Ischemic Stroke System (ISS500) for Acute Ischemic Stroke Neurological Devices Advisory Panel

December 10, 2021

FDA Presentations By: Xiaorui Tang, Ph.D., Claudette Brooks, M.D., Anhua Lin, Ph.D.

Division of Neuromodulation and Rehabilitation Devices (DHT5B)
Office of Neurological and Physical Medicine Devices (OHT5)
Office of Product Evaluation and Quality (OPEQ)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration (FDA)

Outline of FDA Presentations

- Panel Discussion Topics and Device Information: Dr. Xiaorui Tang
- ISS500 Clinical Trial: Dr. Claudette Brooks
- Uncertainty Discussion: Dr. Anhua Lin and Dr. Claudette Brooks
- Benefit/Risk Discussion: Dr. Claudette Brooks

Panel Discussion Topics

1. The impact that subgroup selection following randomization had on the validity of the study results.
2. The generalizability of the study results to the U.S. indicated patient population.
3. The extent that the study results reflect a true treatment effect given the reliance on a prognostic model.
4. Whether the adverse events adequately assess the probable risks to health.
5. The safety of the implantation procedure and the expertise needed to safely and effectively implant the device.

BrainsGate Ltd.'s Acute Ischemic Stroke System (ISS500):

Background Information

Neurological Devices Advisory Panel Meeting
December 10th, 2021

Xiaorui Tang, Ph.D. – Electrical/Biomedical Engineer and Team Lead
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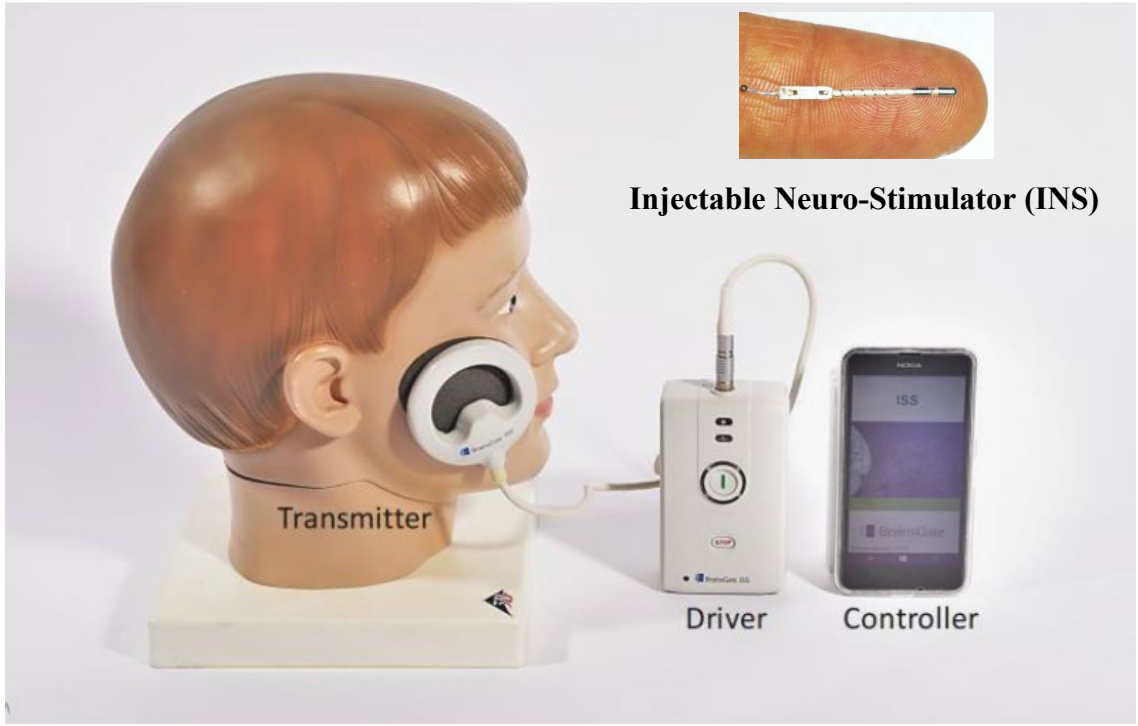
BrainsGate ISS500 Proposed Indications for Use (IFU)

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 and 24 hours from stroke onset (last known well).

Device Description

The Ischemic Stroke System (ISS500) is comprised of a treatment subsystem and an implantation subsystem.



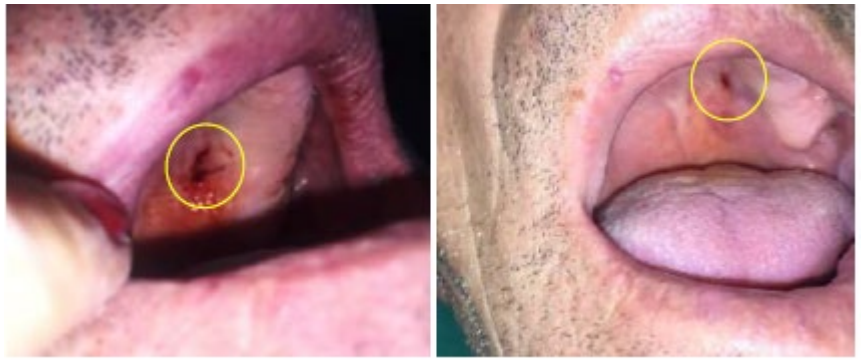
ISS500 Treatment Subsystem

Treatment Subsystem

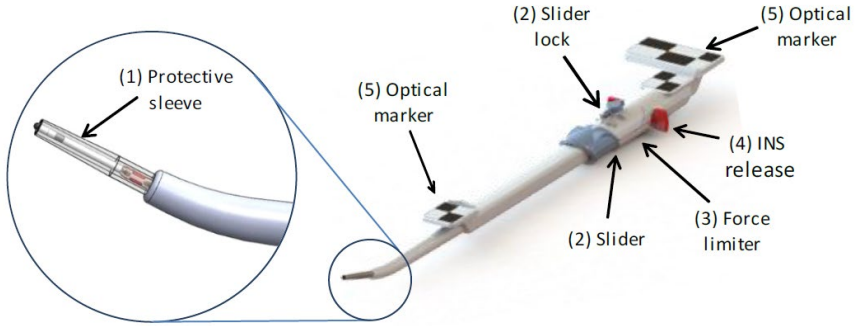
- The Injectable Neuro-Stimulator (INS) is implanted near the sphenopalatine ganglion (SPG).
- An external radiofrequency-coupled Transmitter supplies energy to the INS.
- The INS applies electrical stimulation for a few hours each day over 5 days.
- The stimulation is titrated based on patient comfortable tolerance level.

