CO-1

# Ischemic Stroke System for Treatment of Patients with Acute Ischemic Strokes

**December 10, 2021**

Neurologic Devices Panel

BrainsGate

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## Introduction

**Jeffrey Saver, MD, FAAN, FAHA**

Director, UCLA Comprehensive Stroke and Vascular Neurology Program

SA Vice-Chair and Professor of Neurology, DGSOM

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## Acute Ischemic Strokes are Devastating Events, Result in Lifetime of Disability and Reduced QoL

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- Guidelines recommend timely reperfusion with pharmacologic IV-tPA or Endovascular Thrombectomy
  - Improve neurological outcomes
  - Reduces long-term disability
- Use is time dependent, requires administration within 6 hours
  - Treatment in 6-to-24-hour window limited to select patients

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## ISS500 is First-of-a-Kind Treatment for Patients with Acute Ischemic Stroke

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- Clinical program started in 2006
- 4 clinical trials
  - 2 randomized, sham-controlled
- > 1,400 patients enrolled
- 100 sites globally (11 US)

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## Totality of Evidence Supports Positive Benefit-Risk for Ischemic Stroke System

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- Patients with confirmed cortical involvement, treated 8 to 24 hours after stroke onset, achieved consistent improvements
  - Favorable disability outcomes
  - Improved long-term QoL
- Favorable safety profile
  - Reduced risk of symptomatic ICH
- Final system has efficient and reliable usability

**SPG Stimulation fills treatment gap for many patients who are ineligible or have no access to current reperfusion therapies**

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## Proposed Indication for Ischemic Stroke System

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*"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)."*

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# FDA Discussion Questions / Concerns Addressed in Presentation

| Topic | Keywords |
|---|---|
| Timing of major changes, including CCI subgroup | CCI addition |
| | Device change |
| Generalizability to US population | Generalizability US |
| Use of sliding dichotomous scale | Sliding dichotomy |
| mITT analysis | mITT analysis |
| Overall safety and potential AEs | Safety |
| Implantation skills | Implantation |
| Real-world selection of CCI patients | Patient selection |

FDA Discussion "Keywords"

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| | |
|---|---|
| Ischemic Stroke System | **Tom Devlin, MD, PhD, FSVIN**<br>Director, CHI Memorial Stroke & Neuroscience Center<br>Director, Chattanooga Center for Neurologic Research LLC<br>Professor of Neurology, University of Tennessee Health Science Center |
| Unmet Need & Pathophysiology | **Michael Hill, MD, MSc, FRCPC**<br>President, Canadian Neurological Sciences Federation<br>Professor, Dept Clinical Neuroscience & Hotchkiss Brain Institute<br>Cumming School of Medicine, University of Calgary & Foothills Medical Centre |
| MoA of SPG Stimulation & Effectiveness & Safety Results | **Jeffrey Saver, MD, FAAN, FAHA**<br>Director, UCLA Comprehensive Stroke and Vascular Neurology Program<br>SA Vice-Chair and Professor of Neurology, DGSOM |
| Training & Post-Approval Plan | **Eyal Shai, EMBA**<br>Chief Technology Officer<br>BrainsGate |
| Clinical Perspective | **Michael Hill, MD, MSc, FRCPC** |

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# Additional Experts

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Vice Chair for Clinical Affairs
Department of Neurology, Perelman School of Medicine, University of Pennsylvania
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## Chris Mullin

Statistician
Director, Product Development Strategy
NAMSA

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# Ischemic Stroke System

**Tom Devlin, MD, PhD, FSVIN**

Director, CHI Memorial Stroke & Neuroscience Center
Director, Chattanooga Center for Neurologic Research LLC
Professor of Neurology, University of Tennessee Health Science Center

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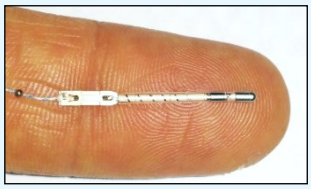
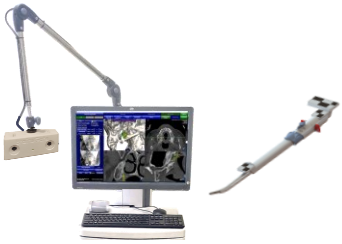
# ISS500 System Components



## Neurostimulator

Positioned next to sphenopalatine ganglion (SPG) via natural canal in hard palate



## Navigation System and Injector

Facilitates safe and accurate positioning while minimizing risks or complications

## External Treatment System

Activates neurostimulator to deliver electrical pulses within predefined range

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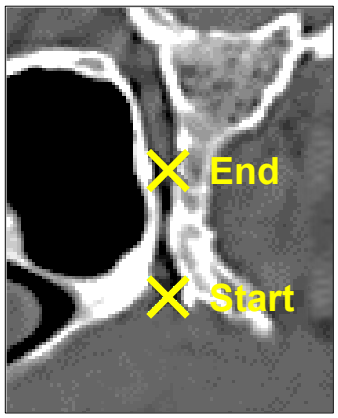
# Preparation for Implant Procedure

1. **Patient Preparation**
   - Reference marker
   - Nose marker
2. **Implantation CT**
3. **Local Anesthesia**
4. **Planning**

**Reference Markers**




**Implanter Marks Canal Path on CT**

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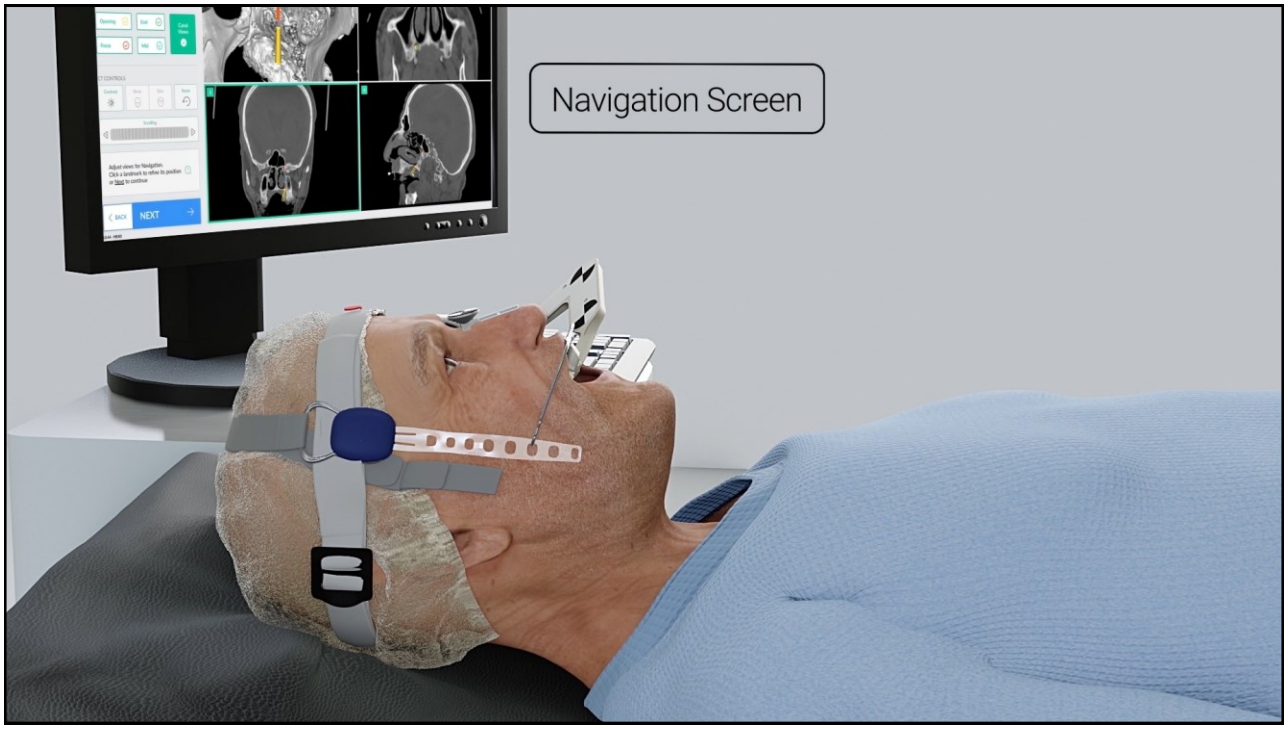


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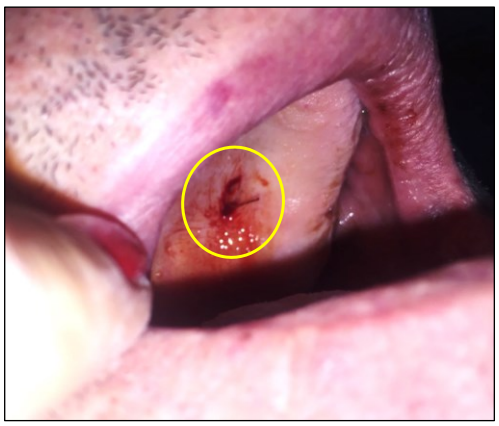
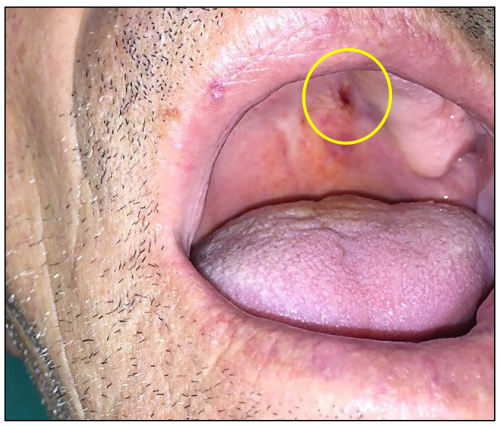
## Simple, Technically Straightforward Procedure Poses Minimal Risk to Patient



**Day 1**
**Immediately after**
**Implant Procedure**



**Day 5**
**After Implant Removed**

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# Current Implant Reduces Procedure Times and Implant Complications

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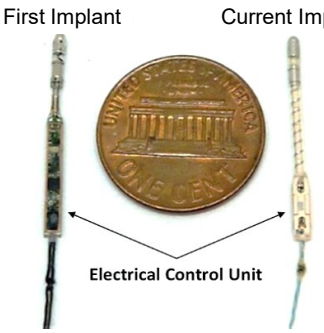


| | First Implant | Current Implant |
|---|---|---|
| Mechanical structure | Fragile | Flexible, strong |
| Requires trocars | Yes | No |
| Stimulation delivery | Identical | |

**All changes intended to optimize implant placement and improve overall safety; stimulation delivery - identical**

**FDA Concern: Device Change**

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# Optimal Dosing Range Identified During Clinical Development

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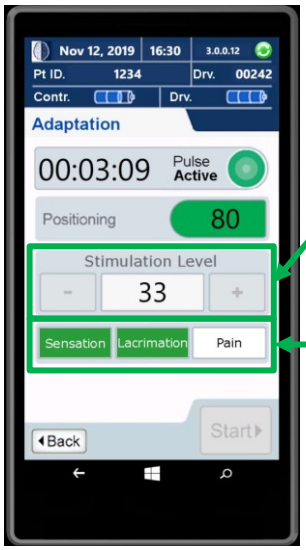
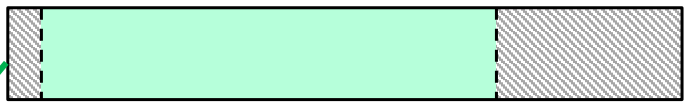



- Final Treatment System delivers stimulation within predefined optimal range




- Stimulation level set based on physiologic signs of SPG activation

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# Unmet Need and Pathophysiology

