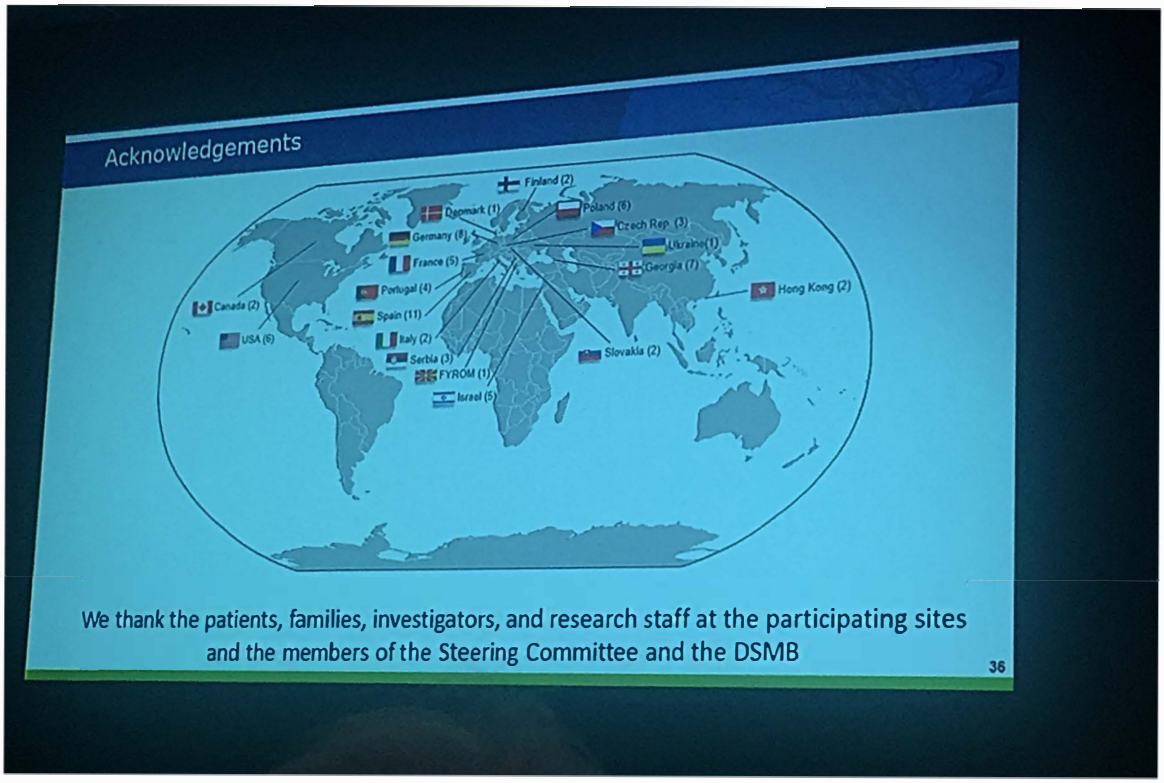
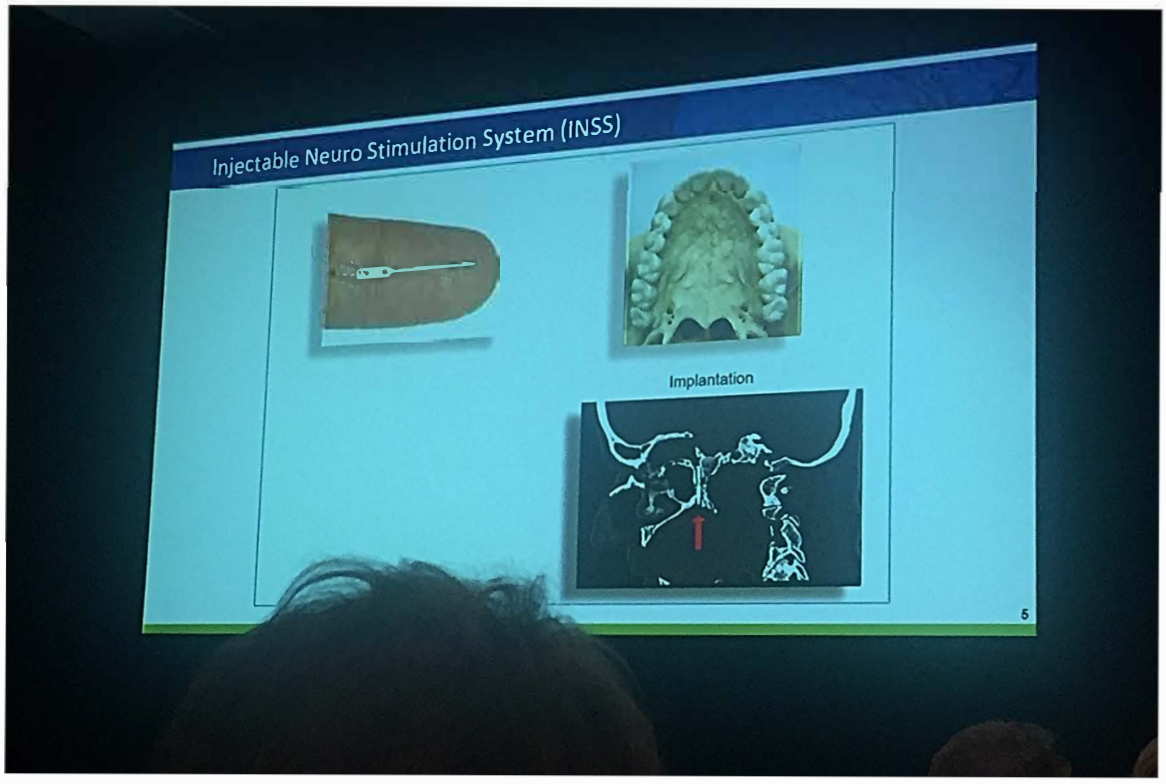