Implantation Procedure

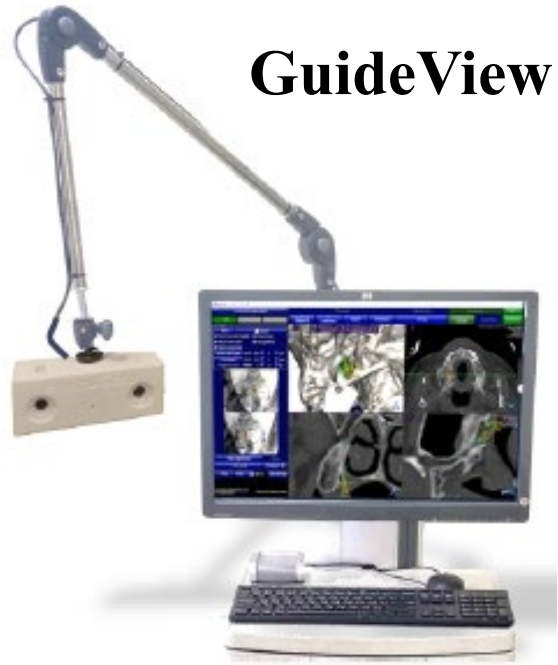
Insertion Location



Introducer Tool



GuideView

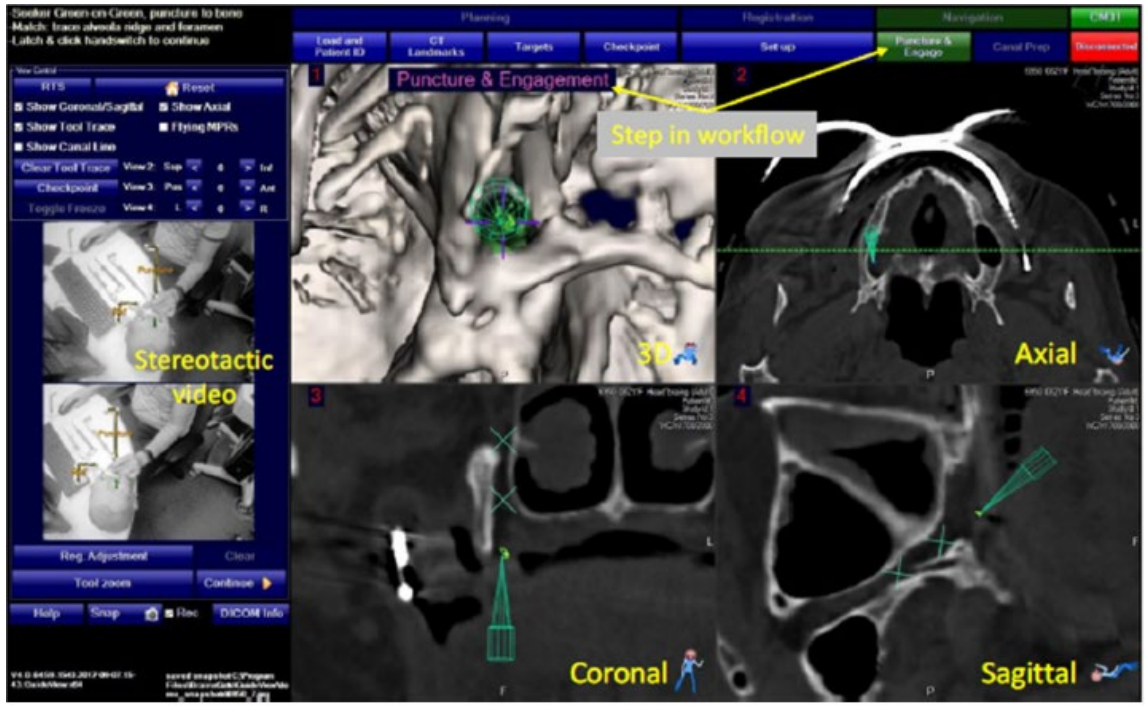


- The INS is implanted under local anesthesia through a 1-3 mm puncture of the mucosa.
- The INS is pre-loaded into the tip of the Introducer tool and is injected into the greater palatine canal.
- The tip of the INS should be placed <5 mm from the SPG.

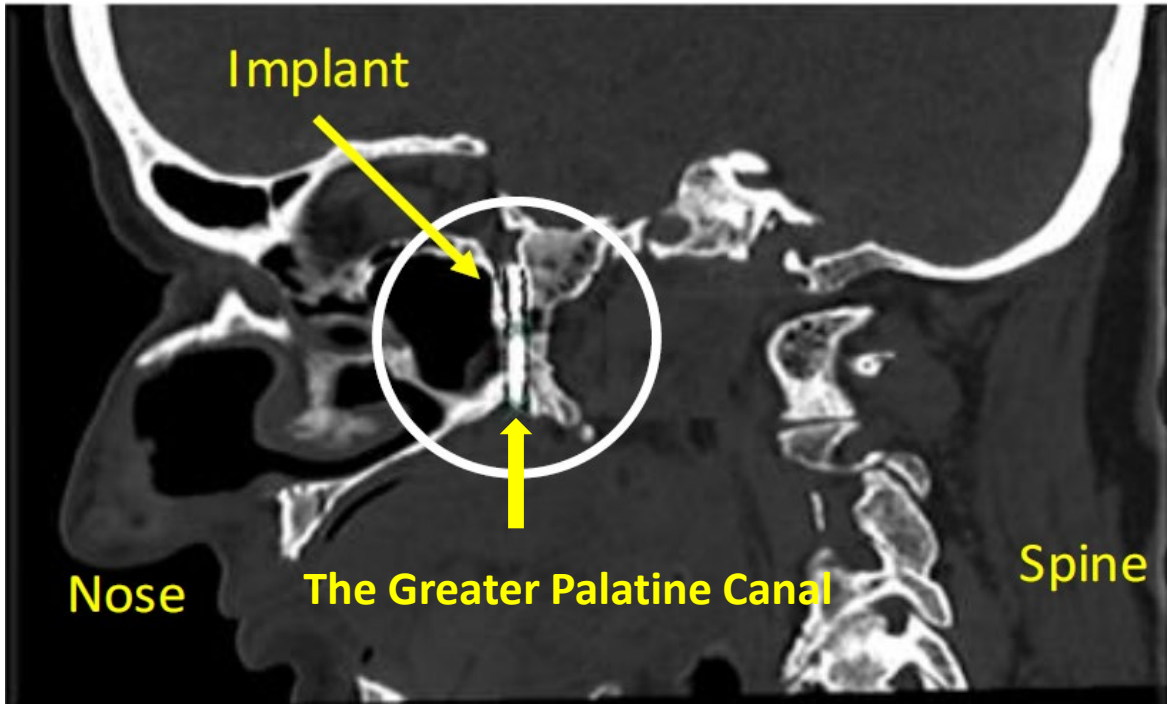
Implantation Procedure - GuideView

This afternoon the Panel will be asked to discuss the safety and expertise that would be needed for the implantation procedure.

- **Implantation**: the INS is implanted with CT image guidance using the GuideView Navigation System.
- **Explantation:** the INS is explanted with forceps at the bedside on Day 5.



Example GuideView screenshot



CT image showing INS500 placement

ISS500 Regulatory Interactions Overview

2007 – 2011
Pilot Study – ImpACT-24A

2007 – Study Approval

2010 – Study halt

2011 – Study resumption OUS

2011 – 2018
Pivotal Study – ImpACT-24B

2011 – Request to resume enrollment in both US and OUS

2012 - Study resumption/approval of ImpACT-24B study

2012 to 2018 – Changes to device design, study protocol and statistical analysis plan were implemented to the IDE.

2018 – After all patients were enrolled (and most had completed all assessments) but before the study was unblinded, the sponsor requested significant changes:

- To add an additional primary endpoint.
- To re-define the modified intent-to-treat (mITT) group.
- To add additional analyses on secondary endpoints.

BrainsGate Ltd.'s Acute Ischemic Stroke System (ISS500):

Clinical Data and Testing - Study Summaries

Neurological Devices Advisory Panel Meeting
December 10th, 2021

Claudette Brooks, M.D. – Neurologist and Clinical Reviewer
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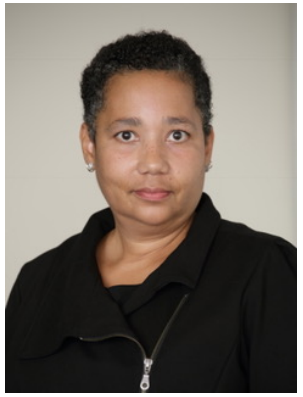


Clinical Evidence: FDA Considerations

- The FDA considers the pre-specified endpoints and data analyses of the pivotal study to the be primary dataset.
- While we have considered the post-hoc analyses because the sponsor has provided them, these carry additional uncertainty.
- Throughout this presentation, we have made the decision to keep nominal p-values for the sake of discussion. However, all p-values, except that which was calculated for the primary, pre-specified outcome, are nominal p-values.

Introduction: Summary of Clinical Data Considered

Study	N (mITT)	Stage	Design	Dates	Main Purposes
ImpACT-24A	253	Pilot	RCT	2007-2011	Exploratory
ImpACT-24B	1000	**Pivotal**	**RCT**	**2011-2018**	**Safety and Effectiveness**
ImpACT-24M	50	Usability	Single-Arm	2017-2018	To Validate Implantation Procedure, Stimulation Level
Total	1303				

ImpACT-24A Study

- The ImpACT-24A study was intended to be a prospective, randomized, double-blind, sham-controlled, multi-national study.
- The primary objective of the study was to assess the safety and effectiveness of SPG stimulation with the ISS device.
- The planned enrollment was 660 subjects (41 US patients) but *terminated early after 303 subjects were randomized due to a high rate of device misplacement, thus underpowered to confirm or reject the hypothesis*.
- Post-hoc analysis probed a signal of potential benefit in patients with aphasia and cortical infarct.