**Michael Hill, MD, MSc, FRCPC**

President, Canadian Neurological Sciences Federation

Professor, Department Clinical Neuroscience & Hotchkiss Brain Institute

Cumming School of Medicine, University of Calgary & Foothills Medical Centre

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## Acute Ischemic Stroke is Major Cause of Death and Disability in United States

- > 800,000 patients experience stroke each year in US
  - ~85% of all strokes are ischemic
- 1st leading cause of acquired neurological disability
- 2nd leading cause of dementia
- 5th leading cause of death in US
  - 100,000 acute ischemic stroke deaths per year in US

AHA Heart Disease and Stroke Statistics, Circulation 2021

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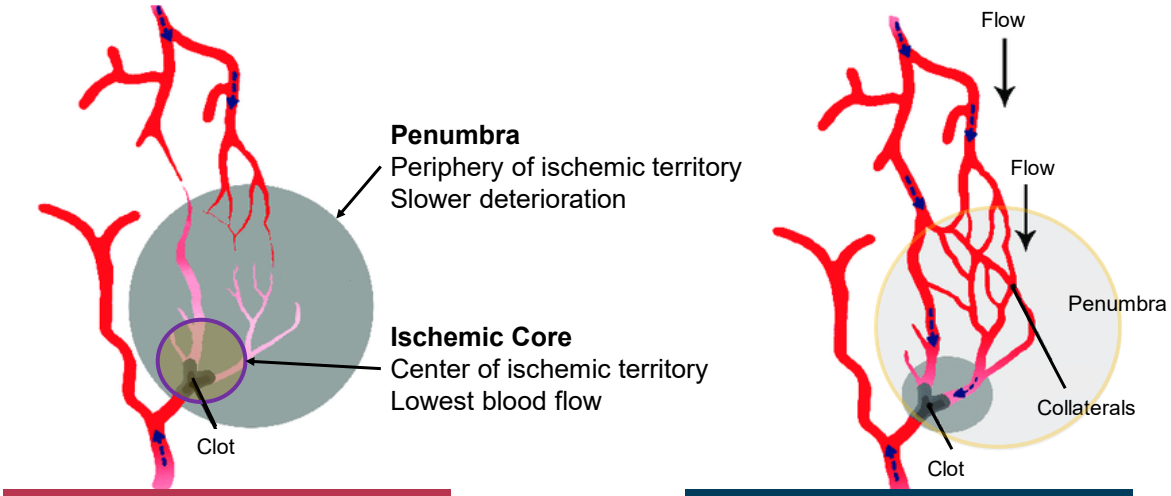
# Strokes Cause Cascade of Cellular and Molecular Events, Leading to Extensive Damage




**Poor Collaterals**
Faster Penumbral Deterioration

**Better Collateral Flow**
Slower Penumbral Deterioration

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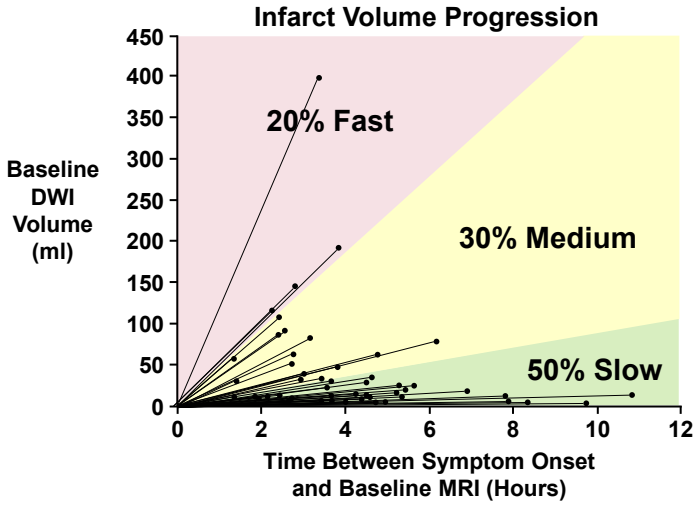
# ~50% of Patients Have Salvageable Tissue 24 Hours After Stoke




Wheeler, 2015

High variability of infarct progression by patient

- **Poor collaterals** "fast progressors"
- **Adequate collaterals** slower progression, more salvageable tissue

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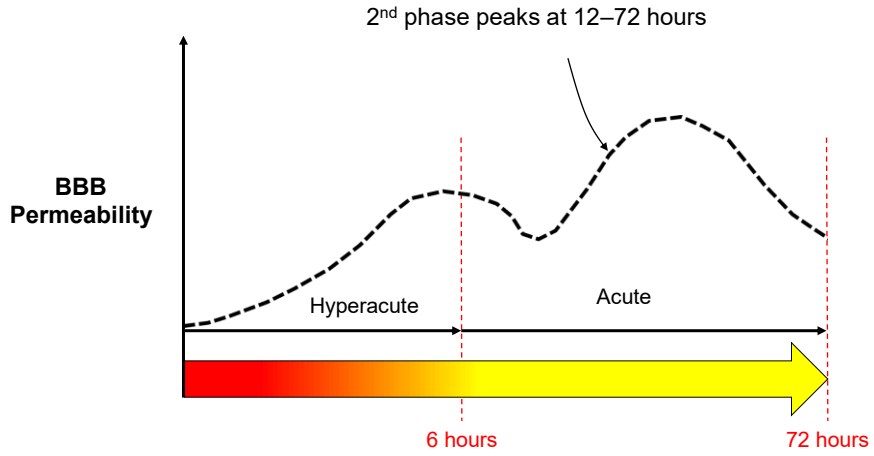
# Blood-Brain-Barrier Compromised Due to Stroke




Bernado-Castro, 2020

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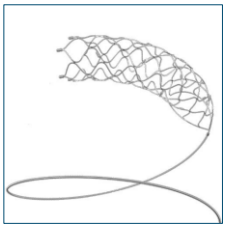
# Two Primary Treatment Options for Patients with Ischemic Stroke

**Pharmacologic IV-tPA**

- First-line therapy
- Recommended initiation within 4.5 hours from stroke onset
  - Use restricted to within 3 hours in US
- Select patients may benefit up to 9 hours post-stroke



**Endovascular Thrombectomy (EVT)**

- Endovascular approach to remove offending thrombus and restore anterograde perfusion
- Typically < 6 hours from onset
- Use limited to select patients between 6 and 24 hours

IV-tPA = intravenous tissue plasminogen activator

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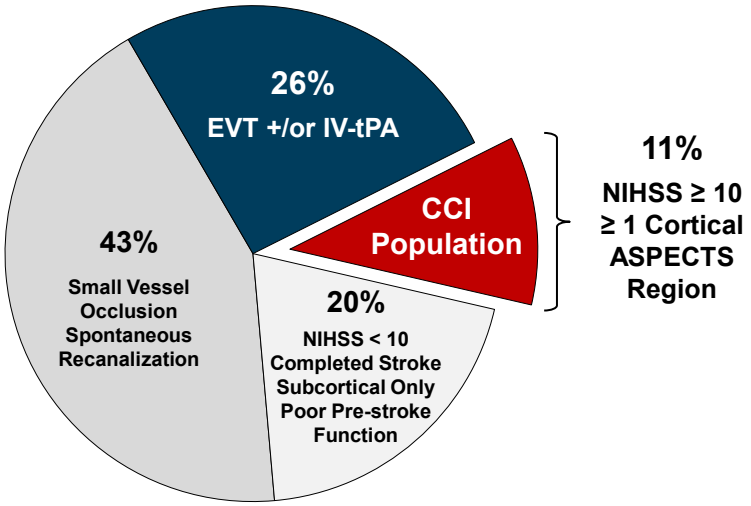
# Unmet Need for Patients with Acute Ischemic Stroke < 24 Hours

**IV-tPA Ineligibility**

- Outside time window
- On anticoagulant

**EVT Ineligibility**

- Clots too distal
- Tortuous anatomy
- Carotid artery chronically occluded
- Damage too extensive




Bahr Hosseini, 2018; Desai 2020

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# SPG Stimulation and Data Supporting MoA

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Director, UCLA Comprehensive Stroke and Vascular Neurology Program

SA Vice-Chair and Professor of Neurology, DGSOM

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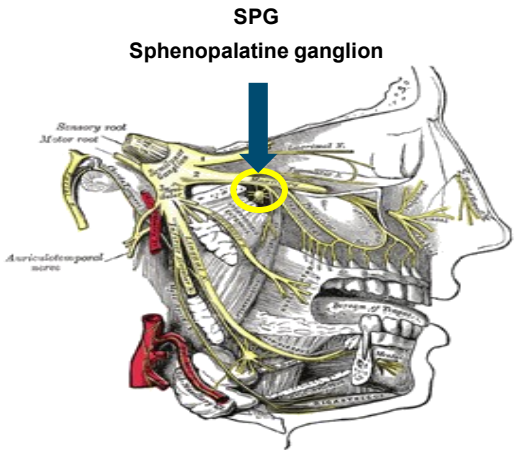
# The Sphenopalatine Ganglion (SPG)

- Anatomy
  - Pterygopalatine fossa
  - Posterior to maxillary sinus
  - 3 mm, 60,000 nerve cells
- Components
  - Parasympathetic cell bodies
  - Traversing sympathetic and sensory
- Functions
  - Dilation of anterior cerebral circulation
  - Dilation of meningeal and dural vessels
  - Secretomotor function to nasopharyngeal mucosa and lacrimal gland

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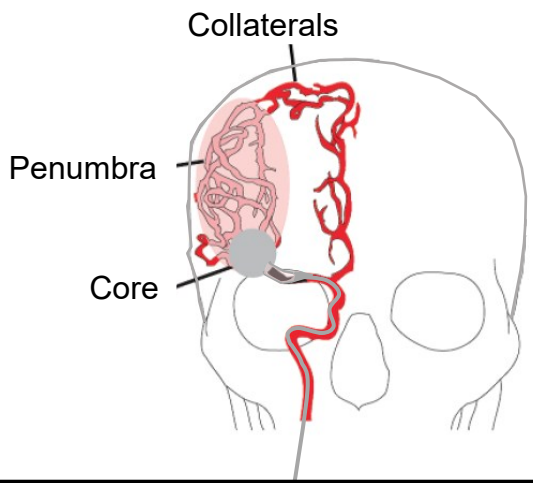
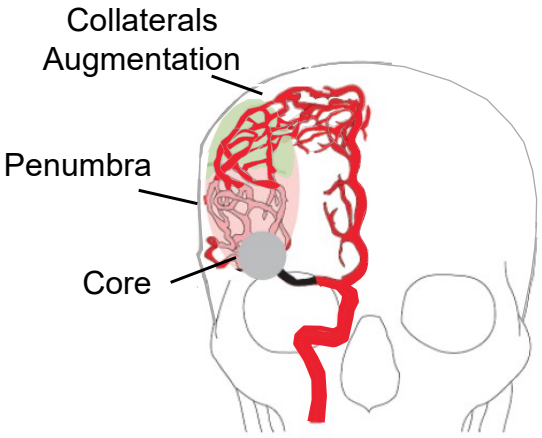
# Direct Reperfusion vs Collateral Flow Augmentation