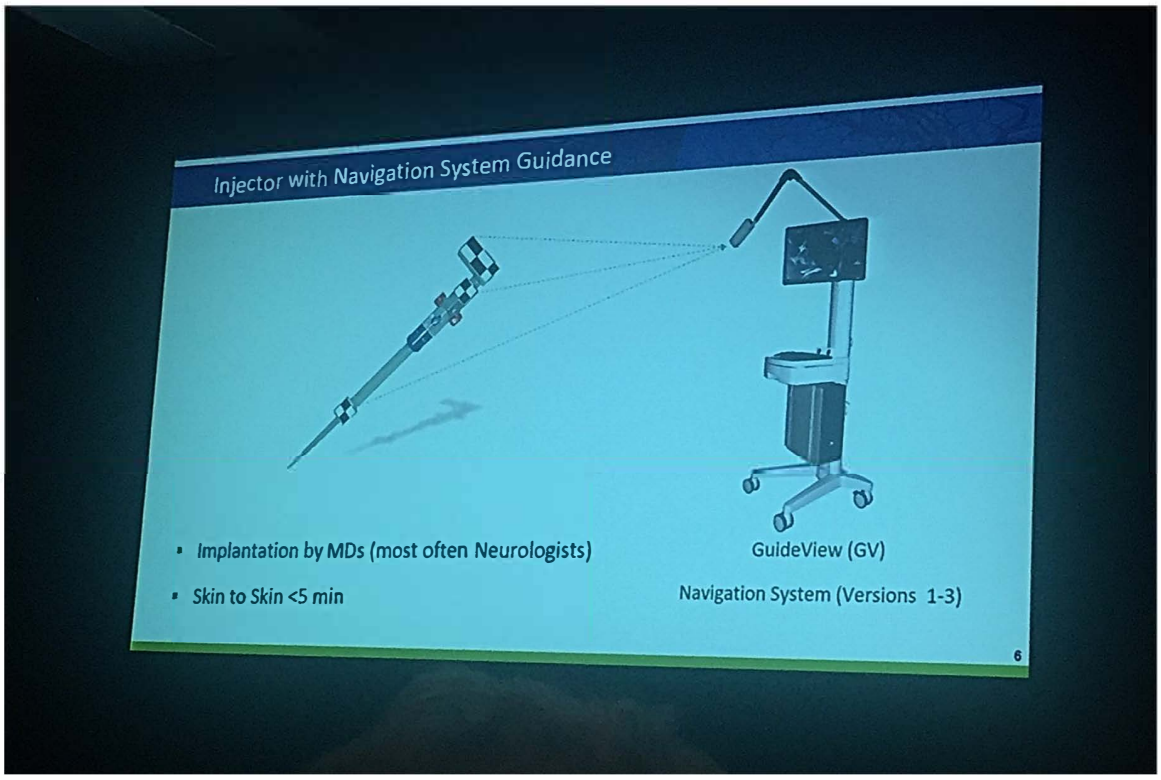
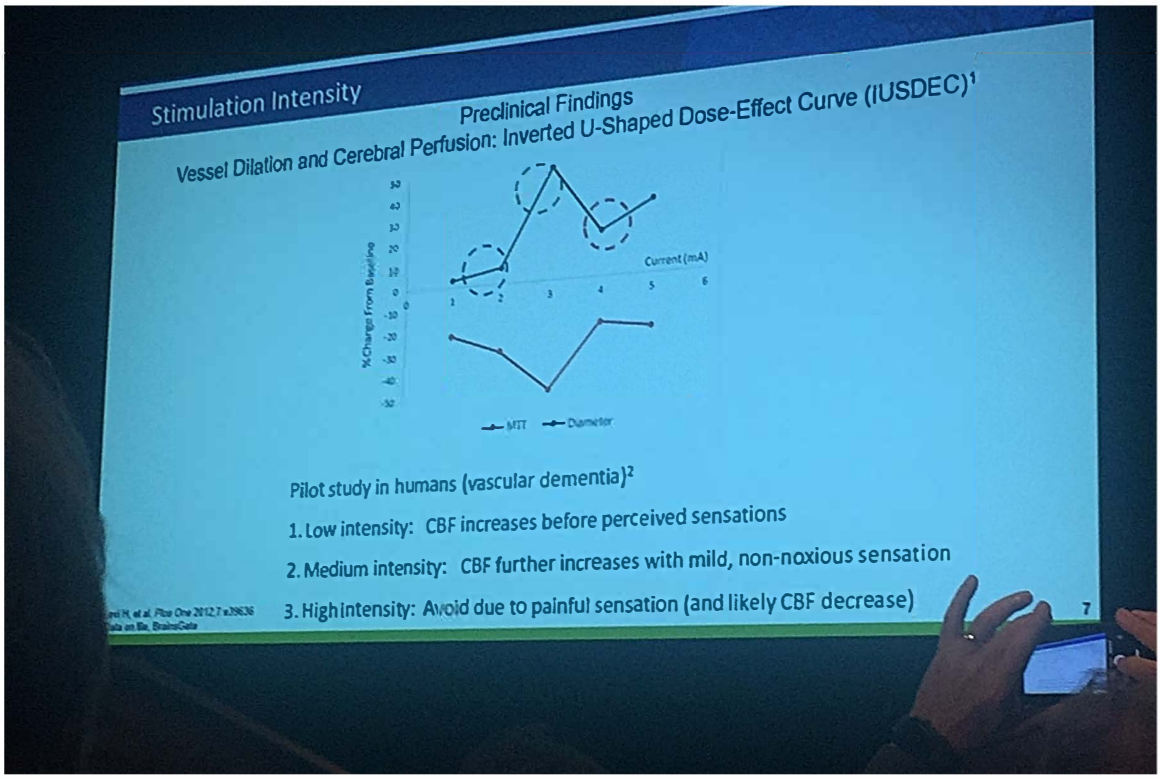