ImpACT-24B Pivotal Study

2011 to 2018

ImpACT-24B Pivotal Study Design

- A prospective, multi-national, sham controlled, randomized trial of 1078 patients from up to 73 total sites (7 in the US).
- Active group: stimulation with the ISS device.
- Sham group: punctured the palate without implanting the ISS device. Used vibration of the transmitter coil to mimic the tingling sensation of SPG activation.
- All patients (active and sham) received usual clinical care.
- Blinding:
  - The protocol provided procedures for blinding treatment assignment to the patients, the sponsor, and the raters, but not the treating investigators.
  - Blood flow measurements were not performed during stimulation sessions to avoid un-blinding of the patient's treatment allocation.

ImpACT-24B Pivotal Study Key Eligibility Criteria

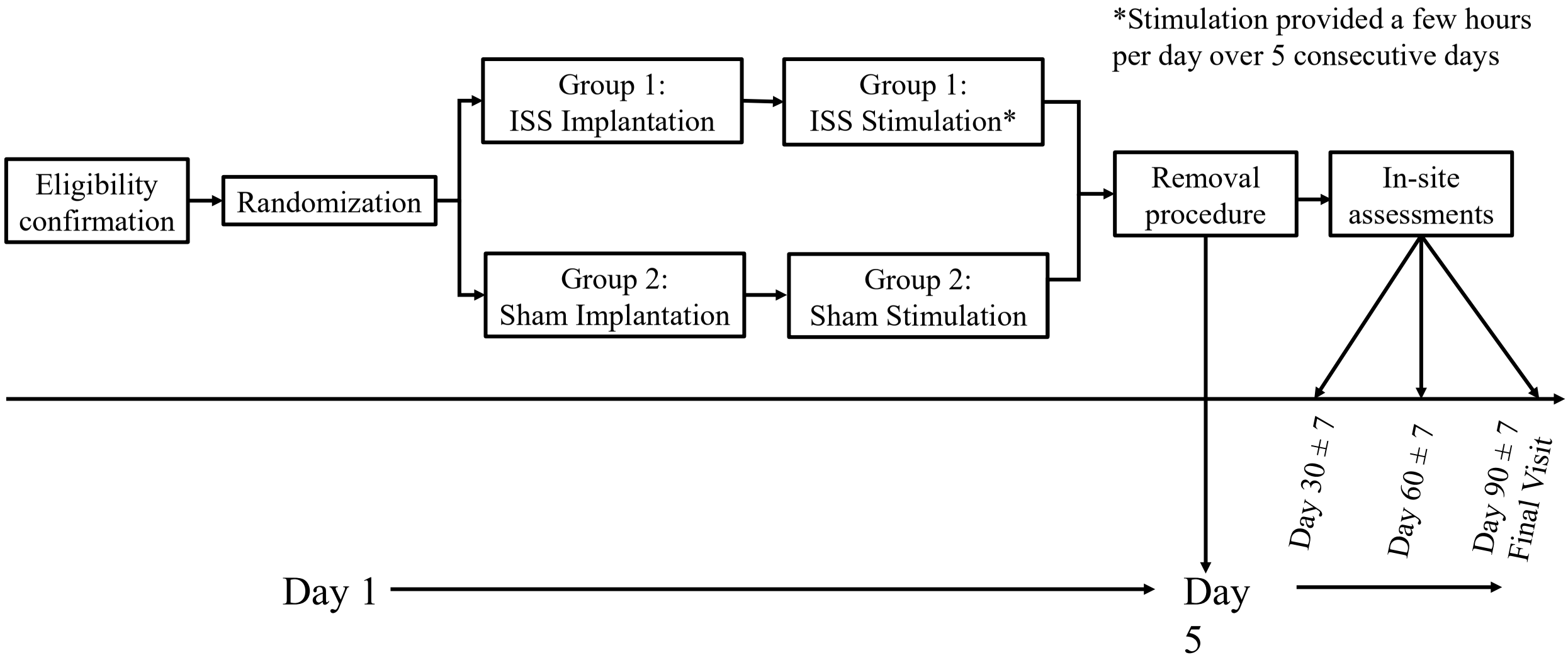
- Key Inclusion Criteria:
  - Age: between 40 to 80 years for males, and 40 to 85 for females (inclusive)
  - Clinical diagnosis of an acute ischemic stroke in the Carotid, Middle or Anterior Cerebral Artery territories *based on general physical examination and neurological examination*
  - *Imaging findings demonstrating signs of ischemia in the anterior circulation*
  - Baseline NIHSS between 7 and 18 within 2 hours of device implantation
  - Ability to initiate treatment within 8-24 hours from stroke onset

- Key Exclusion Criteria:
  - Treated with IV-tPA, IA-tPA or neurothrombectomy devices for the current stroke.

ImpACT-24B Pivotal Study Imaging Methods

- Used non-contrast CT without relying on “advanced perfusion imaging that might not be available in all hospitals.”
- Radiology data was collected and reviewed by blinded central radiologists to assess patient eligibility and cortical involvement.
- After the last stimulation session on Day 5, imaging was performed again to assess ischemic lesion size, detect cases of hemorrhagic transformation, and assess implant position.
- The methods and criteria used to assess eligibility and monitor adverse events via imaging were not specified in the study protocol.

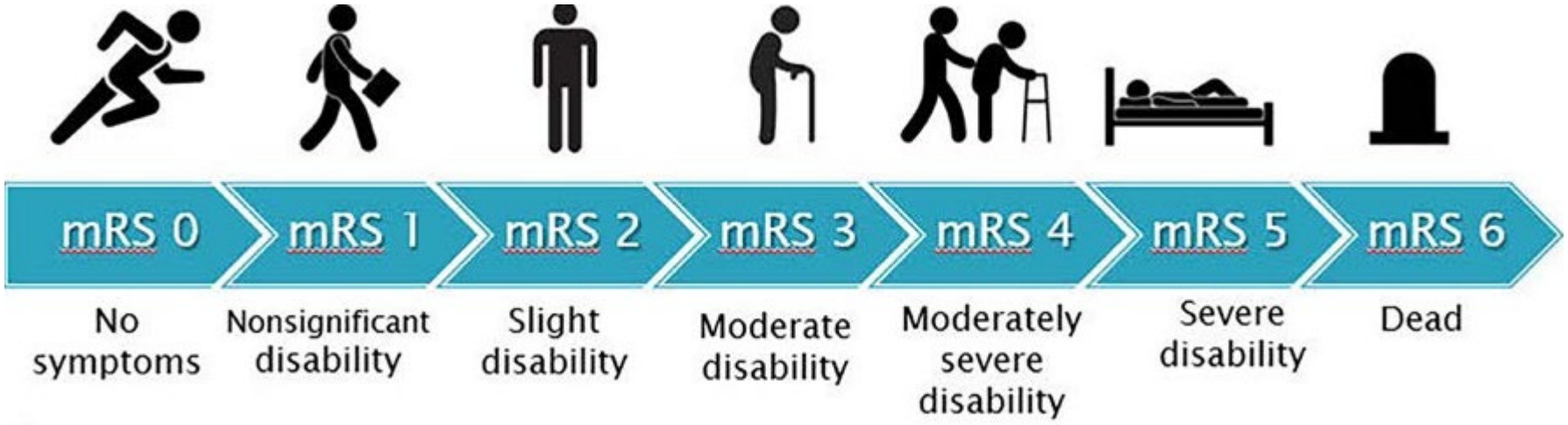
ImPACT-24B Study Timeline



ImpACT-24B: Study Outcomes

- **Primary Effectiveness Outcome:**
  - Modified Rankin Scale (mRS) evaluated on Day 90±7 using Sliding Dichotomy in ***the mITT*** and ***confirmed cortical involvement (CCI)**** subpopulations

  - Conceptually, this effectiveness outcome is a responder rate analysis based on a model prediction of patient natural history.



*The CCI was added in 2018, the last year of the study before the study was locked.

ImpACT-24B: Primary Effectiveness Sub-Populations

- **mITT sub-population:** Randomized subjects receiving at least the minimal exposure of one treatment (ISS Stimulation or Sham Control) session out of the five planned sessions.

- **CCI sub-population:** Patients with NIHSS≥10 whose 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.

*The CCI was added in 2018, the last year of the study before the study was locked.