**EVT**




**SPG Stimulation**

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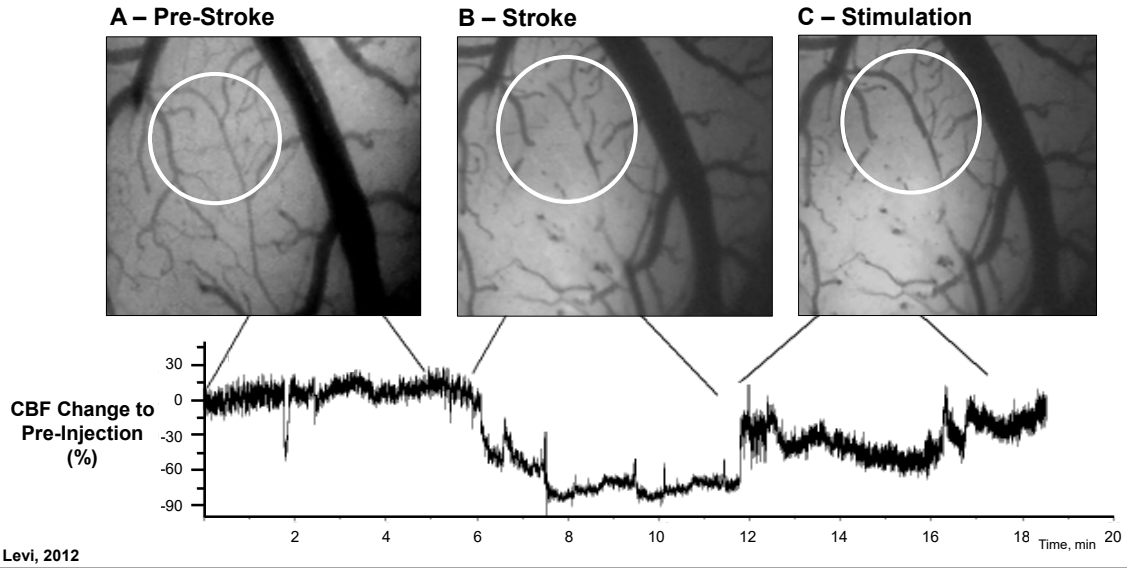
# SPG Stimulation Increases Blood Flow in Ischemic Penumbra




Levi, 2012

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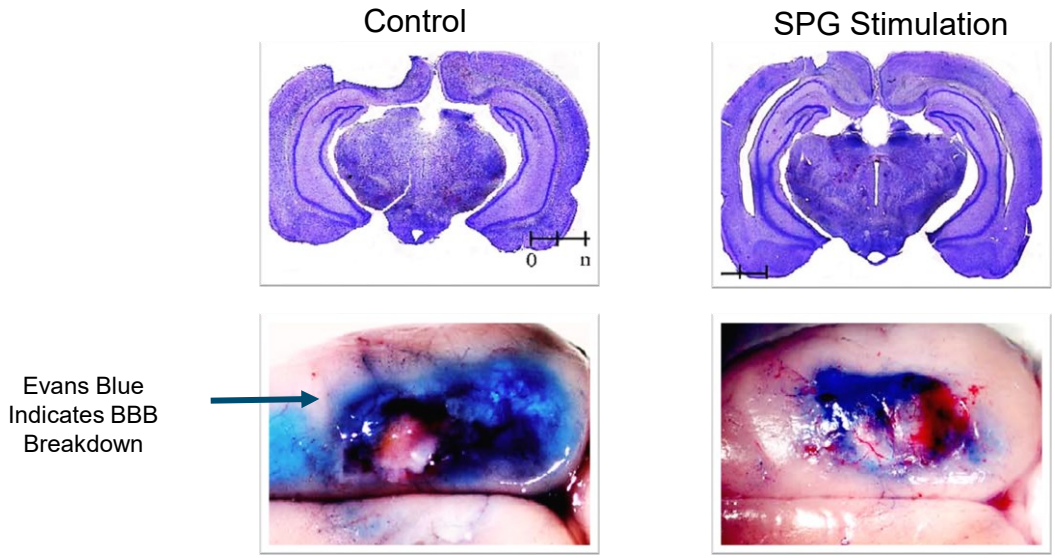
# SPG Stimulation Reduces Infarct Volume and Stabilizes Blood Brain Barrier




Levi, 2012

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# Cerebral Blood Flow Increases in Inverse U-Shaped Dose Response

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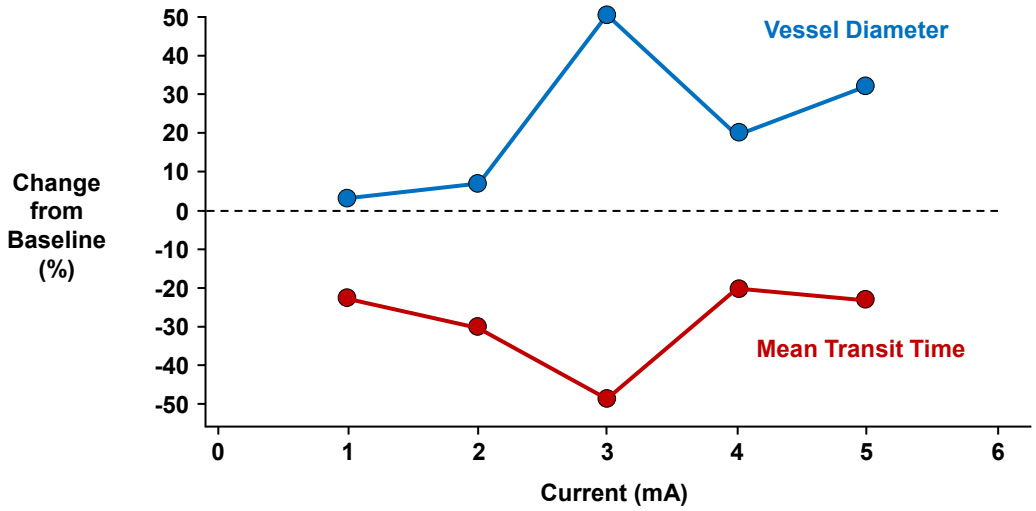


Levi H, 2012

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# Case Study Shows Greatest SPG Effect on Cortical Region After Stimulation

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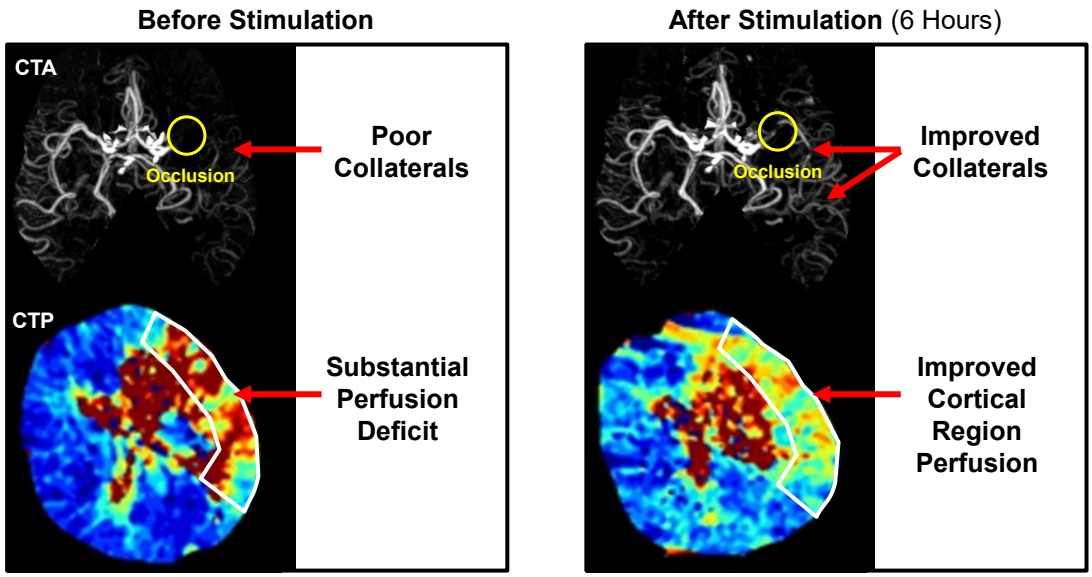


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# Clinical Trial
# Effectiveness & Safety Findings

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## Clinical Studies – Over 1,400 Patients in 4 Trials

| | ImpACT-1 | ImpACT-24A | ImpACT-24B | ImpACT-24M |
|---|---|---|---|---|
| Aim | Feasibility Tolerability | Supportive | Pivotal | Usability |
| Design | Single Arm | Phase 2B RCT | Pivotal RCT | Single Arm |
| Primary Endpoint(s) | Rx Completion SAEs | mRS at 3 Months | mRS at 3 Months | Optimized Delivery CCA Flow/Hand Strength |
| Dates | 2006 – 2008 | 2009 – 2011 | 2011 – 2018 | 2017 – 2018 |
| Patients (N) | 98 | 253 | 1000 | 50 |
| Centers | 12 OUS | 6 US / 35 OUS | 7 US / 66 OUS | 4 OUS |

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# ImpACT-24B Pivotal Trial

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## ImpACT-24B: Prospective Randomized, Double Blind, Sham-Controlled, Parallel Arm, Multi-Center Trial

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| | Study Design |
|---|---|
| **Objective** | Efficacy & safety in anterior circulation stroke in 8 – 24h window |
| **Design** | Randomized, double-blind, sham-controlled |
| **Primary endpoint** | mRS improvement beyond expectations at 3 months (sliding dichotomy) |
| **Enrollment** | 18 countries, 73 sites, 1,000 mITT patients, June 2011 – March 2018 |

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# Key Inclusion / Exclusion Criteria

| Inclusion | Criteria |
|---|---|
| **Age** | Male 40–80<br>Female 40–85 |
| **NIHSS** | 7–18 |
| **Time from stroke onset** | 8–24h |
| **Clinical & radiological** | Anterior circulation |

| Exclusion | Criteria |
|---|---|
| **Imaging** | ▪ ICH<br>▪ Massive (>2/3)<br>▪ Lacunar<br>▪ Posterior circulation |
| **Reperfusion therapy** | ▪ IV thrombolysis<br>▪ EVT |

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# ImpACT-24B Study Flow

| Time Period | Activity |
|---|---|
| **Day 1** | ▪ Baseline imaging<br>▪ 1:1 dynamic randomization<br>▪ Neurostimulator / Sham implantation |
| **Days 1-5** | ▪ Daily SPG / Sham stimulation |
| **Day 5** | ▪ Follow-up imaging<br>▪ Implant / Sham removal<br>▪ Day 5 mRS, NIHSS |
| **Follow-up** | ▪ Day 30, 60 mRS, NIHSS<br>▪ Day 90 mRS (blinded observer), NIHSS, SIS-16 |

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# Blinding in ImpACT-24B Was Extensive and Effective

| Study Procedure | SPG | Sham Control |
|---|---|---|
| **Baseline CT** | Brain + PGP canal and fossa | Brain |
| **Patient reference / navigation marker** | Y | Y |
| **Local anesthesia** | Y | Y |
| **Implantation procedure** | Mucosa puncture + implant placement | Mucosa puncture |
| **5 days treatment** | Stimulation + vibration | Vibration |
| **Transmitter sticker/positioning** | Y | Y |
| **Stimulation adaptation** | Comfortable tolerance level (stim) | Comfortable tolerance level (vib) |
| **Day 5 follow-up CT** | Brain + electrode position | Brain |
| **Implant removal** | Mucosa touching + implant removal | Mucosa touching |
| **Assessments by blinded observer** | Y | Y |

*James Blinding Index: blinding success in patients and assessors*

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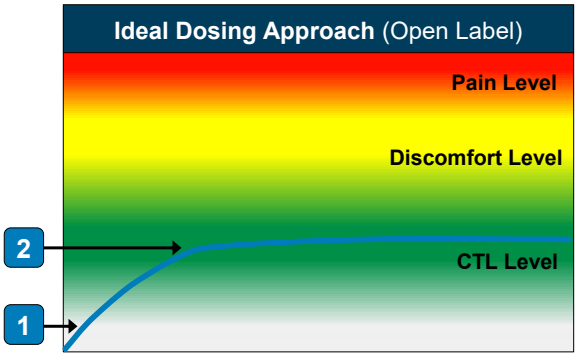
# Individualized Dose Selection Method Had to Be Modified to Maintain Blinding in ImpACT-24B