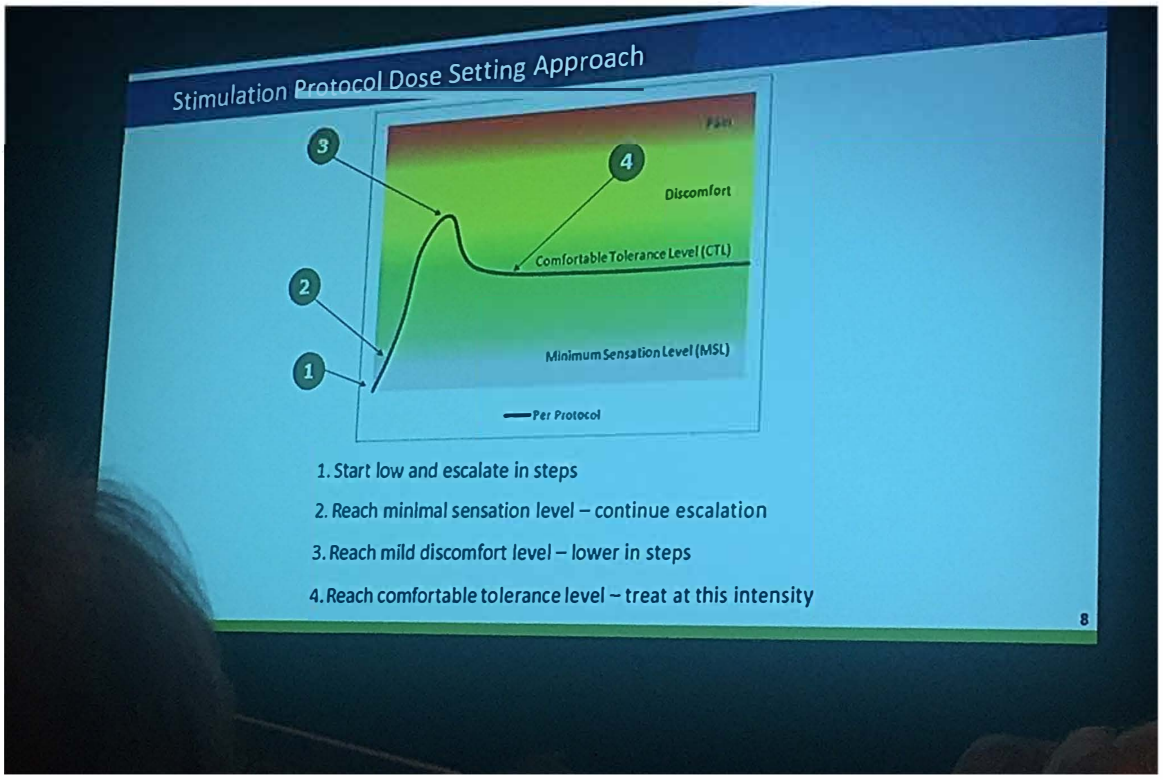
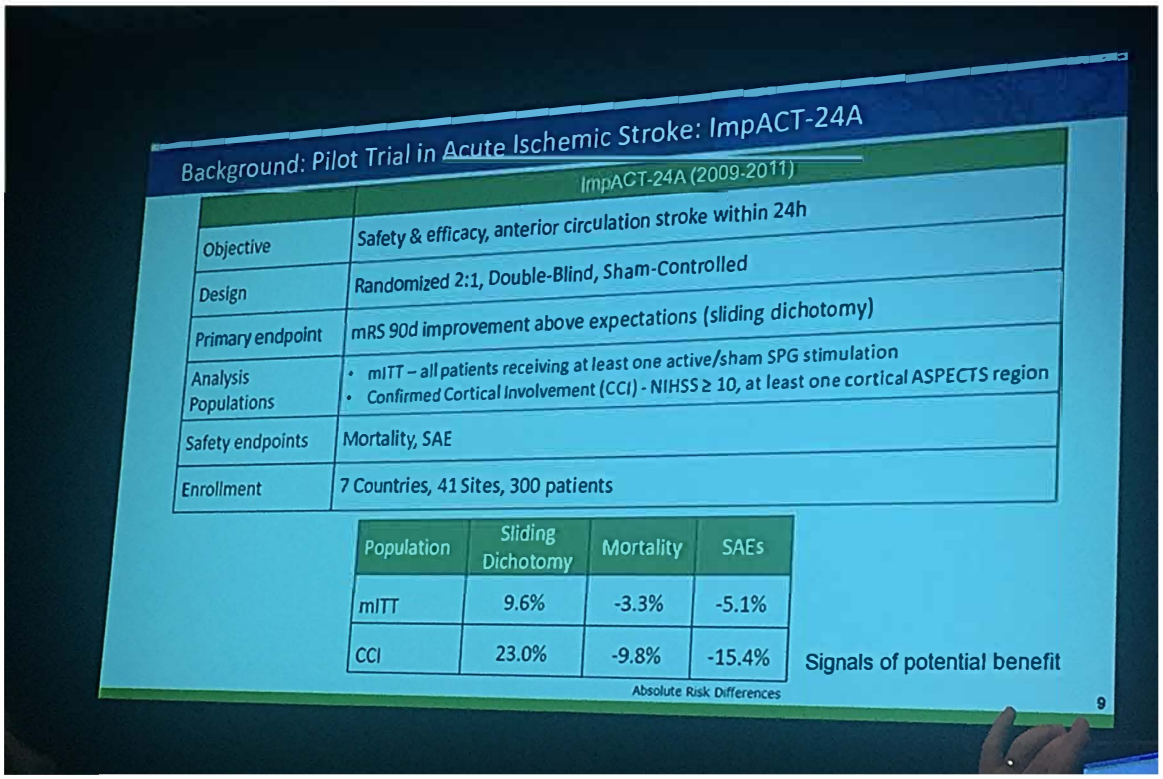