ImpACT-24B: Safety Outcomes

- Safety outcomes of special interest:
  - Incidence of Serious Adverse Events (% of patients with at least one event)
  - Incidence of neurological deterioration (increase of ≥4 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 were adjudicated as device-related or procedure-related by the investigators.
  - Proportion of failed implantations (%)
  - 90-day mortality

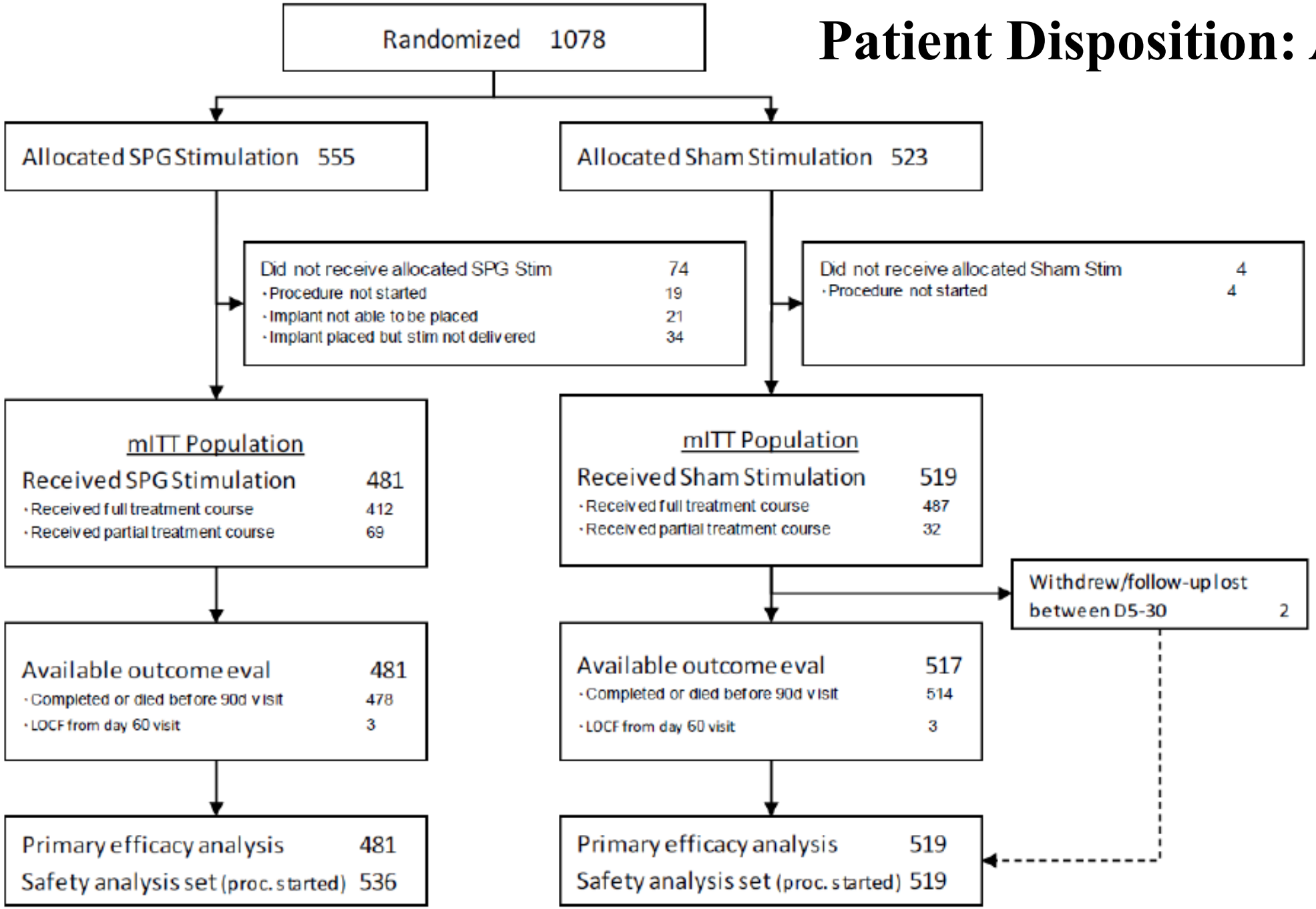
- Serious adverse events of special interest include symptomatic intracranial hemorrhage (sICH) and pneumonia.

ImpACT-24B: Statistical Analysis

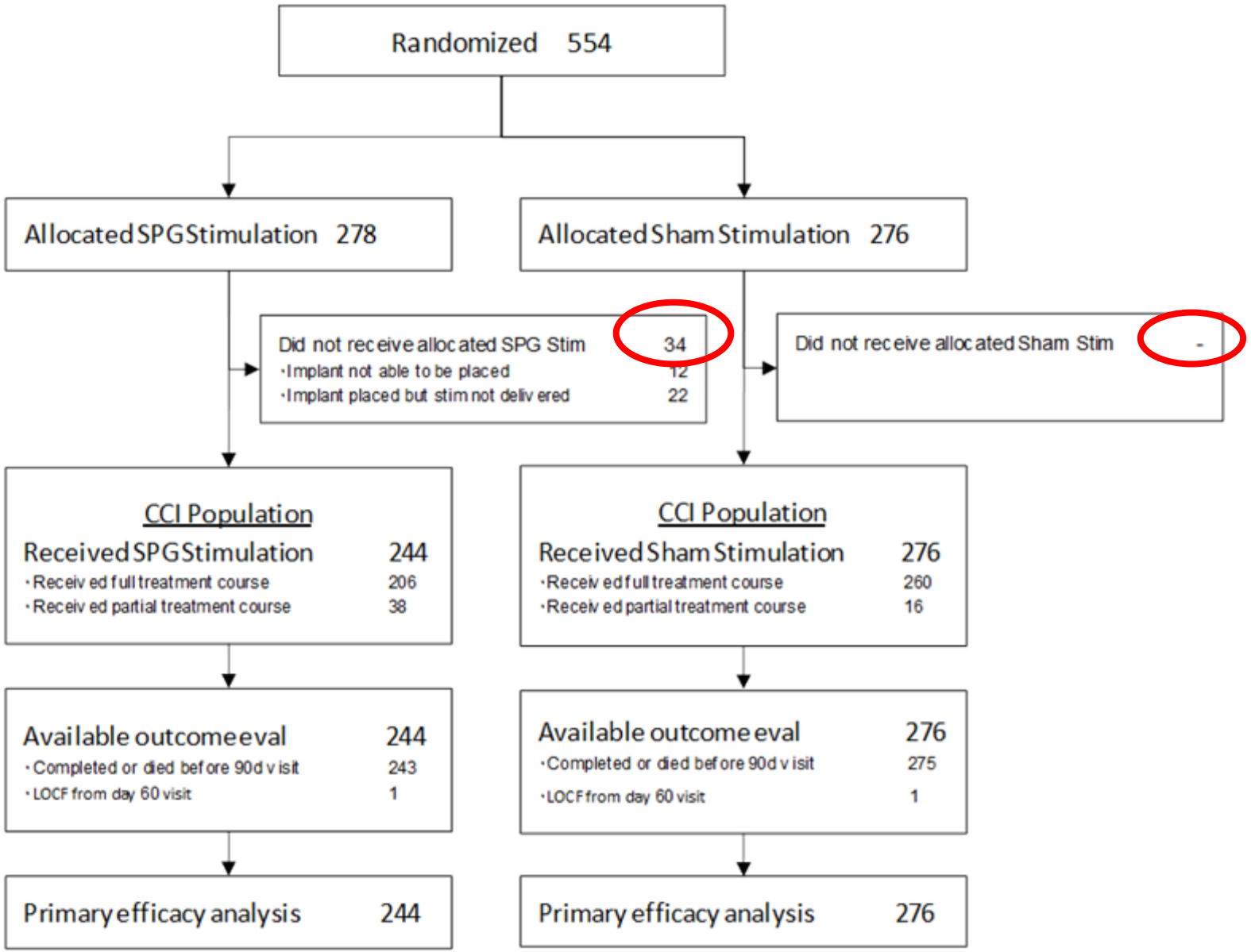
The statistical hypotheses corresponding to the primary effectiveness outcome for mITT and CCI subgroups were tested by Chi-squared test at level of two-sided alpha 0.05 adjusted by Hochberg procedure to control the overall type-I error.

Odds-ratios were estimated by logistic regression.