1. Start low, escalate in steps
2. Reach minimal sensation / lacrimation level, set as comfortable tolerance level (CTL)
   Treat at this intensity

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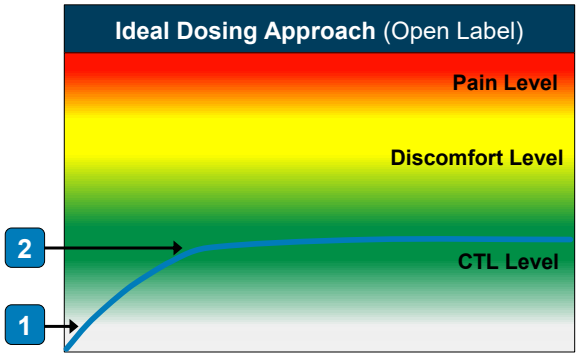
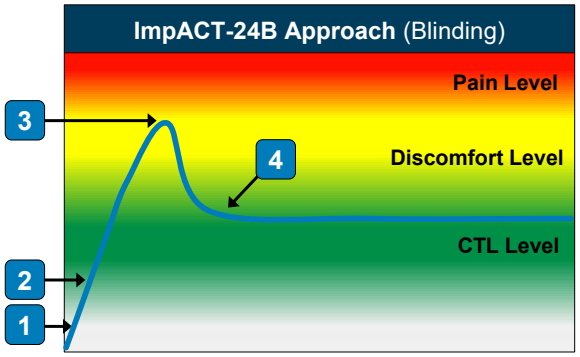
# Individualized Dose Selection Method Had to Be Modified to Maintain Blinding in ImpACT-24B




1. Start low, escalate in steps
2. Reach minimal sensation / lacrimation level, set as comfortable tolerance level (CTL) Treat at this intensity




1. Start low and escalate in steps
2. Minimal sensation level – continue escalation
3. Mild discomfort level – lower in steps
4. Reach CTL - Treat at this intensity

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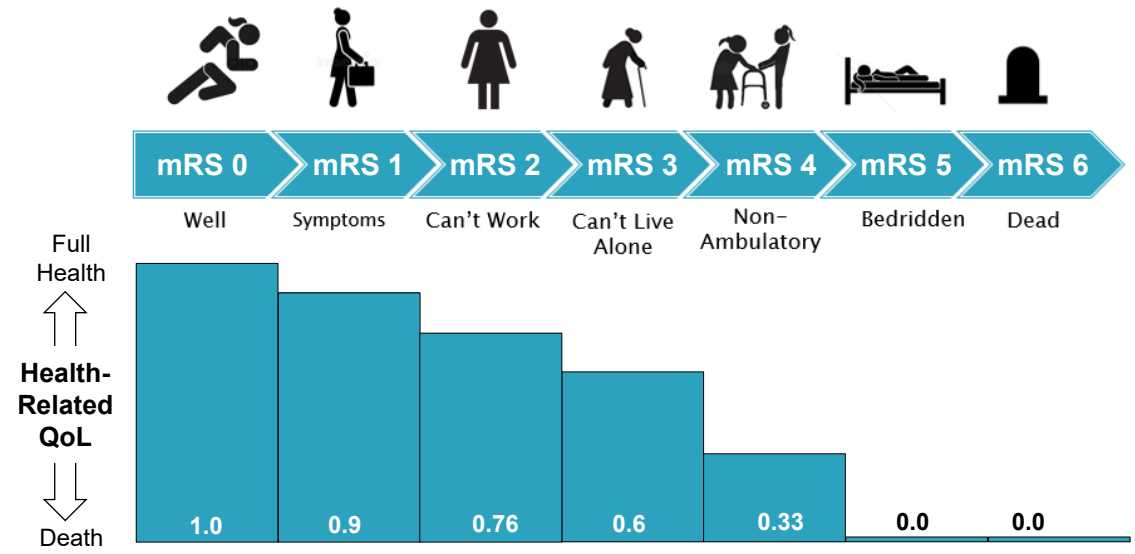
# Primary Endpoint – Disability (mRS) at 90d




Chaisinanunkul, 2015

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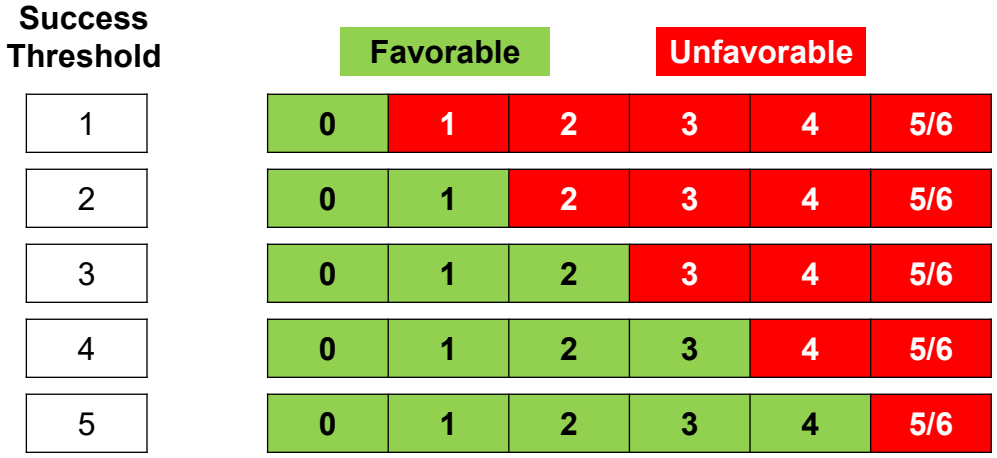
## Primary Endpoint: Success Threshold Based on Patient Age, NIHSS, Brain Side (VISTA Model)




Hosmer Lemeshow goodness of fit: Good model performance

FDA Question: Sliding Dichotomy

AbESTT II, 2008; PAIS, 2009; European Stroke Organization Outcomes Working Group, 2012; Stroke Therapy Academic Industry Roundtable, 2013

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## Two Pre-Specified Primary Analysis Populations

1. Modified intention to treat (mITT)
   - All patients in SPG and sham-control groups who received at least 1 full stimulation session

2. Confirmed cortical involvement (CCI)
   - All mITT patients with
     - NIHSS ≥ 10
     - At least one cortical ASPECTS region

FDA Concern: Patient Selection

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## Multiplicity Controlled Using Hochberg Procedure

- Study succeeds if:
  - $p < 0.05$ in both populations

  **or**
  - $p < 0.025$ in one population

Hochberg, 1988; Multiple Endpoints in Clinical Trials: FDA Draft Guidance, 2017; Lees, 2018

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## CCI Addition Approved By FDA Prior To Unblinding

| | |
|---|---|
| **2014 & 2016** | Interim analyses (sample size / futility)<br>▪ No subgroup analyses conducted by DSMB<br>▪ **Sponsor and steering committee blinded** |
| **Jun 2017** | External development– DAWN result<br>▪ 1st study to show benefit in 24-hour window<br>▪ Salvageable tissue identifiable by NIHSS & imaging<br>▪ Post-hoc evaluation on ImpACT-24A |
| **Jan 2018** | CCI added as co-primary analysis population<br>▪ FDA approved – Jun 2018 |
| **Jul 2018** | **ImpACT-24B data unblinded** |

**FDA Question: CCI Addition**

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## Secondary Efficacy Endpoints

- At Day 90
  - Functional independence (mRS 0 – 2 vs 3 – 6)
  - Able to walk + body self-care (mRS 0 – 3 vs 4 – 6)
  - Stroke-related QoL (Stroke Impact Scale [SIS]-16)
  - Disability-related QoL (utility-weighted mRS, post-hoc)

- Long-term (at 180 and 360 days)
  - Patient-reported stroke-impact assessment (RIKS-Stroke)

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## Demographics

| | mITT Population | | CCI Population | |
|---|---|---|---|---|
| | **SPG** N = 481 | **Control** N = 519 | **SPG** N = 244 | **Control** N = 276 |
| **Age; median** (years) | **70** | **71** | **70** | **72** |
| **Female** | **50%** | **52%** | **48%** | **49%** |
| **Pre-stroke mRS > 0** | **8.5%** | **5.6%** | **8.6%** | **6.2%** |
| **Hypertension** | **87%** | **84%** | **87%** | **85%** |
| **Diabetes** | **24%** | **27%** | **22%** | **24%** |
| **Atrial Fibrillation** | **25%** | **26%** | **34%** | **31%** |

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# Baseline Characteristics

| | mITT Population | | CCI Population | |
|---|---|---|---|---|
| | **SPG** N = 481 | **Control** N = 519 | **SPG** N = 244 | **Control** N = 276 |
| **NIHSS; median** (IQR) | **12** (9, 14) | **12** (9, 14) | **13** (12, 15) | **13** (11, 15) |
| **Left Brain Stroke** | **57%** | **50%** | **57%** | **52%** |
| **ASPECTS; median** (IQR) | **7** (6, 9) | **7** (6, 9) | **7** (5, 8) | **7** (5, 8) |
| **Time from last-known-well to first stimulation; median** (hours) | **19.9** | **18.7** | **19.7** | **18.5** |

47

CO-48

# Primary Efficacy Results

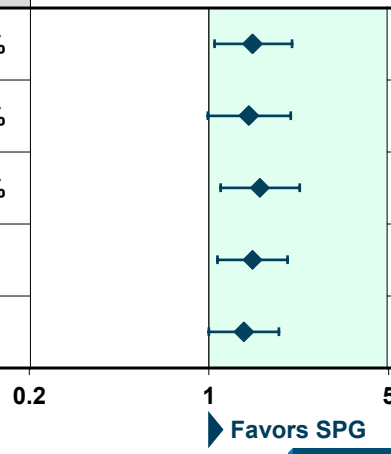
| | SPG | Control | Absolute Difference | Odds Ratio (95% CI) | p-value | Threshold |
|---|---|---|---|---|---|---|
| **mITT** (N = 1000) | **48.6%** | **45.5%** | **3.2%** | **1.14** (0.89, 1.46) | **0.31** | **0.05** |
| **CCI** (N = 520) | **49.6%** | **39.9%** | **9.7%** | **1.48** (1.05, 2.10) | **0.0258** | **0.025** |

48

CO-49

# Consistent Effect Indicated by All Primary and Secondary Efficacy Endpoints

| CCI | SPG N = 244 | Control N = 276 | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **Primary Endpoint** Sliding Dichotomy mRS | **49.6%** | **39.9%** | **1.48** (1.05, 2.10) | **0.0258** |
| **Functional Independence** Dichotomy mRS 0-2 | **34.8%** | **27.2%** | **1.43** (0.99, 2.08) | **0.06** |
| **Walk and Self Care** Dichotomy mRS 0-3 | **62.3%** | **51.1%** | **1.58** (1.11, 2.25) | **0.01** |
| **Stroke-Related QoL** 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** |