Acknowledgements
Finland (2)
Denmark (1)
Poland (6)
Czech Rep. (3)
Germany (8)
Ukraine (1)
France (5)
Georgia (7)
Portugal (4)
Hong Kong (2)
Canada (2)
Spain (11)
USA (6)
Italy (2)
Slovakia (2)
Serbia (3)
FYROM (1)
Israel (5)
We thank the patients, families, investigators, and research staff at the participating sites and the members of the Steering Committee and the DSMB
36

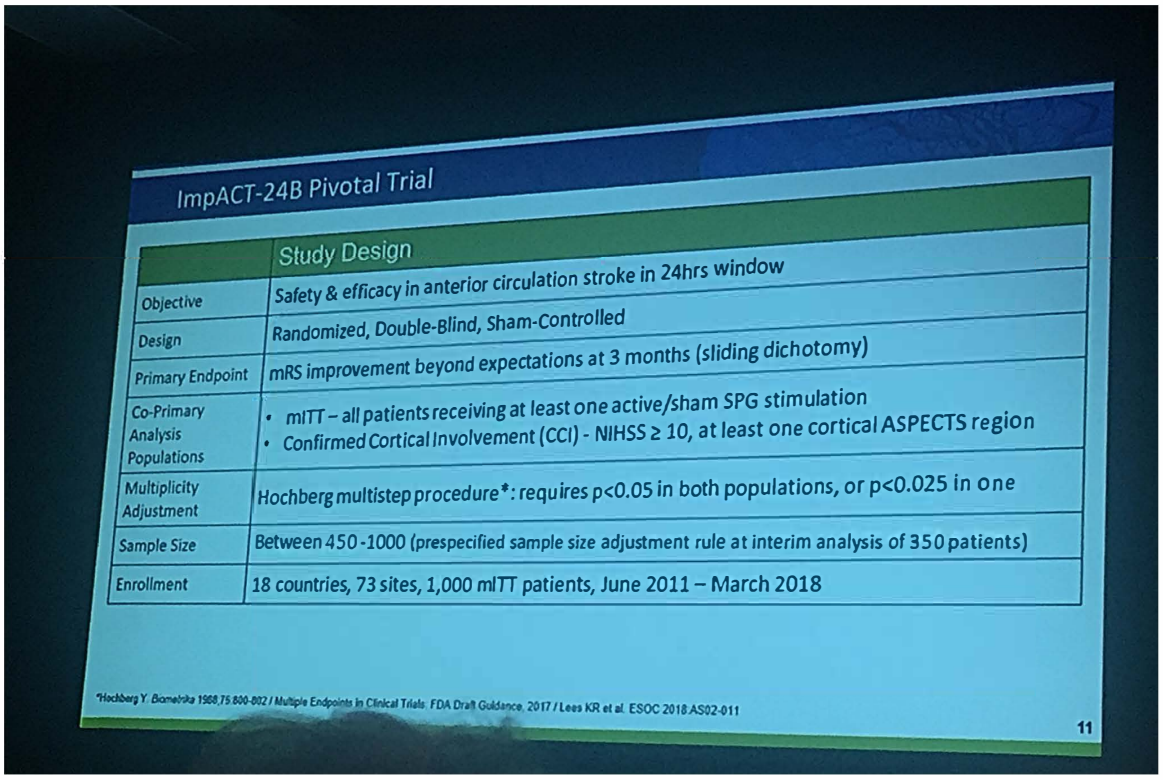

Injectable Neuro Stimulation System (INSS)
Implantation
5

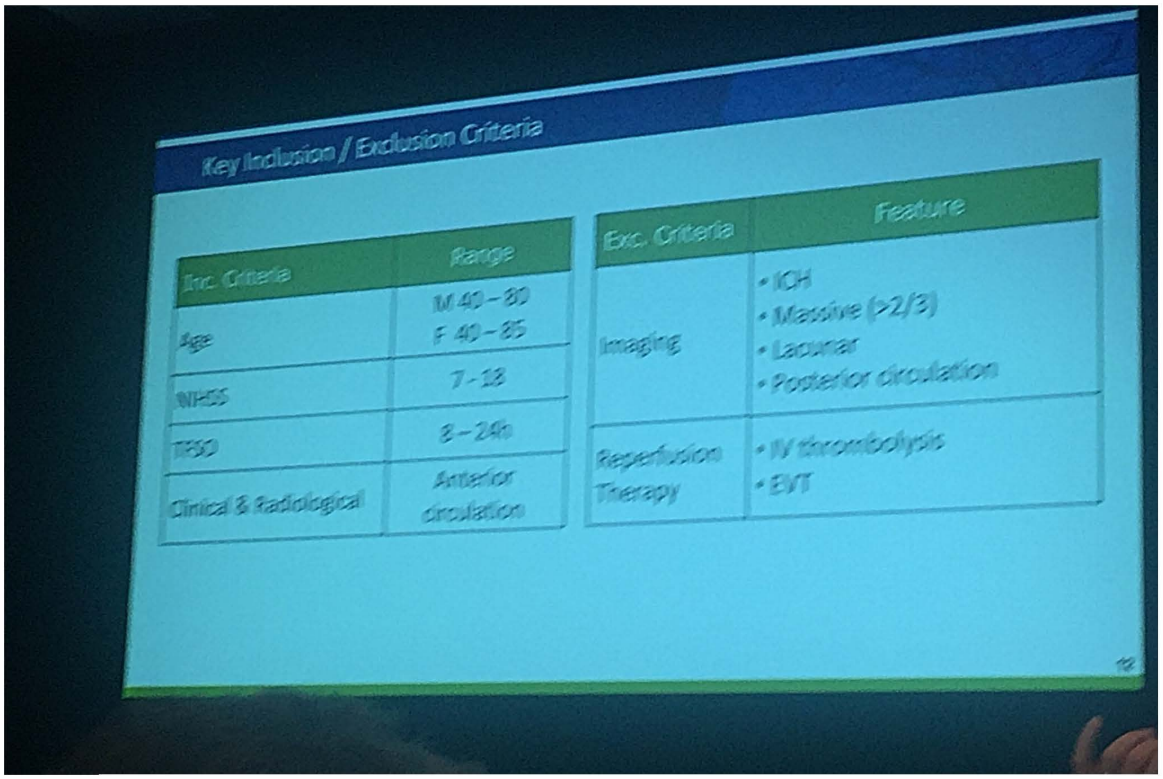

Injector with Navigation System Guidance
Implantation by MDs (most often Neurologists)
Skin to Skin <5 min
GuideView (GV)
Navigation System (Versions 1-3)
6