Patient Disposition: All patients



Patient Disposition: CCI patients



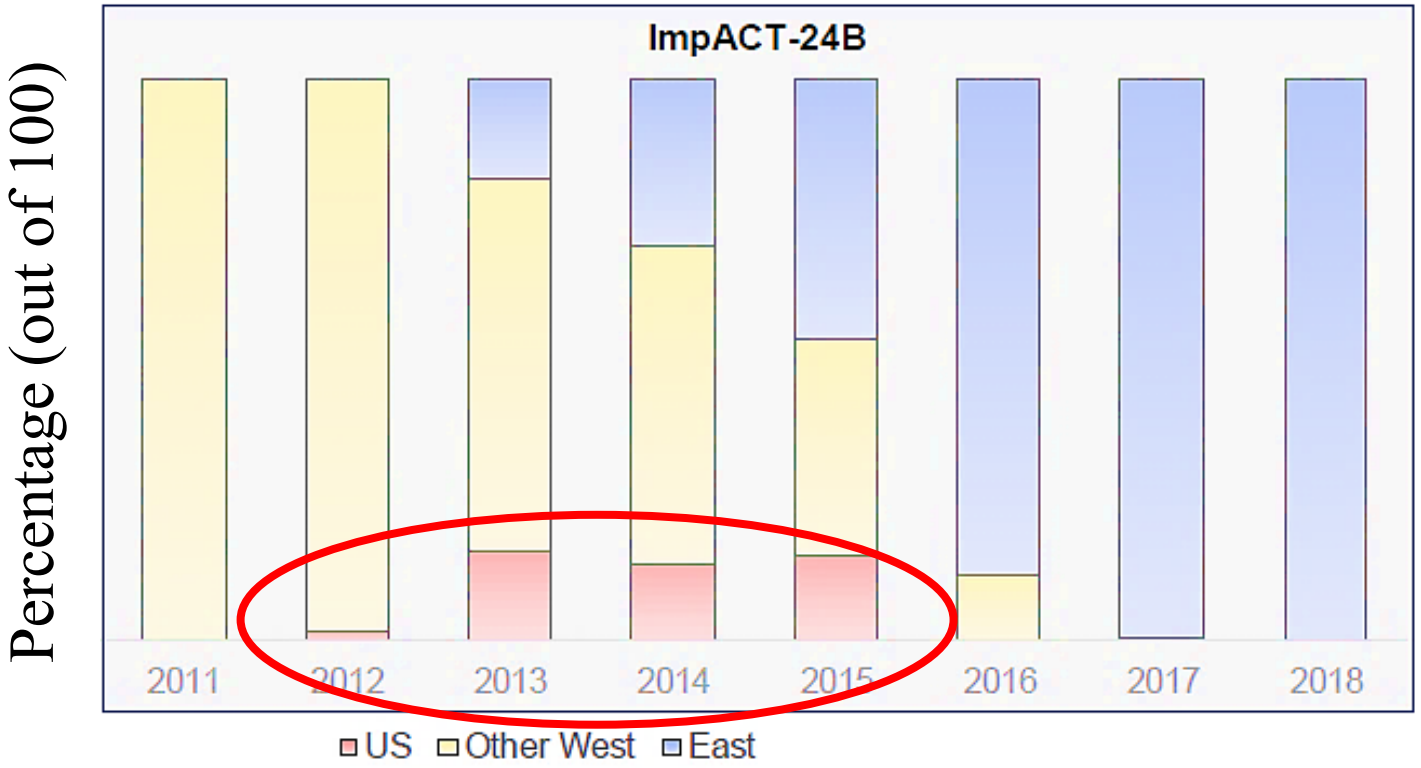
Of the 544 CCI patients randomized:

- 520 entered the mITT population,
- 244 were allocated to SPG stimulation,
- 276 allocated to sham stimulation.

Patients were removed:

- **34** from SPG stimulation.
- **0** from sham stimulation.

Enrollment by Country and Region



- The study only enrolled 60 mITT US subjects:
  - 33 SPG stimulation
  - 27 sham
- The last US patient was enrolled in 2015, and last visit of the study was in 2018.

*Endovascular therapy cleared in **2016** to improve functional outcomes

Primary Effectiveness Results in mITT and CCI

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

- The result on mITT is not statistically significant.
- The result on CCI is not statistically significant at the multiplicity-adjusted threshold of $p = 0.025$.
- Interpretation of clinical benefit is unclear.

ImpACT-24B: Other Study Outcomes

Added in the last year of the study, recommended by the steering committee.

- **Secondary Effectiveness Outcomes** (recommended by the Steering Committee in the last year of the study)**:**
  - mRS 0-2 (Functional independence) at day 90
  - mRS 0-3 (Capable of self-care or better) at day 90

- **Additional Effectiveness Outcomes**
  - SIS-16 (Stroke-related quality of life) at day 90
  - Covariate analysis of the primary and secondary efficacy parameters
  - Longitudinal analysis of ordinal mRS
  - RIKS-Stroke assessment at 180 and 360 days

Secondary and Additional Effectiveness Results on mITT and CCI

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

- The study did not meet its pre-specified primary effectiveness outcome measure.
- These results are presented for exploratory purposes for Panel consideration.

Subgroup Analysis in the ImpACT-24B CCI Population

- US CCI subgroup analysis on primary endpoint had a difference of 2.6% in SPG stimulation vs. Sham.

CCI subgroup

	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

- However, US mITT subgroup analysis on the primary endpoint favored sham stimulation.

mITT subgroup

	US Subjects			OUS Subjects			Interaction P-value
	SPG stim (N=33)	Sham stim (N=27)	Odds ratio (95% CI)	SPG stim (N=448)	Sham stim (N=492)	Odds ratio (95% CI)	
Sliding Dichotomy	36.4% (12/33)	48.1% (13/27)	36.4% (12/33)	49.6% (222/448)	45.3% (223/492)	1.18 (0.92-1.53)	0.23
mRS 0–2	39.4% (13/33)	51.9% (14/27)	39.4% (13/33)	44.4% (199/448)	41.3% (203/492)	1.14 (0.88-1.47)	0.24
mRS 0–3	69.7% (23/33)	74.1% (20/27)	69.7% (23/33)	67.4% (302/448)	62.4% (307/492)	1.25 (0.95-1.63)	0.46

Safety Evaluation

- The pre-specified safety analysis population included all patients in whom the implantation/sham procedure was initiated:
  - 536 SPG stimulation patients
  - 519 sham control patients

- Safety results are also presented for the two primary effectiveness analysis populations, the mITT and CCI populations.

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

Safety Evaluation: Serious Adverse Events

- The sponsor reported a similar safety profile between SPG and sham groups in the pre-specified safety outcomes, including:
  - Serious adverse events (SAEs)
  - 90-day mortality
  - Pneumonia
  - Neurological deterioration
  - Symptomatic intracranial hemorrhages (sICH)

Incidence of Serious Adverse Events

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

Incidence of sICH

	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

Safety Evaluation: Implantation Procedure

- Implantation / explantation serious adverse events by implant type:

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%)

- The number of failed implantations improved over time with device design modifications:

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

Safety Evaluation: Stimulation-Related Events

- No SAE was classified by investigators as definitely or probably related to the stimulation.
- The following events were classified as possibly related:

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

- Other stimulation-related events that occurred in at least 1% of the patients in either group:

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

ImpACT-24B: Important Points

- Primary effectiveness was analyzed on two patient populations (mITT and CCI subpopulations) of the ITT population.
  - Both subgroups did not meet the statistical threshold for the pre-specified primary outcomes.
- Only 6% of patients were US patients (31 CCI patients).
- The observed treatment effect was smaller in US patients than OUS patients.
- The device, study design, and statistical analysis plan were modified throughout the study. *The final device in the PMA was not studied in the ImPACT-24B pivotal study.*
- The sponsor reported that SPG stimulation did not increase the incidence of serious adverse events, symptomatic intracranial hemorrhage, or mortality compared to sham.
- Interpretation of clinical benefit is unclear, as will be discussed later.

ImpACT – 24M
(Usability Study)

2018

ImpACT-24M: Usability Study in Mild Stroke

- A prospective, multicenter, single arm 7-day usability study in 50 OUS patients evaluating the final ISS500 device design.
- Participants were mild stroke patients (NIHSS between 1 and 6).
- Hand strength was assessed and found increased in the SPG group on the second treatment day.
- Blood flow in the neck was measured by common carotid duplex (CCD) readings of blood velocity and vessel diameter and found increased in the SPG group on the second treatment day.
- High rate of successful implantation, short time and fewer AEs with the improved GuideView navigation system.