FDA Question: Sliding Dichotomy

49

CO-50

# Benefits Persisted Through 1-Year Follow-up Further Confirming the Positive Effects of SPG Stimulation

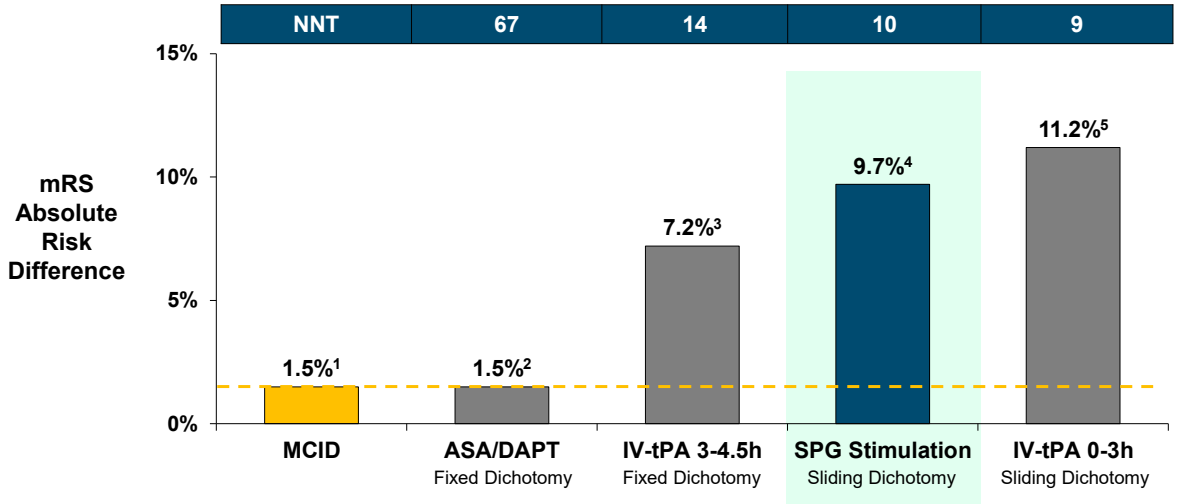
| CCI RIKS – 360 Days | Odds Ratio (95% CI) | p-value |
|---|---|---|
| **Dependency** | **1.37** (0.99, 1.88) | **0.06** |
| **Residence** | **1.26** (0.91, 1.73) | **0.16** |
| **Mobility** | **1.34** (0.97, 1.86) | **0.07** |
| **Toileting** | **1.37** (0.96, 1.94) | **0.08** |
| **Dressing** | **1.58** (1.11, 2.23) | **0.01** |


SPG Stimulation (N=241); Sham-Control (N=271)

50

CO-51

# SPG Effect Magnitude Consistent with Standard of Care for Ischemic Stroke



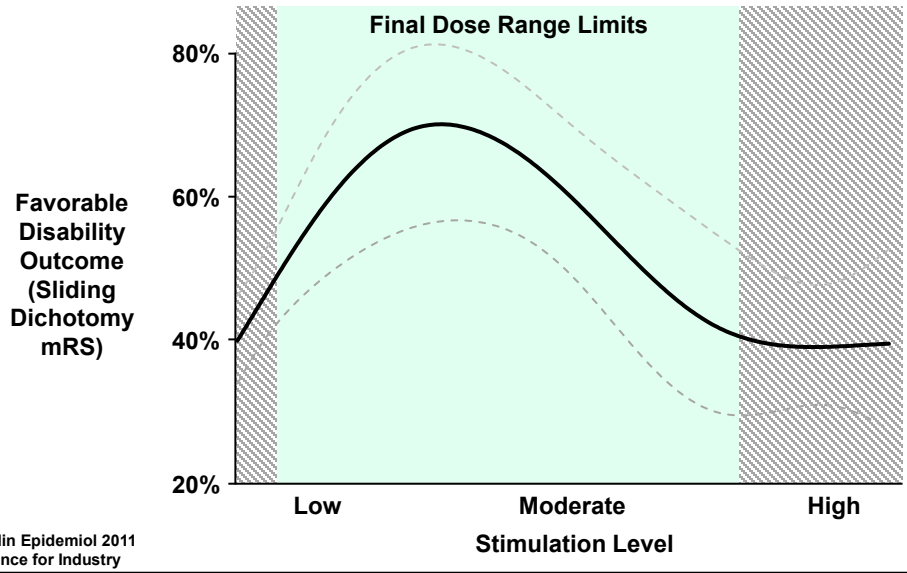

1. Cranston, 2017; 2. IST1+CAST, 2000, POINT, 2018; 3. ECASS, 2008
4. ImpACT-24B, 2019; 5. NINDS-tPA Study, Yafeh, 2007

FDA Question: Sliding Dichotomy

51

CO-52

# Strong Dose Response Relationship (CCI)




1. Guyat, J Clin Epidemiol 2011
2. FDA Guidance for Industry

52

CO-53

# Greatest Benefit Seen When Stimulation Delivered Within Optimal Final Dose Range

| CCI Final Dose Range | SPG N = 117 | Control N = 276 | Odds Ratio (95% CI) |
|---|---|---|---|
| **Primary Endpoint** Sliding Dichotomy mRS | **59.0%** | **39.9%** | **2.17** (1.40, 3.37) |
| **Functional Independence** Dichotomy mRS 0-2 | **44.4%** | **27.2%** | **2.14** (1.37, 3.37) |
| **Walk and Self Care** Dichotomy mRS 0-3 | **73.5%** | **51.1%** | **2.66** (1.65, 4.27) |
| **Stroke-Related QoL** SIS-16 | **60.1** | **43.9** | **2.19** (1.47, 3.26) |
| **Global Disability Level** Utility Weighted mRS | **58.3** | **43.9** | **2.11** (1.41, 3.12) |


53

CO-54

# US vs OUS: No Statistical Differences

| Sliding Dichotomy | US | OUS | Interaction p-value |
|---|---|---|---|
| **Odds ratio** (95% CI) | **1.11** (0.26, 4.72) | **1.50** (1.05, 2.15) | **0.69** |

- No evidence of treatment effect difference
  - Non-significant interaction for treatment by geography
- Despite randomization, comparisons of geographic subgroups are sensitive to small imbalances in baseline covariates

**FDA Question: Generalizability US**

54

CO-55

# Adjusted Analyses Show Large, Consistent Benefit in US and OUS Patients

| Sliding Dichotomy | US | OUS | Interaction p-value |
|---|---|---|---|
| **Odds ratio** (95% CI) | **1.62** (0.30, 8.63) | **1.46** (0.98, 2.18) | **0.91** |

- Differences in baseline characteristics of US subgroup between SPG stimulation and sham-control groups
- Patients in all geographic regions received similar standard of care for ischemic stroke per guidelines, including medications

**FDA Question: Generalizability US**

55

CO-56

# No Bias Introduced by mITT Analysis

| | CCI Patients Allocated SPG included in Primary Analysis N = 520 | Patients Allocated SPG not included in Primary Analysis N = 34 |
|---|---|---|
| **Mean Age, years (SD)** | **70 (10)** | **71 (10)** |
| **Sex (female)** | **49%** | **50%** |
| **NIHSS (mean)** | **13.5 (2.5)** | **13.8 (2.1)** |
| **Stroke side (left brain)** | **55%** | **47%** |
| **Median ASPECTS** (IQR) | **7 (5, 8)** | **7 (5, 7)** |
| **Time from stroke onset (hours); median** (IQR) | **16.3** (13.5, 19.4) | **15.4** (13.2, 18.3) |

**FDA Concern: mITT Analysis**

56

CO-57

# ImpACT-24A – "Phase 2B" RCT

## Consistent Findings Supportive of Pivotal Trial

57

CO-58

# ImpACT-24A Greatest Benefit in CCI Population

**Primary mRS Sliding Dichotomy**

| mITT | SPG | Control | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **ImpACT-24A** (N = 253) | **49.7%** | **40.0%** | **1.48** (0.89, 2.47) | **0.13** |

| CCI | SPG | Control | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **ImpACT-24A** (N = 87) | **50.0%** | **27.0%** | **2.70** (1.08, 6.73) | **0.03** |

**FDA Question: CCI Addition**

58

CO-59

# ImpACT-24A Consistent with ImpACT-24B

## Primary mRS Sliding Dichotomy

| mITT | SPG | Control | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **ImpACT-24A** (N = 253) | **49.7%** | **40.0%** | **1.48** (0.89, 2.47) | **0.13** |
| **ImpACT-24B** (N = 1000) | **48.6%** | **45.5%** | **1.14** (0.89, 1.46) | **0.31** |

| CCI | SPG | Control | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **ImpACT-24A** (N = 87) | **50.0%** | **27.0%** | **2.70** (1.08, 6.73) | **0.03** |
| **ImpACT-24B** (N = 520) | **49.6%** | **39.9%** | **1.48** (1.05, 2.10) | **0.0258** |

59

CO-60

# Efficacy Conclusions Supported by Pooled Analysis

## Primary mRS Sliding Dichotomy

| mITT | SPG | Control | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **ImpACT-24A** (N = 253) | **49.7%** | **40.0%** | **1.48** (0.89, 2.47) | **0.13** |
| **ImpACT-24B** (N = 1000) | **48.6%** | **45.5%** | **1.14** (0.89, 1.46) | **0.31** |
| **Pooled mITT** (N = 1253) | **48.9%** | **44.6%** | **1.20** (0.96, 1.49) | **0.12** |

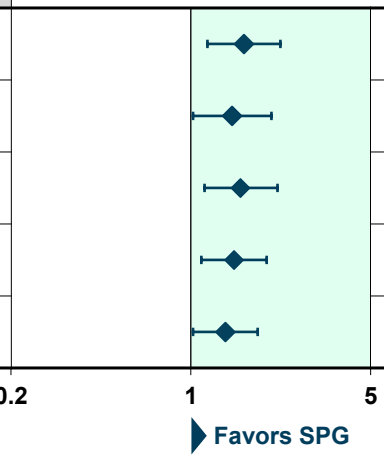
| CCI | SPG | Control | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **ImpACT-24A** (N = 87) | **50.0%** | **27.0%** | **2.70** (1.08, 6.73) | **0.03** |
| **ImpACT-24B** (N = 520) | **49.6%** | **39.9%** | **1.48** (1.05, 2.10) | **0.0258** |
| **Pooled CCI** (N = 607) | **49.7%** | **38.3%** | **1.61** (1.16, 2.23) | **0.004** |

60

CO-61

# Pooled CCI: Consistent Effect in All Endpoint

| Pooled CCI | SPG N = 294 | Control N = 313 | Odds Ratio (95% CI) |
|---|---|---|---|
| **Primary Endpoint** Sliding Dichotomy mRS | **49.7%** | **38.3%** | **1.61** (1.16, 2.23) |
| **Functional Independence** Dichotomy mRS 0-2 | **34.0%** | **26.5%** | **1.45** (1.02, 2.06) |
| **Walk and Self Care** Dichotomy mRS 0-3 | **59.2%** | **49.2%** | **1.56** (1.13, 2.17) |
| **Stroke-Related QoL** SIS-16 | **50.7** | **42.5** | **1.47** (1.10, 1.97) |
| **Global Disability Level** Utility Weighted mRS | **48.6** | **42.7** | **1.36** (1.02, 1.82) |

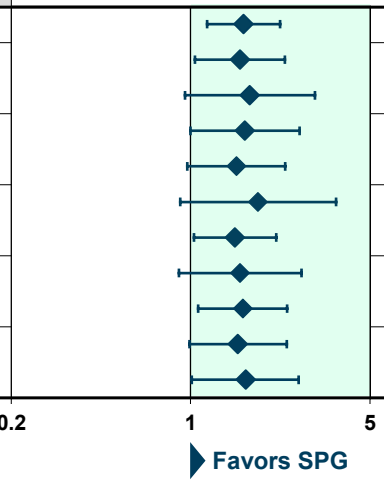



61

CO-62

# Pooled CCI: Homogenous Treatment Effect in All Subgroups

| Primary Endpoint Sliding Dichotomy mRS | SPG N = 294 | Control N = 313 | Odds Ratio (95% CI) |
|---|---|---|---|
| **Pooled CCI Population** | **49.7%** | **38.3%** | **1.61** (1.16, 2.23) |
| **NIHSS < 15** | **58.0%** | **46.9%** | **1.56** (1.04, 2.33) |
| **NIHSS 15–18** | **34.9%** | **23.9%** | **1.70** (0.95, 3.05) |
| **Right Brain** | **42.0%** | **30.7%** | **1.63** (1.00, 2.66) |
| **Left Brain** | **55.8%** | **45.6%** | **1.51** (0.97, 2.34) |
| **Diabetes – Yes** | **35.7%** | **23.3%** | **1.83** (0.91, 3.69) |
| **Diabetes – No** | **54.0%** | **44.1%** | **1.49** (1.03, 2.16) |
| **Atrial Fib – Yes** | **47.5%** | **36.7%** | **1.56** (0.90, 2.71) |
| **Atrial Fib – No** | **50.8%** | **39.2%** | **1.60** (1.07, 2.38) |
| **Age ≤ 75** | **48.3%** | **37.9%** | **1.53** (0.99, 2.37) |
| **Age > 75** | **51.0%** | **38.9%** | **1.64** (1.01, 2.64) |