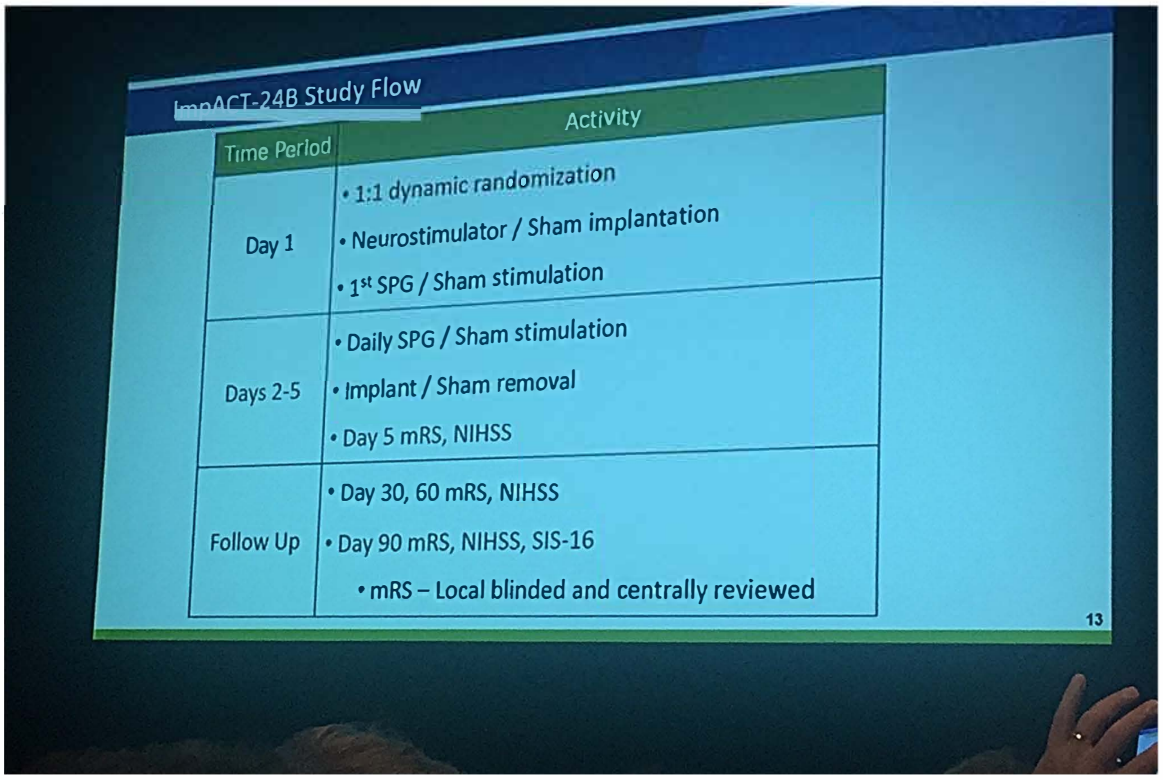

Stimulation Intensity
Preclinical Findings
Vessel Dilation and Cerebral Perfusion: Inverted U-Shaped Dose-Effect Curve (IUSDEC)1
% Change From Baseline
Current (mA)
MTT
Diameter
Pilot study in humans (vascular dementia)2
1. Low intensity: CBF increases before perceived sensations
2. Medium intensity: CBF further increases with mild, non-noxious sensation
3. High Intensity: Avoid due to painful sensation (and likely CBF decrease)
7

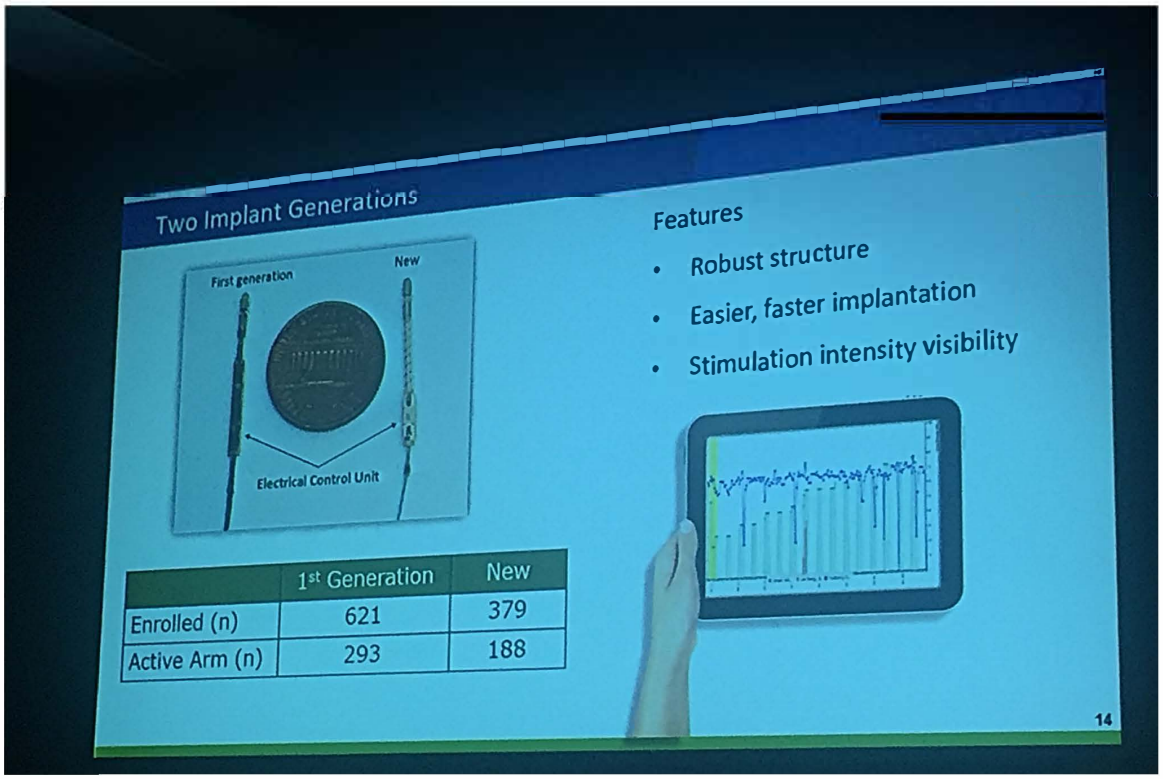

Stimulation Protocol Dose Setting Approach
Pain
Discomfort
Comfortable Tolerance Level (CTL)
Minimum Sensation Level (MSL)
Per Protocol
1
2
3
4
1. Start low and escalate in steps
2. Reach minimal sensation level – continue escalation
3. Reach mild discomfort level – lower in steps
4. Reach comfortable tolerance level – treat at this intensity
8