BrainsGate Ltd.'s Acute Ischemic Stroke System (ISS500):

Statistical Uncertainties of ImpACT-24B

Neurological Devices Advisory Panel Meeting
December 10th, 2021

Anhua Lin, Ph.D. – Mathematical Statistician
Division of Clinical Evidence & Analysis 2 (DCEA2)
Office of Clinical Evidence & Analysis (OCEA)
Office of Product Evaluation and Quality (OPEQ)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration (FDA)

Uncertainty - Few US Patients, Smaller Treatment Difference in US Patients

FDA is concerned that the US enrollment was low, and the treatment effect is smaller in the US compared to OUS; therefore, it is not clear whether the study results are applicable to the indicated US patients:

- US CCI enrollment was only 31 patients (active: 19, sham: 12) out of 520 total CCI patients in the final analysis set.

- Further, the treatment difference observed in the US CCI patients was smaller (US CCI patients: 2.6% difference from sham vs. 9.7% in all CCI patients).

BrainsGate's Justification for Smaller US Treatment Effect

- US CCI set was not balanced in some variables, including sex, diabetes, atrial fibrillation, obesity, and blood glucose.
- BrainsGate created a Logistic Regression Model based on 12 variables to account for the imbalance in these 5 variables, trained on all CCI patients.

	Sliding Dichotomous mRS Odds Ratio (OR) [95% CI]
OUS Treatment v.s. Sham	1.459 [0.972, 2.177]
US Treatment v.s. Sham	1.618 [0.303, 8.633]

- BrainsGates concluded "*once the imbalance is accounted for, the effect in the US is as good as (or even slightly higher than) the effect in other countries.*"

FDA's Discussion of BrainsGate's Analysis

FDA is not certain of BrainsGate's conclusion, because of:

- The small sample size and imbalanced variables. The US CCI SPG group (19) and US CCI Sham group (12) may not represent the indicated US patient population.
- The lower limit of the confidence interval for odds ratio of responder probability in US (0.303) is less than that in OUS (0.972).
- Post-hoc analysis naturally carries uncertainty as the result may not generalize to other US patients.

	Sliding Dichotomous mRS Odds Ratio (OR) [95% CI]
OUS Treatment v.s. Sham	1.459 [0.972, 2.177]
US Treatment v.s. Sham	1.618 [0.303, 8.633]

Uncertainty -- Few US Patients, Smaller Treatment Difference in US Patients

Uncertainty - Poolability of Countries

FDA is concerned that the data may not be poolable across countries and regions, because there are many low enrollment countries and a large variability in the difference of responder rates across countries.

COUNTRY	ACTIVE GROUP (N)	ACTIVE RESPONDER (%)	SHAM GROUP (N)	SHAM RESPONDER (%)	(ACTIVE - SHAM) RESPONDER (%)
GEORGIA	76	55.3%	72	48.6%	6.7%
SERBIA	49	40.8%	67	40.3%	0.5%
SPAIN	36	50.0%	50	40.0%	10.0%
UNITED STATES	19	52.6%	12	50.0%	2.6%
CZECH REPUBLIC	11	27.3%	10	10.0%	17.3%
POLAND	9	55.6%	15	33.3%	22.2%
FRANCE	7	57.1%	6	50.0%	7.1%
ISRAEL	6	50.0%	8	12.5%	37.5%
GERMANY	5	100.0%	11	9.1%	90.9%
PORTUGAL	5	0.0%	5	80.0%	-80.0%
MACEDONIA	5	40.0%	2	50.0%	-10.0%
HONG KONG	5	20.0%	6	33.3%	-13.3%
ITALY	3	66.7%	1	0.0%	66.7%
CANADA	3	33.3%	3	66.7%	-33.3%
SLOVAKIA	2	100.0%	0	.	.
FINLAND	2	100.0%	6	16.7%	83.3%
DENMARK	1	100.0%	1	100.0%	0.0%
UKRAINE	0	.	1	0.0%	.

BrainsGate's Poolability Analysis

- BrainsGate performed a poolability analysis using a Logistic Regression Model and reported a p-value of the interaction term between treatment and country = 0.52 for the CCI population.

- BrainsGate stated that "*the p-value was >0.15, a commonly used significance level of evaluating poolability of data.*"

- **FDA has concern with this analysis because there were so many countries with very low enrollment; therefore, poolability analysis might not have sufficient power to detect heterogeneity across countries.**
  - **In other words, a large p-value does not mean that there was no heterogeneity.**

FDA's Exploratory Analysis of Responder Rate by Country Enrollment

FDA conducted an exploratory analysis comparing the responder rate in the top 4 CCI enrollment countries to the rest of the countries in the study.

- Top four countries in CCI enrollment (Georgia, Serbia, Spain, United States):
  - 381 CCI patients
  - active: 50%, sham: 43.8%, **difference: 6.2%**

- The remaining 13 countries and Hong Kong:
  - 139 CCI patients
  - active: 48.4%, sham: 29.3%, **difference: 19.1%.**

This large difference further makes FDA concern about the poolability of the data and whether claim mainly based on OUS data is applicable to indicated US patient population.

Given the study uncertainty due to few US patients, smaller US treatment effect and poolability of countries, this afternoon, the panel will be asked to consider whether the overall results of the trials can be generalized to the U.S. indicated population.

Uncertainty - ITT Analysis/Validity of Randomization

FDA is concerned that the validity of randomization may not hold in the mITT-CCI population, because there was a significant imbalance in patient exclusion rate (12% vs. 0%) between SPG and sham groups.

Responder Performance in ITT and mITT				
	SPG	**Sham**	**Total**	**P-value**
mITT-CCI	244	276	520	0.026
ITT-CCI	278	276	554	0.12

Uncertainty - Sliding Dichotomy Accuracy

FDA is concerned that the sliding dichotomy scale (responder analysis) used as the primary study endpoint may not be accurate in measuring the device treatment effect in this clinical study.

- Sliding dichotomy mRS outcome used a logistic regression type of prognostic model, termed VISTA.
- The VISTA model took the baseline NIHSS, age, and stroke side, and predicted a patient's 90-day disease natural history outcome in mRS.
- A patient was considered a responder if the observed 90-day mRS:
  - Less than 5, and
  - Less than the predicted 90-day mRS from the VISTA model.

Validity of the VISTA Model Application

- Sliding dichotomy analysis with the VISTA model could be a good measure of effectiveness **IF the VISTA model were accurate** at predicting patients' disease natural history outcome.

- However, if the VISTA model predictions **were not accurate**:
  - A patient might be labelled as a responder simply because the VISTA model predicted too pessimistically, even if the treatment had no effect.
  - A patient might be labelled as a non-responder simply because the VISTA model predicted too optimistically, even if the treatment had some effect.

VISTA Model Accuracy (Using Original Model)

FDA is concerned with the low accuracy (22%) of the VISTA model predictions in this trial:

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

Original VISTA Sliding Scale Model

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

Actual mRS in Sham Group

Uncertainty - Sliding Dichotomy Accuracy

VISTA Model Accuracy (Using Revised Model)

VISTA model accuracy improved slightly (22% → 24%) when using a revised model that incorporated data from more recent stroke clinical trials:

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

Sponsor's Revised Sliding Scale Model

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

Can Randomization Account for VISTA Model Inaccuracy?

- Randomization may be sufficient for balancing non-confounders or weak confounders.

- It is not clear whether randomization can resolve the potential uncertainty caused by VISTA model inaccuracy.

- Moreover, the validity of randomization in the CCI analysis may not hold (as discussed in a previous uncertainty related to patient exclusions in ITT population, 12% for SPG vs. 0% for sham).

- **It is not clear to FDA to what extent that the observed results of the clinical trial were truly due to the device effect.**

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FDA Exploratory Analysis: Shift Analysis

- Null hypothesis: receiving SPG or Sham treatment was not associated with 90-day mRS
- More powerful than sliding dichotomy and crude fixed dichotomy methods in detecting treatment effect (according to a simulation study by BrainsGate).

	90-day mRS							
Frequency (row %)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**Total (row)**
SPG	9 (3.7%)	34 (13.9%)	42 (17.2%)	67 (27.5%)	20 (8.2%)	29 (11.9%)	43 (17.6%)	244
Sham	15 (5.4%)	23 (8.3%)	37 (13.4%)	66 (23.9%)	43 (15.6%)	45 (16.3%)	47 (17.0%)	276
Total (column)	24	57	79	133	63	74	90	520
CCI (p-value = 0.0748)								

- **The relatively large nominal p-value (0.0748) seems to indicate that the data do not provide strong statistical evidence to support the claim that SPG is superior to Sham treatment.**

Given the uncertainty raised from the validity of randomization and the accuracy of the VISTA model, this afternoon, the Panel will be asked to what extent they think the evidence shows that treatment with the ISS500 causes the difference observed in the clinical study.