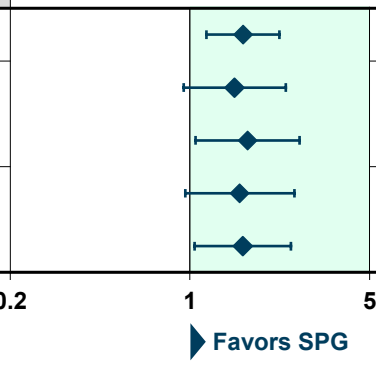



62

CO-63

# Benefits Achieved Regardless of Core Size and Time from Stroke Onset

| Primary Endpoint<br>Sliding Dichotomy mRS | SPG | Control | Odds Ratio (95% CI) |
|---|---|---|---|
| **Pooled CCI Population** | **49.7%** | **38.3%** | **1.61** (1.16, 2.23) |
| **ASPECTS ≥ 7** | **54.3%** | **44.3%** | **1.49** (0.94, 2.36) |
| **ASPECTS < 7** | **45.1%** | **32.9%** | **1.68** (1.05, 2.67) |
| **TFSO ≤ 18** | **49.6%** | **38.6%** | **1.56** (0.96, 2.55) |
| **TFSO > 18** | **49.7%** | **38.1%** | **1.61** (1.04, 2.47) |




TFSO = Time from Stroke Onset

63

CO-64

## Safety Results

64

CO-65

## Safety Analysis Populations

1. All patients
   - SPG stimulation and sham-control patients who had mucosal puncture performed

2. CCI
   - All safety population patients with
     - NIHSS ≥ 10
     - At least one cortical ASPECTS region

65

CO-66

## Safety Endpoints

**Pre-Specified**

- SAEs
- Neurological deterioration (≥ 4 NIHSS within 1st 10 days)
- Mortality by day 90
- Stimulation-related SAEs & AEs
- Implantation-related SAEs & AEs
- Failed implantations

**Additional**

- Pneumonia SAEs
- Symptomatic Intracranial Hemorrhage (sICH)

66

# All Patients: No Increase in Risk of Mortality, SAEs or Other Common Stroke Complications

CO-67

| All – ImpACT-24B | SPG N = 536 | Control N = 519 | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|
| Mortality | 14.2% | 12.3% | **1.17** (0.82, 1.68) | **0.38** |
| SAEs | 30.0% | 28.1% | **1.10** (0.84, 1.43) | **0.50** |
| Neurologic Deterioration | 7.6% | 6.7% | **1.15** (0.72, 1.83) | **0.57** |
| Pneumonia SAE | 4.3% | 5.4% | **0.79** (0.45, 1.38) | **0.40** |
| Symptomatic ICH | 0.7% | 2.1% | **0.35** (0.11, 1.10) | **0.06** |


Favors SPG

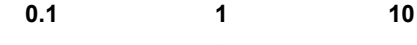
FDA Question: Safety

67

# CCI: Consistent Favorable Safety Profile with SPG Stimulation

CO-68

| CCI – ImpACT-24B | SPG N = 278 | Control N = 276 | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|
| Mortality | 18.3% | 17.0% | **1.09** (0.71, 1.69) | **0.68** |
| SAEs | 33.8% | 36.2% | **0.90** (0.63, 1.27) | **0.55** |
| Neurologic Deterioration | 8.6% | 9.4% | **0.91** (0.51, 1.63) | **0.75** |
| Pneumonia SAE | 5.0% | 7.2% | **0.68** (0.34, 1.37) | **0.28** |
| Symptomatic ICH | 0.7% | 2.9% | **0.24** (0.05, 1.15) | **0.05** |




Favors SPG

68

CO-69

# Stimulation Related SAEs in Both Groups

| Possibly Related Events* | All – ImpACT-24B | |
|---|---|---|
| | SPG N = 536 | Control N = 519 |
| **Total stimulation SAE** | **3 (0.6%)** | **2 (0.4%)** |
| Stroke in evolution | 1 (0.2%) | 1 (0.2%) |
| Hemorrhagic transformation stroke | 1 (0.2%) | 1 (0.2%) |
| Epileptic seizure | 1 (0.2%) | - |

*** No events were classified as "definitely" or "probably" related**

69

CO-70

# Non-Serious Stimulation Related AEs (> 1%)

| Related Events | All – ImpACT-24B | |
|---|---|---|
| | SPG N = 536 | Control N = 519 |
| **Lacrimation increased** | **71 (13.2%)** | **3 (0.6%)** |
| **Headache** | **19 (3.5%)** | **4 (0.8%)** |
| **Pain** | **118 (22.0%)** | **4 (0.8%)** |
| **Medical device discomfort** | **5 (0.9%)** | **6 (1.2%)** |

- All transient
- Lacrimation: known sign of SPG activation, resolves at end of treatment session
- Headache may be side effect of SPG activation
- Facial pain & discomfort: avoidable by not exceeding CTL

70

CO-71

# Implantation Related SAEs with ISS500; All Resolved Without Sequela

| Preferred Term | ImpACT-24B | |
|---|---|---|
| | Current Implant N = 197 | First Implant N = 339 |
| **Total implant related SAE** | **1 (0.5%)** | **2 (0.6%)** |
| Complication of device removal | 1 (0.5%) | 1 (0.3%) |
| Device breakage | - | 1 (0.3%) |

71

CO-72

# Implantation is Safe

| | ImpACT-24B | |
|---|---|---|
| | Current Implant N = 197 | First Implant N = 339 |
| **Skin-to-skin (minutes); median** (IQR) | **17** (12, 23) | **35** (25, 52) |
| **SAE** | **0.5%** | **0.6%** |
| **AE** | **7.6%** | **36.9%** |
| **Misplacements** | **2.0%** | **8.3%** |
| **Incomplete procedures** | **2.0%** | **5.0%** |

72

CO-73

# Modified Implant Mitigated Implantations Risks

## Implantation-Related Non-Serious AEs – FDA's List of Concerns

| | ImpACT-24B | |
|---|---|---|
| | Current Implant N = 197 | First Implant N = 339 |
| **Acute pain** | **1%** (2) | **11.5%** (39) |
| **Bleeding (implant site hemorrhage)** | **0** | **3.8%** (13) |
| **Swelling (including Infection, Erythema)** | **0** | **1.5%** (5) |
| **Chronic neuropathic pain / nerve injury** | **0** | **1.5%** (5) |
| **Micro-aspiration** | | |
| Pneumonia Aspiration | **0** | **0.6%** (2) |
| Bronchopneumonia | **0** | **0.3%** (1) |
| **Apnea** | **0** | **0.3%** (1) |
| **Airway endangerment / Laryngospasm** | **0** | **0** |
| **Palate laceration** | **0** | **0** |

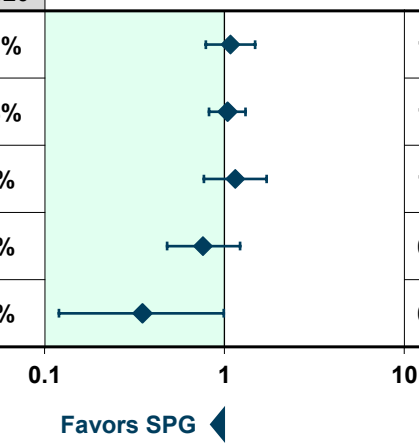
**FDA Question: Safety**

73

CO-74

# All Patients Pooled: Safety Results Further Support Favorable Safety Profile

| 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** |
| **SAEs** | **30.1%** | **29.4%** | **1.04** (0.82, 1.31) | **0.77** |
| **Neurologic 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** |

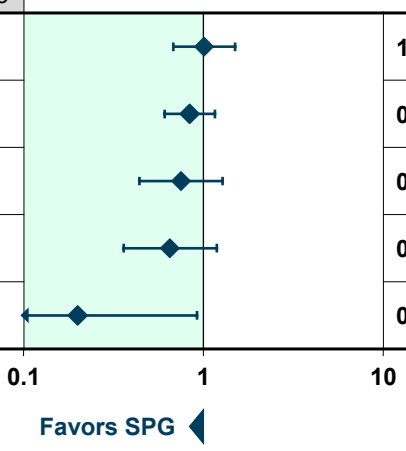



74

CO-75

# CCI Pooled: Consistent Safety Results

| 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** |
| SAEs | 34.0% | 38.0% | **0.84** (0.61, 1.16) | **0.28** |
| Neurologic 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** |




FDA Question: Safety

75

CO-76

# Overall Benefit-Risk Assessment

76

CO-77

# Efficacy Summary

### Consistent Effect Indicated by All Primary and Secondary Efficacy Endpoints

CO-49

| CCI | SPG N = 244 | Control N = 276 | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **Primary Endpoint** Sliding Dichotomy mRS | 49.6% | 39.9% | 1.48 (1.05, 2.10) | 0.0258 |
| **Functional Independence** Dichotomy mRS 0-2 | 34.8% | 27.2% | 1.43 (0.99, 2.08) | 0.06 |
| **Walk and Self Care** Dichotomy mRS 0-3 | 62.3% | 51.1% | 1.58 (1.11, 2.25) | 0.01 |
| **Stroke-Related QoL** 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 |

0.2 1 5

Favors SPG

FDA Question: Sliding Dichotomy

### Benefits Achieved Regardless of Core Size and Time from Stroke Onset

CO-63

| Primary Endpoint Sliding Dichotomy mRS | SPG | Control | Odds Ratio (95% CI) |
|---|---|---|---|
| **Pooled CCI Population** | 49.7% | 38.3% | 1.61 (1.16, 2.23) |
| **ASPECTS ≥ 7** | 54.3% | 44.3% | 1.49 (0.94, 2.36) |
| **ASPECTS < 7** | 45.1% | 32.9% | 1.68 (1.05, 2.67) |
| **TFSO ≤ 18** | 49.6% | 38.6% | 1.56 (0.96, 2.55) |
| **TFSO > 18** | 49.7% | 38.1% | 1.61 (1.04, 2.47) |

0.2 1 5

Favors SPG

TFSO = Time from Stroke Onset

### Benefits Persisted Through 1-Year Follow-up Further Confirming the Positive Effects of SPG Stimulation

CO-59

| CCI RIKS – 360 Days | 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 |
| **Toileting** | 1.37 (0.96, 1.94) | 0.08 |
| **Dressing** | 1.58 (1.11, 2.23) | 0.01 |

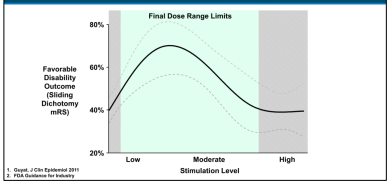
0.2 1 5

Favors SPG

SPG Stimulation (N=241); Sham-Control (N=271)