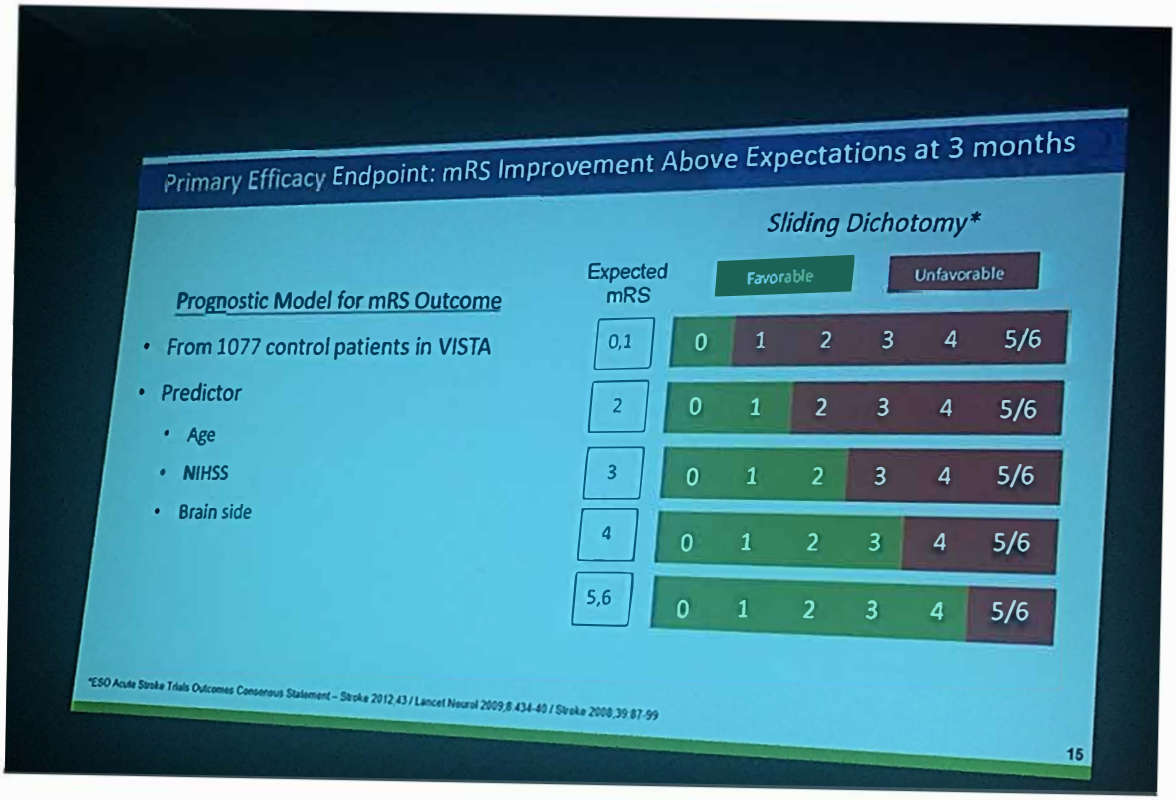

Background: Pilot Trial in Acute Ischemic Stroke: ImpACT-24A
ImpACT-24A (2009-2011)
Objective
Safety & efficacy, anterior circulation stroke within 24h
Design
Randomized 2:1, Double-Blind, Sham-Controlled
Primary endpoint
mRS 90d improvement above expectations (sliding dichotomy)
Analysis Populations
• mITT – all patients receiving at least one active/sham SPG stimulation
• Confirmed Cortical Involvement (CCI) - NIHSS ≥ 10, at least one cortical ASPECTS region
Safety endpoints
Mortality, SAE
Enrollment
7 Countries, 41 Sites, 300 patients
Population
Sliding Dichotomy
Mortality
SAEs
mITT
9.6%
-3.3%
-5.1%
CCI
23.0%
-9.8%
-15.4%
Absolute Risk Differences
Signals of potential benefit
9