Summary of Statistical Uncertainties

- Low US enrollment, small treatment difference in US patients
- Poolability of countries
- ITT analysis / Validity of randomization
- Sliding dichotomy accuracy

BrainsGate Ltd.'s Acute Ischemic Stroke System (ISS500):

Clinical Uncertainties of ImpACT-24B

Neurological Devices Advisory Panel Meeting
December 10th, 2021

Claudette Brooks, M.D. – Neurologist and Clinical Reviewer
Division of Neuro-interventional Devices (DHT5A)
Office of Neurological and Physical Medicine Devices (OHT5)
Office of Product Evaluation and Quality (OPEQ)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration (FDA)

Uncertainty – Clinical Trial Changes in ImpACT-24B

2011-2012 — Begin ImpACT-24B OUS and US enrollment

Feb 2014 — First Interim Analysis

Oct 2015 — Last US subject enrolled in ImpACT-24B trial

May 2016 — Second Interim Analysis

Jan-Feb 2018 — BrainsGate requested changes to statistical analysis plan and device:

- Add CCI subgroup analysis as a primary outcome, use Shift Analysis for the CCI subgroup.
- Redefine mITT patients as those in which the INS is placed < 5mm from the SPG (instead of 15 mm).

FDA **strongly** recommended that the sponsor use the dichotomous mRS analysis for the CCI subgroup analysis.

Mar-Apr 2018 — BrainsGate requested sliding dichotomous mRS analyses for both mITT and CCI populations.

FDA continued to recommended using the fixed dichotomous mRS as the primary analysis for the mITT and CCI.

June 2018 — FDA stopped communicating its recommendation to use fixed dichotomous mRS analysis.

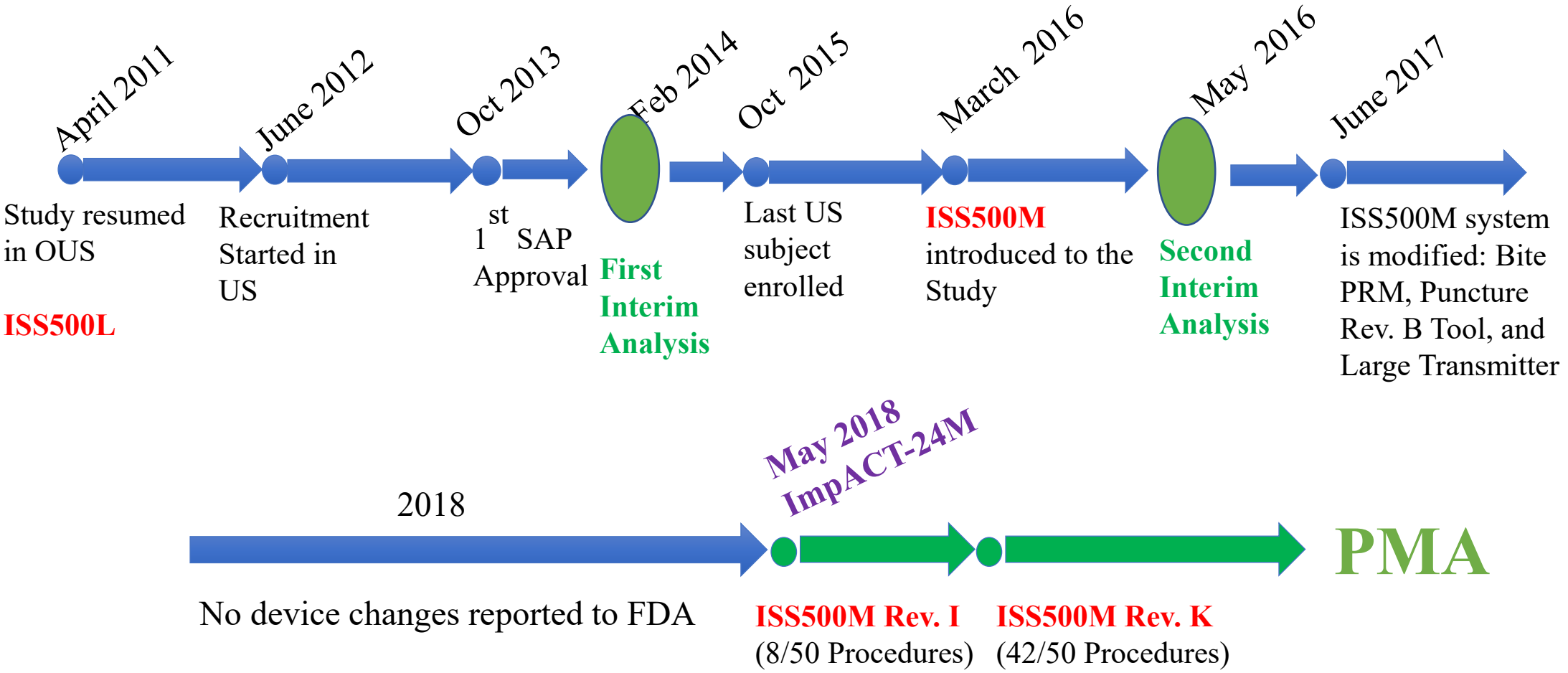
July 2018 — Last subject completed ImpACT-24B trial. After completion, BrainsGate requested:

- Addition of secondary effectiveness analyses dichotomy mRS 0-2 and dichotomy mRS 0-3
- Subgroup analyses by age, history of diabetes, history of atrial fibrillation.

May-Sept 2018 — ImPACT-24M usability study initiated and completed

Feb 2020 — **PMA Submitted to FDA**

Uncertainty – Clinical Trial Device Changes in 24B & 24M



A change in device design and how it was studied may have an impact on the effectiveness observed in clinical trials. Given the uncertainties raised from the changes implemented on the device, study design and statistical analysis plan, this afternoon, the Panel will be asked to consider whether the evidence from the clinical studies sufficient to accurately predict the effectiveness of the ISS500 in the proposed IFU population.

Uncertainties – Device Safety

The following uncertainties are about the safety of the device. After considering these uncertainties, the Panel will be asked to comment on the safety of the device, including:

- The risks of increasing cerebral blood flow in the target population,
- The rate of expected hemorrhage in the target population,
- Safety considerations related to the implantation/explantation procedure.

Risk Associated with Increasing Cerebral Blood Flow in Stroke Patients

- The sponsor claims that the device mechanism of action is to increase cerebral blood flow (CBF).
- There are several significant uncertainties about the safety of increasing cerebral blood flow in this clinical study, including:
  - Cerebral Perfusion Injury
    - The natural history of hemorrhagic transformation in acute ischemic stroke patients without intervention.
    - Concern that asymptomatic or symptomatic intracerebral hemorrhages that did not meet the threshold for neurologic deterioration and formal definition of sICH in the trial may not have been found or reported.
    - Use of the device and increasing CBF in days 2 through 5 while tissue is in a fragile state
  - CBF dose curve uncertain – changes in regional as well as systemic hemodynamics uncertain (systemic blood pressure, cerebral perfusion pressure, mean arterial pressure).

Uncertainty – Hemorrhage Transformation (HT) Rates

- ImpACT-24B reported low rate of sICH across both patient groups.

ImpACT-24B
Incidence of sICH

	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

- For comparison:
  - The rates reported for AIS patients without revascularization are 20-43%[1]
  - Incidence of spontaneous HT 38-71% in autopsy studies and 13-43% in CT studies with symptomatic HT ranging from 0.6-20%[2]

- It is not clear whether the imaging and surveillance methods used in the clinical trial were adequate to assess for sICH across all sites, leading to uncertainty about the rate of sICH/HT in the patient population.