### Strong Dose Response Relationship (CCI)

CO-52




1. Cucchi J Clin Epidemiol 2011
2. FDA Guidance for Industry

### Greatest Benefit Seen When Stimulation Delivered Within Optimal Final Dose Range

CO-53

| CCI Final Dose Range | SPG N = 117 | Control N = 276 | Odds Ratio (95% CI) |
|---|---|---|---|
| **Primary Endpoint** Sliding Dichotomy mRS | 59.0% | 39.9% | 2.17 (1.40, 3.37) |
| **Functional Independence** Dichotomy mRS 0-2 | 44.4% | 27.2% | 2.14 (1.37, 3.37) |
| **Walk and Self Care** Dichotomy mRS 0-3 | 73.5% | 51.1% | 2.66 (1.65, 4.27) |
| **Stroke-Related QoL** SIS-16 | 60.1 | 43.9 | 2.19 (1.47, 3.26) |
| **Global Disability Level** Utility Weighted mRS | 58.3 | 43.9 | 2.11 (1.41, 3.12) |

0.2 1 5

Favors SPG

77

CO-78

# Safety Conclusion

### Implantation is Safe

CO-72

| | ImpACT-24B | |
|---|---|---|
| | Current Implant N = 197 | First Implant N = 339 |
| **Skin-to-skin (minutes); median** (IQR) | 17 (12, 23) | 35 (25, 52) |
| **SAE** | 0.5% | 0.6% |
| **AE** | 7.6% | 36.9% |
| **Misplacements** | 2.0% | 8.3% |
| **Incomplete procedures** | 2.0% | 5.0% |

### All Patients: No Increase in Risk of Mortality, SAEs or Other Common Stroke Complications

CO-67

| All – ImpACT-24B | SPG N = 536 | Control N = 519 | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **Mortality** | 14.2% | 12.3% | 1.17 (0.82, 1.68) | 0.38 |
| **SAEs** | 30.0% | 28.1% | 1.10 (0.84, 1.43) | 0.50 |
| **Neurologic Deterioration** | 7.6% | 6.7% | 1.15 (0.72, 1.83) | 0.57 |
| **Pneumonia SAE** | 4.3% | 5.4% | 0.79 (0.45, 1.38) | 0.40 |
| **Symptomatic ICH** | 0.7% | 2.1% | 0.35 (0.11, 1.10) | 0.06 |

0.1 1 10

Favors SPG

FDA Question: Safety

78

CO-79

# ImpACT-24M Trial

**Usability**

79

CO-80

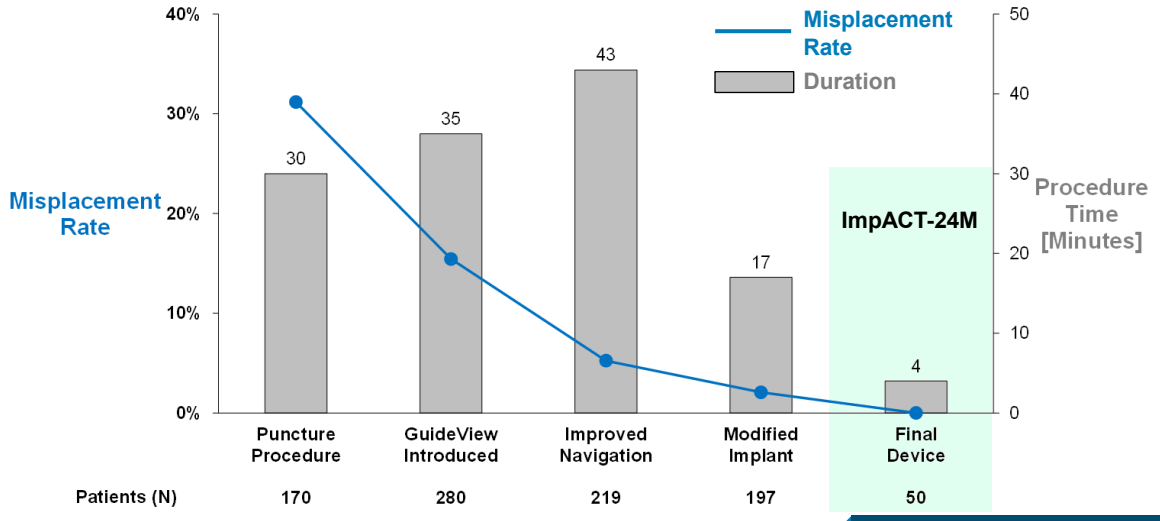
## ImpACT-24M Objectives

1. Speed and accuracy of implantation with final device
2. Confirm dose of SPG stimulation can be efficiently set by non-noxious physiological effects

80

CO-81

# Implantation in ImpACT-24M Accurate and Efficient




FDA Question: Implantation

81

CO-82

# Implantation is Safe and Simple (< 5 minutes)

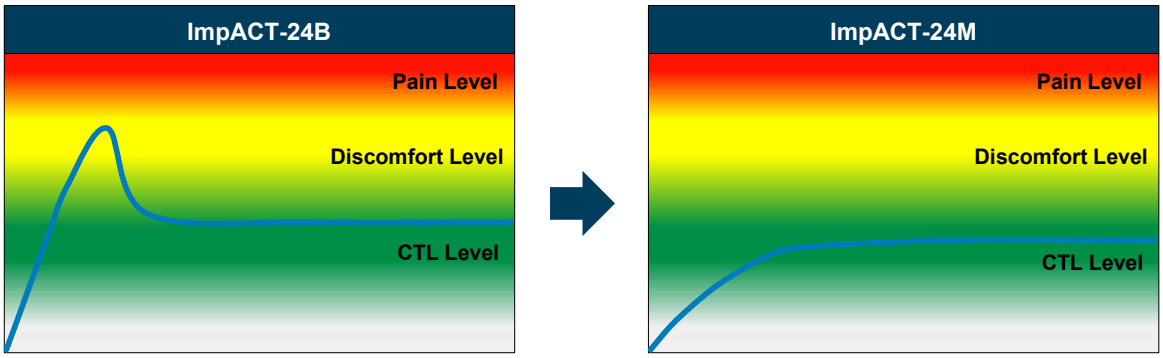
| | ImpACT-24M | ImpACT-24B | |
|---|---|---|---|
| | Final Device N = 50 | Current Implant Old Navigation N = 197 | First Implant Old Navigation N = 339 |
| **Skin-to-skin (minutes); median** (IQR) | **4** (3, 7) | **17** (12, 23) | **35** (25, 52) |
| **SAE** | **0% (0)** | **0.5% (1)** | **0.6% (2)** |
| **AE** | **2% (1)** | **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)** |

FDA Question: Safety

82

CO-83

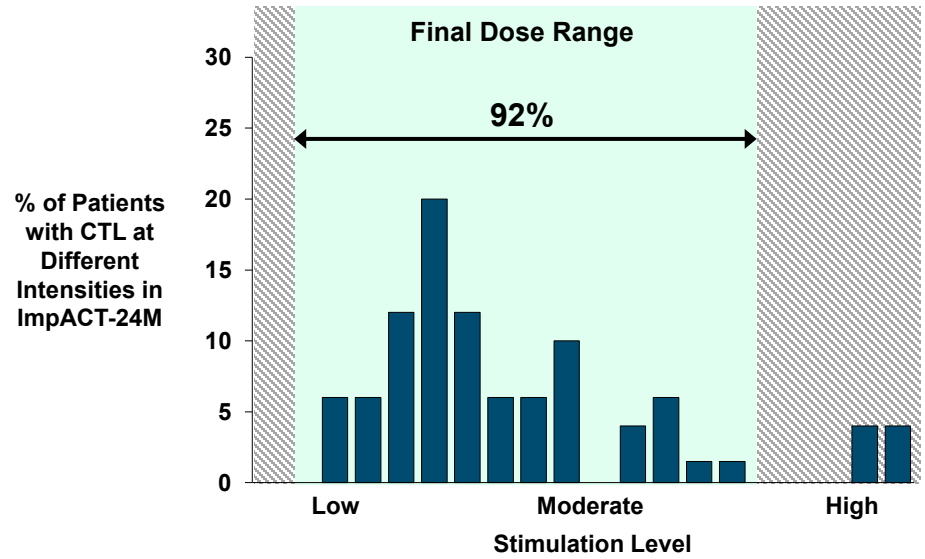
# ImpACT-24M Stimulation Level Set Based on Non-Noxious Physiologic Signs of SPG Activation




83

CO-84

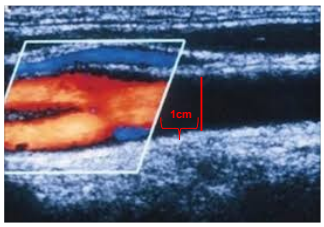
# 92% of Patients Treated Within Final Dose Range Using CTL Identification




84

# Correct Stimulation Validated by Increased Common Carotid Artery Flow Volume

CO-85




Ultrasound doppler image of common carotid artery

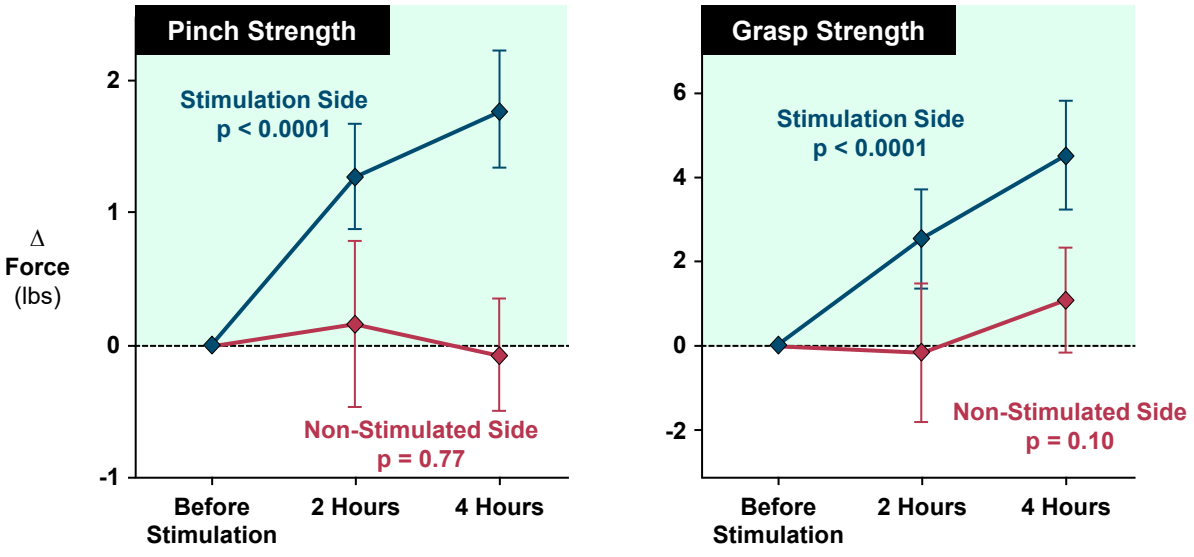
| | Baseline | During Stimulation | Increase | p-value |
|---|---|---|---|---|
| **Diameter** (mm) | 8.0 | 8.9 | 11% | <0.0001 |
| **Peak systolic velocity** (cm/s) | 65.6 | 76.8 | 17% | 0.0001 |
| **Peak systolic flow** (cc/s) | 32.5 | 46.9 | 44% | <0.0001 |
| **End diastolic velocity** (cm/s) | 14.0 | 17.1 | 22% | 0.0004 |
| **End diastolic flow** (cc/s) | 7.1 | 10.8 | 52% | <0.0001 |

Parameters assessed between 45-60 minutes after initiation of stimulation

85

# Improved Motor Deficit Confirms Correct Stimulation Setting

CO-86




86

CO-87

## ImpACT-24M Supports Applicability to Real-World Clinical Practice

- Current device facilitates accurate and simple implantation
  - Shortened procedure time
  - 100% correct placements
  - No SAEs
- Setting stimulation intensity using non-noxious physiologic markers yields intensity levels in optimal range
- Immediate effects on blood flow and motor function