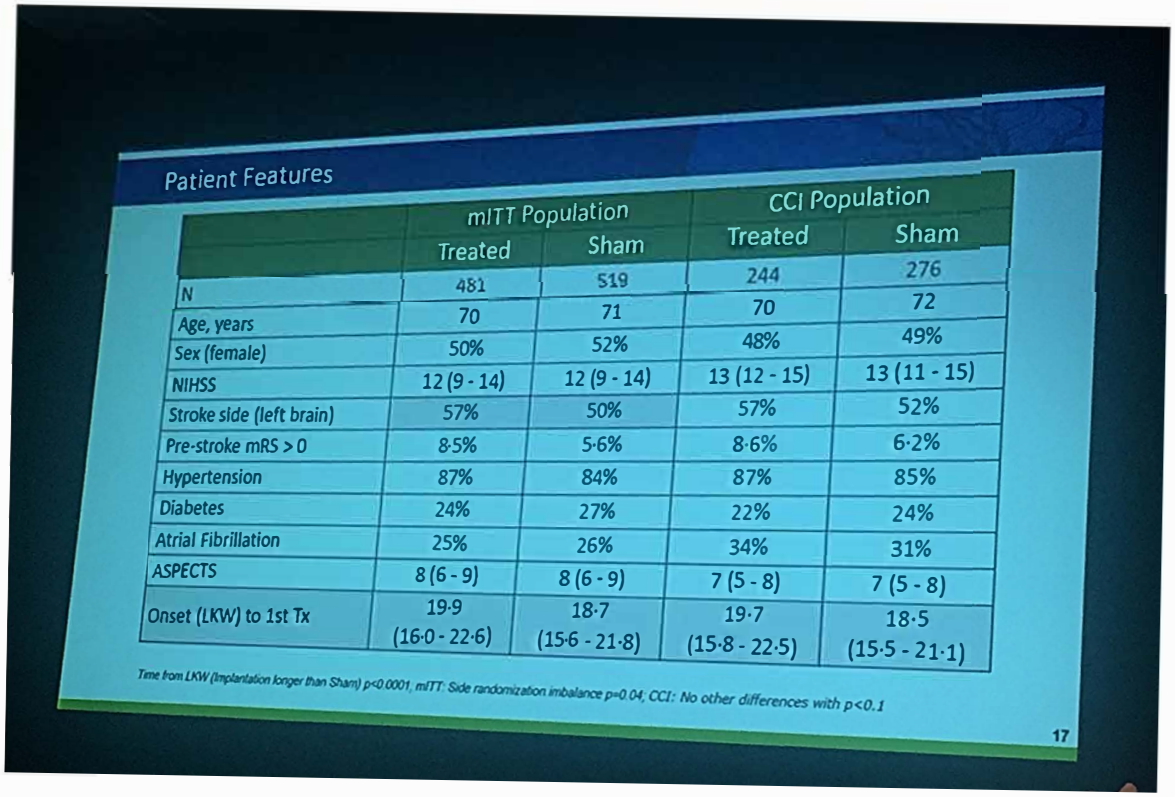

ImpACT-24B Pivotal Trial
Study Design
Objective
Safety & efficacy in anterior circulation stroke in 24hrs window
Design
Randomized, Double-Blind, Sham-Controlled
Primary Endpoint
mRS improvement beyond expectations at 3 months (sliding dichotomy)
Co-Primary Analysis Populations
• mITT – all patients receiving at least one active/sham SPG stimulation
• Confirmed Cortical Involvement (CCI) - NIHSS ≥ 10, at least one cortical ASPECTS region
Multiplicity Adjustment
Hochberg multistep procedure*: requires p<0.05 in both populations, or p<0.025 in one
Sample Size
Between 450-1000 (prespecified sample size adjustment rule at interim analysis of 350 patients)
Enrollment
18 countries, 73 sites, 1,000 mITT patients, June 2011 – March 2018
