and the EVT rate in these centers has also increased.

While we do not have reliable information on the growing number of inter-hospital transfers (from PSC to CSC), several recent studies analyzed the rate of futile transfers and the rate of EVT eligibility beyond 6 hours from stroke onset. [41, 42, 62] These studies showed that 40%-73% of the transferred patients are no longer eligible for EVT after transfer and that only 2.3%-2.7% of the late-arriving patients (>6h) meet the DAWN or DEFUSE3 criteria. [1] The primary reason for ineligibility was larger core and/or smaller penumbra in repeated perfusion imaging compared to the indication for late EVT.

[i] According to the American Heart Association 2020 update on Heart Disease and Stroke Statistics, there are ~795,000 new strokes each year in the US, of which 87% are ischemic.

A more recent study used data from a single large CSC which already used a tissue-based approach for patient selection for late EVT. This study showed that while the rate of EVT in large CSC has increased to 22%, still 30% of all AIS patients have medium or large vessel occlusion and are ineligible for IV-tPA and EVT in the <24-hour time window. [43] The article also lists the reasons for ineligibility, including:

- Occlusion too distal to reach
- Neurologic deficit too mild (low NIHSS)
- Temporally advanced ischemic core injury
- Large ischemic core volume
- Chronic cervical ICA occlusion precluding intracranial access
- Poor baseline function
- Atheromatous chronic occlusion of target intracranial vessel
- Extracranial tortuosity precluding intracranial access

The patients who had LVO/MVO and were ineligible for EVT had median ASPECTS 7 (same as the CCI population in ImpACT-24B), indicating that most of them had confirmed cortical involvement. Based on that, it is conservative to assume that 50% of these patients would be eligible for SPG stimulation. The estimate for CSCs, based on extrapolation of the data from this article, is summarized in the following table (assuming the proportion of AIS patients arriving at CSCs has grown to 50%, including transfers from PSCs):

	%	#
Total patients[i]	100%	350,000
Patient without no LVO/MVO	43%	154,000
Patients treated with IV-tPA alone	3%	10,500
Patients receiving EVT (with or without IV-tPA)	22%	77,000
Patients with MVO/LVO ineligible for IV-tPA and EVT	31%	108,500
Patients eligible for SPG	15%	52,500

Table 80 – SPG Stimulation Eligibility in the Comprehensive Centers in the US

We assume that the percentage of patients arriving at CSCs and treated with EVT will continue to grow and we have used a more conservative estimate of 10% of the patients that will be eligible for SPG stimulation in CSCs.

Eligibility to SPG stimulation in PSCs was based on stroke severity distribution data, which shows that the proportion of patients with moderate-severe AIS varies with the distance from large urban centers (possibly due to tendency in rural areas not to go to the hospital with mild strokes). This leads to a slightly higher rate of "SPG candidates" (patients with anterior AIS, NIHSS between 10-18 and cortical involvement) in PSCs compared to general population. We estimate this rate to be 15%-20% in PSCs.

The use of recanalization therapies in SPG candidates also varies between centers. We estimate that ~20% of the patients that could be eligible for SPG stimulation in PSCs will not be eligible due to

[i] Assuming that 50% of all AIS patients in the US arrive at CSCs.

earlier treatment with IV-tPA. We also estimate that additional 15-20% of the SPG candidates will be ineligible due to other, less frequent reasons.

The estimate for PCSs is summarized in the following table (not including transfers to CSCs):

	PSC
% of AIS patients	50%
Overall # of patients	350,000 - 350,000
% of SPG candidates	15% - 20%
Number of SPG candidates	52,500 - 70,000
Overlap between NIH 10-18 and recanalization	20%
SPG Candidates after exclusion of IVT and EVT	42,000 - 56,000
Other exclusions	15% - 20%
SPG Eligible	33,600 - 47,600
% of SPG Eligible	10% - 14%

Table 81 – SPG Stimulation Eligibility in the Comprehensive Centers in the US

In summary, the number of patients who will be eligible for SPG stimulation and will be ineligible or will have no access to either IV-tPA or EVT exceeds 10% of the annual number of AIS patients in the US.

Appendix M – ImpACT-24M Adverse Events

The following table shows all adverse events during the 7-day follow-up period of the trial:

SOC	PT	# of Events (% of patients)
Gastrointestinal disorders	Constipation	1 (2%)
Gastrointestinal disorders	Chronic Gastritis	1 (2%)
Gastrointestinal disorders	Nausea	1 (2%)
Blood and lymphatic system disorders	Anemia	1 (2%)
Cardiac disorders	Heart insufficiency Stage I	1 (2%)
Respiratory, thoracic and mediastinal disorders	Acute Bronchitis	1 (2%)
Eye disorders	Age Related Cataract	1 (2%)
Nervous System Disorders	Headache	2 (4%)

Table 82 – ImpACT-24M All Adverse Events

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