1. Hornig, et al 1986 2. Zhang, J et al 2014

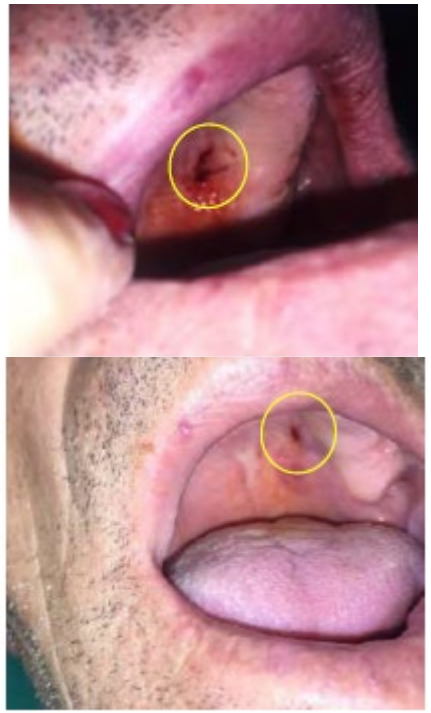
This afternoon, the Panel will be asked to consider:

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

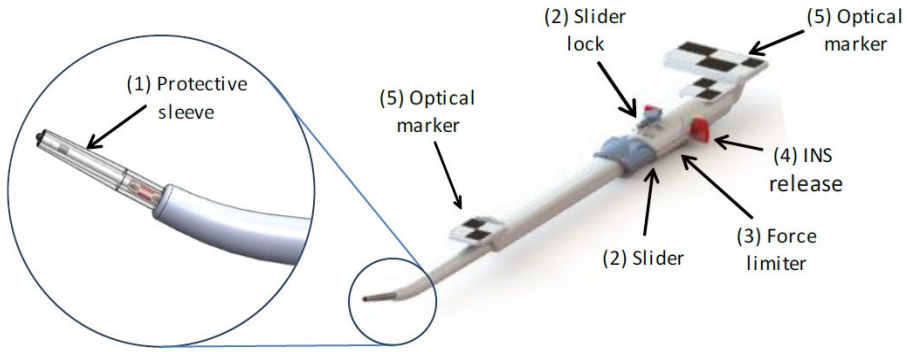
b) The rate of hemorrhage was quite a bit lower than expected in this population. Were the imaging methods and data adequate to assess this adverse event?

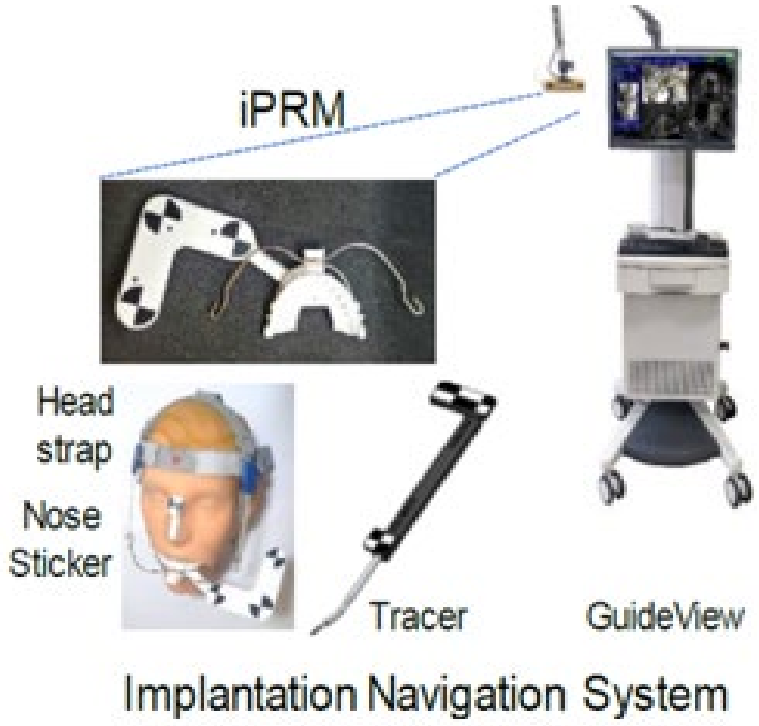
Uncertainty – Risks of Implantation/Explantation of the INS

Risk associated with direct and indirect consequences of implantation of the device and subsequent use that may have been under-represented in the clinical studies.



Introducer





Uncertainty – Risks of INS Implantation/Explantation

- Technical insertion difficulties for stroke patients who are already being treated with NSAIDs may result in palate laceration and bleeding and swelling, which could result in:
  - Airway endangerment,
  - Laryngospasm,
  - Microaspiration,
  - Chronic neuropathic pain,
  - Bleeding and hematoma formation,
  - Infection within the implantation site or extension to involve the SPG,
  - The associated serious subsequent consequences with the above.

- Risk to patients with sleep apnea or other chronic pulmonary conditions.
- The use or initiation of antiplatelet or antithrombotic drugs before, during or post implantation and explantation of the INS.
- The effects of pain secondary to the procedures on an acute stroke patient may include tachycardia and increased blood pressure.
- These adverse events were not observed in the study reports.

Procedural Performance and Expertise

- The sponsor reported that 306 of 481 (63.6%) of the ImPACT-24B implant procedures were performed by neurologists.
- The remaining 175 procedures were performed by neuroradiologists, surgeons, and anesthesiologists.

In the US:

- Neuroradiologists, surgeons, and anesthesiologists normally do not have experience with intervention in the oral cavity.
- Additionally, surgeons and anesthesiologists are not generally in attendance in stroke units in the United States.

- FDA is uncertain whether there be significant challenges for the implantation technique to be widely adopted in the US where the required implantation technique is not part of the traditional skillset of stroke teams.

Given uncertainty on the performance and expertise needed for the implantation procedure, this afternoon the Panel will be asked:

a) Do you have any concerns regarding the safety of using the Implantation Navigation System to implant the INS in a location near the SPG?

b) What expertise would be needed to safely and effectively use the device based on the training program proposed by the sponsor?

BrainsGate Ltd.'s Acute Ischemic Stroke System (ISS500):

Benefit/Risk Discussion of ImpACT-24B

Neurological Devices Advisory Panel Meeting
December 10th, 2021

Claudette Brooks, M.D. – Neurologist and Clinical Reviewer
Division of Neuro-interventional Devices (DHT5A)
Office of Neurological and Physical Medicine Devices (OHT5)
Office of Product Evaluation and Quality (OPEQ)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration (FDA)

Proposed Indications For Use

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

Benefits

- The 90-day sliding dichotomous mRS analysis in the ImpACT-24B study was reported:
  - In the mITT population, SPG stimulation vs. sham was 48.6% vs. 45.5% (p=0.31).
  - In the CCI population, SPG treatment vs. sham was 49.6% vs 39.9% (p=0.0258).

- Other analyses in the mITT and CCI sub-populations showed minimal improvement in outcomes over sham.

- Device is to be used in patients unable to obtain other available stroke treatments in less than 24 hours.

Uncertainty Surrounding Benefits

- Concerns about whether there is actual treatment effect that benefits patients:
  - Study results did not reach pre-specified effectiveness threshold.
  - Changes throughout the clinical study in:
    - Clinical protocol
    - Statistical analysis plan
    - Device design
    - Device implantation ‘success’ criteria
  - It is not clear that randomization validity held.
  - Whether the study has external validity, particularly to US CCI population:
    - Small sample size
    - Poolability
    - Risk factor imbalances between sham and stimulation.
  - Sham outperformed SPG stimulation in some outcome assessments.

Risks

- Approximately 1/3 of patients experienced serious adverse events in the ImPACT-24B clinical trials.

- Rates of adverse events were similar in active and sham arms, except for pain and lacrimation (which were significantly higher in active arm).

- One seizure occurred in the active arm, which is a known consequence of neurostimulation.

- Cerebral reperfusion injury occurred in both arms.

Uncertainties Related to Risk

- The usual adverse events seen in acute ischemic stroke patients were not observed (based on clinical literature).
- It is unclear whether the imaging and monitoring methods were sufficient to capture all reperfusion injury related events, including hemorrhagic transformation and edema.
- The safety of cerebral reperfusion during the initial 8-24 hours and subsequent 4 days of SPG stimulation.
  - CBF and the dose response curve in the intended patient population.
  - Actual cerebral blood flow increase in the intended population.
- Long term adverse events related to pain syndromes related to implantation

Summary of Benefit and Risk

- The observed effectiveness in the treatment population and other clinically relevant outcomes at 90 days did not meet pre-specified thresholds for significance.
- There are areas of uncertainty related to the data and results surrounding the device's effectiveness and its applicability to its target population of US patients with acute ischemic stroke, due to a small sample size and reduced treatment effect in US patients, imbalance in risk factors between US and overall study populations, and reliance on an inaccurate model.
- While the rate of adverse events observed in the study did not differ significantly between active and sham groups, there is uncertainty as to whether all notable adverse events could be adequately captured, long-term pain syndromes, and the safety of cerebral reperfusion during the device's treatment duration.

Closing Remarks

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Thank You