87

CO-88

## Training and Post-Approval Plan

**Eyal Shai**

Chief Technology Officer

BrainsGate

88

CO-89

## Implanter Training Program

- Implantation performed by medical doctor and an assistant
- One day in-person training
  - Didactic session (2 hours)
  - Practice on head model (5 hours)
- 5 Implantations, remote guidance & support
- Qualification - 3 procedures with remote supervision

FDA Question: Implantation

89

CO-90

## Treatment Training Program

- Online training for healthcare professionals
  - Physiological markers identification
  - System operation
  - Online test

FDA Question: Implantation

90

CO-91

## Post Approval Study Plans

1. System's performance (Automatic data collection)
   - Guidance system accuracy
   - Implantation procedure time
   - Stimulation level
2. Registry Data collection
   - Clinical outcome
   - Failed implantations
   - Complications (device-related), safety incidents
   - FDA identified theoretical risks

**FDA Question: Safety**

91

CO-92

## Clinical Perspective

**Michael Hill, MD, MSc, FRCPC**

President, Canadian Neurological Sciences Federation

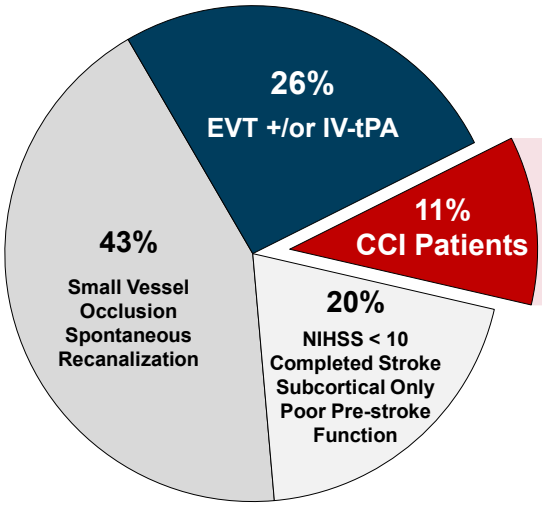
Professor, Department Clinical Neuroscience & Hotchkiss Brain Institute

Cumming School of Medicine, University of Calgary & Foothills Medical Centre

92

# Unmet Need for Patients Who are Ineligible or Unable to Receive Current SoC

CO-93



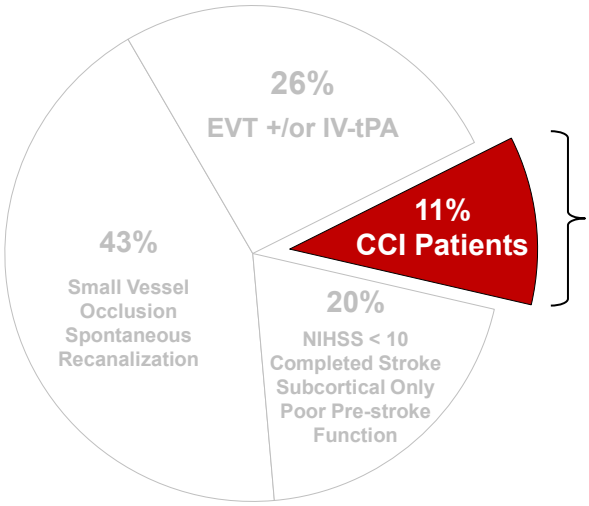

**No effective alternatives to reduce disabling effects of acute ischemic stroke**

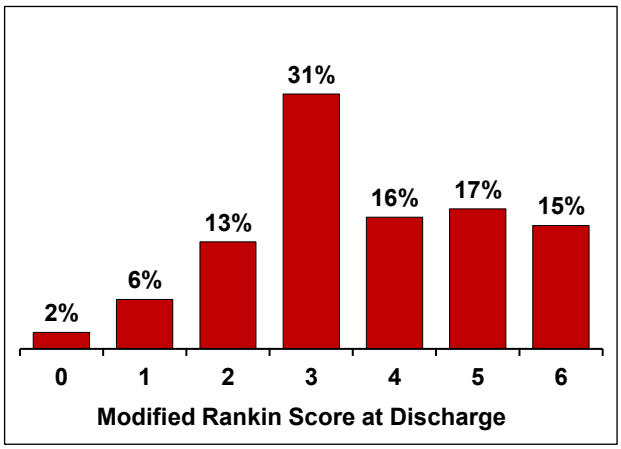
Bahr Hosseini, 2018; Desai 2020

93

# > 75% of Patients in Treatment Gap have Worse Outcomes with mRS > 3 at Discharge

CO-94



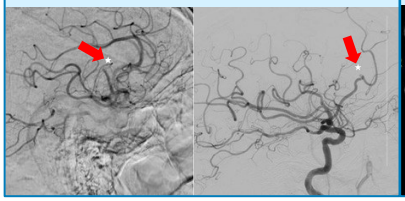
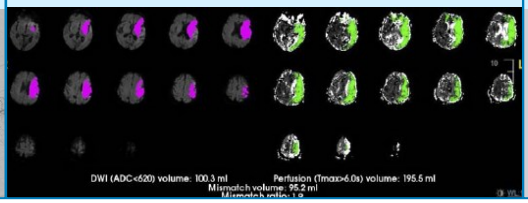
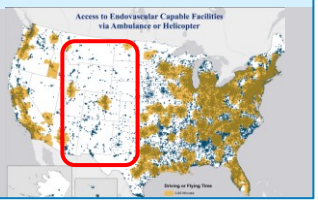
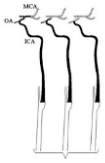
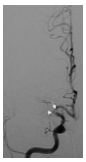

Bahr Hosseini, 2017; Desai 2020

LVO = Large Vessel Occlusion; MVO = Medium Vessel Occlusion; SVO = Small Vessel Occlusion

94

CO-95

## Clinical Situations Where ISS500 Could Provide Benefit for Patients Presenting within 24 Hours but Ineligible for SOC

| Distal MVOs (e.g. M2/M3/M4/A1/A2/A3) | Large Core But Salvageable Penumbra Present | Thrombectomy-Capable Centers Too Far Away |
|---|---|---|
|  |   |   |
| **Chronic Cervical ICA Occlusion+ Acute MCA/ACA Thrombus** | **Chronic Cervical or Intracranial Occlusion + Hemodynamic Failure** | **Tortuous Aortic / ICA Anatomy** |
|  |   |  |

Menon, 2018; Grossberg, 2018; Chen 2018; Momjian-Mayor, 2005; Saba, 2015; Bahr Hosseini, 2018; Adeoye, 2014

95

CO-96

## Identification of CCI Patients Based on Practices Routinely Used Today

- CCI determined by neurological examination using assessments routinely done in clinical practice
  - Combination of NIHSS and ASPECT score
  - Non-contrast CT and other standard imaging modalities

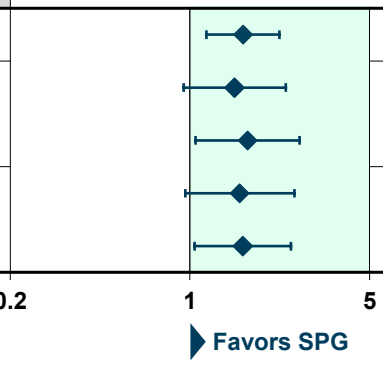
**FDA Concern: Patient Selection**

96

CO-97

# Data Demonstrate that SPG Stimulation is Effective Treatment Option: Addresses Treatment Gap

| **Primary Endpoint** Sliding Dichotomy mRS | SPG | Control | **Odds Ratio** (95% CI) |
|---|---|---|---|
| **Pooled CCI Population** | **49.7%** | **38.3%** | **1.61** (1.16, 2.23) |
| **ASPECTS ≥ 7** | **54.3%** | **44.3%** | **1.49** (0.94, 2.36) |
| **ASPECTS < 7** | **45.1%** | **32.9%** | **1.68** (1.05, 2.67) |
| **TFSO ≤ 18** | **49.6%** | **38.6%** | **1.56** (0.96, 2.55) |
| **TFSO > 18** | **49.7%** | **38.1%** | **1.61** (1.04, 2.47) |




TFSO = Time from Stroke Onset

97

CO-98

# Safety Profile Well-Characterized, Demonstrating Minimal Risks Associated with SPG Stimulation

- SPG stimulation associated with mild, transient stimulation AEs
  - Pain, lacrimation and headache
  - Resolved during stimulation, or upon completion of therapy
- No increased risk of mortality
- SAEs, neurological deterioration and pneumonia less common with SPG compared with Control
- SPG significantly reduces rate of symptomatic ICH

98

## Simplifications to Implant Procedure Designed to Ensure Safe Transition to Real-World Use

CO-99

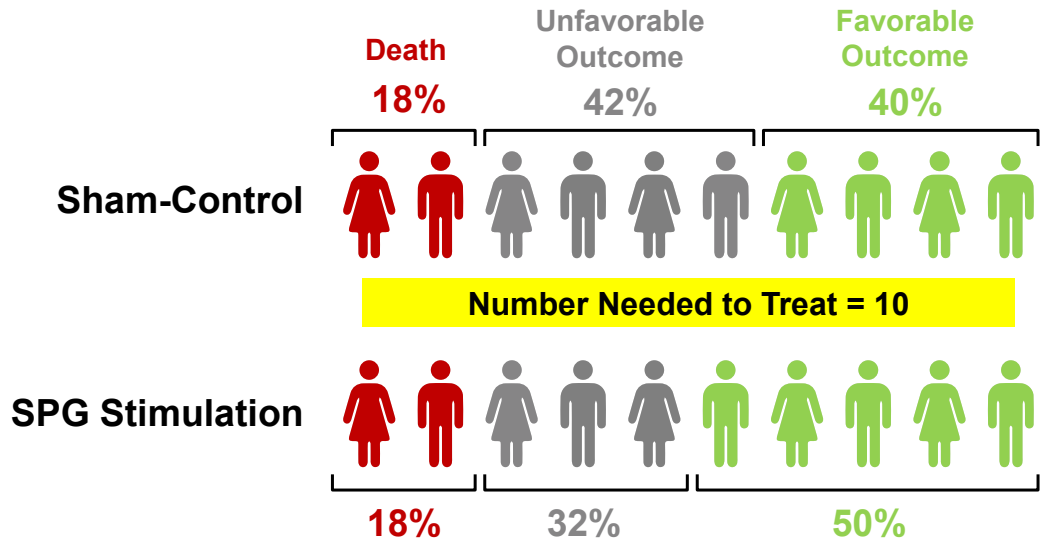
- Simple bedside procedure
- Navigation system facilitates safe and accurate positioning of the neurostimulator
  - Minimizes risk of implant complications
- Final device ensures stimulation within optimal range

FDA Question: Implantation

99

## Effectiveness and Safety Results Represent Clinical Meaningful Outcomes for Patients

CO-100




100

CO-101

# Totality of Evidence Supports Positive Benefit-Risk for Ischemic Stroke System

| Unmet Need | Effectiveness | Safety |
|---|---|---|
| ▪ Guidelines recommend reperfusion therapies<br>▪ Use is time dependent<br>▪ Many patient's ineligible or do not have access to care | ▪ Target CCI population achieved consistent improvements<br>▪ Benefits regardless of stroke severity and time from stroke onset<br>▪ Final device ensures optimal stimulation | ▪ Favorable safety profile<br>▪ Significantly reduced risk of sICH<br>▪ Final device reduces procedure time and implant complications |

101

CO-102

# Ischemic Stroke System for Treatment of Patients with Acute Ischemic Strokes

**December 10, 2021**

Neurologic Devices Panel

BrainsGate

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