*Hochberg Y. Biometrika 1988;75:800-802 / Multiple Endpoints in Clinical Trials: FDA Draft Guidance, 2017 / Lees KR et al. ESOC 2018:AS02-011
11

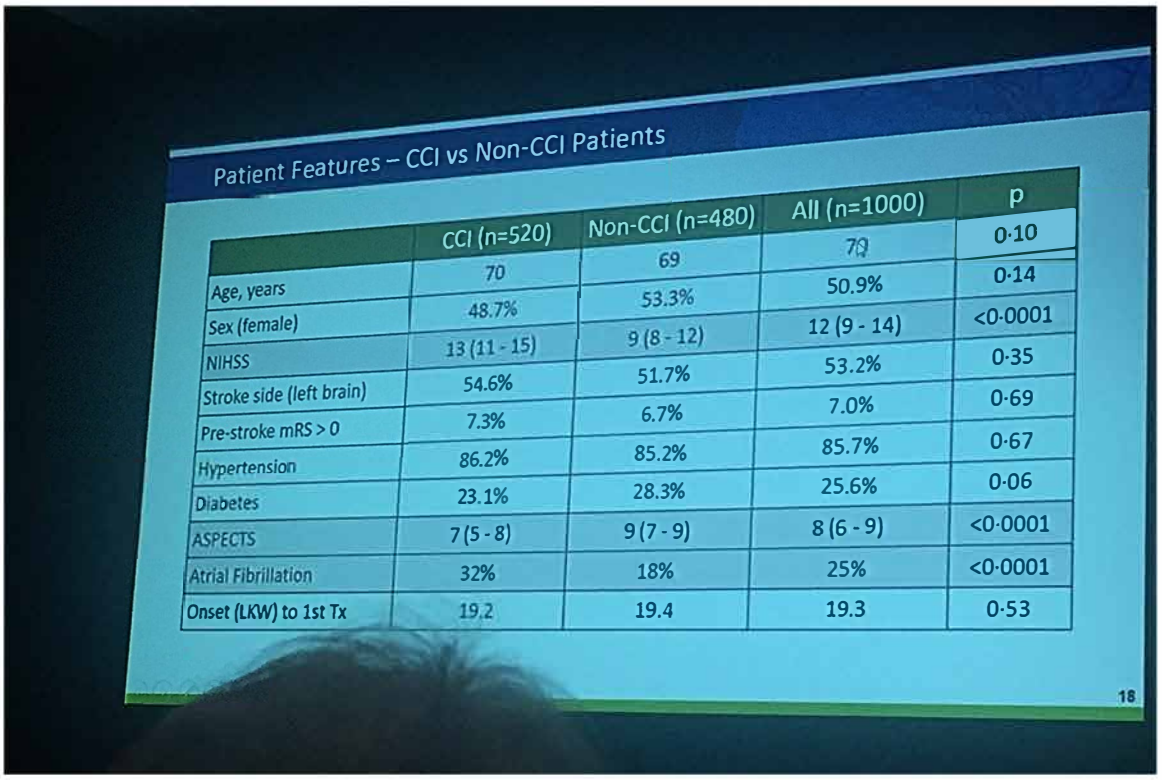

Key Inclusion / Exclusion Criteria
Inc. Criteria
Range
Age
M 40 – 80
F 40 – 85
NIHSS
7 - 13
TPSO
8 – 24h
Clinical & Radiological
Anterior circulation
Exc. Criteria
Feature
Imaging
• ICH
• Massive (>2/3)
• Lacunar
• Posterior circulation
Reperfusion Therapy
• IV thrombolysis
• EVT


ImpACT-24B Study Flow
Time Period
Activity
Day 1
• 1:1 dynamic randomization
• Neurostimulator / Sham implantation
• 1st SPG / Sham stimulation
Days 2-5
• Daily SPG / Sham stimulation
• Implant / Sham removal
• Day 5 mRS, NIHSS
Follow Up
• Day 30, 60 mRS, NIHSS
• Day 90 mRS, NIHSS, SIS-16
• mRS – Local blinded and centrally reviewed
13

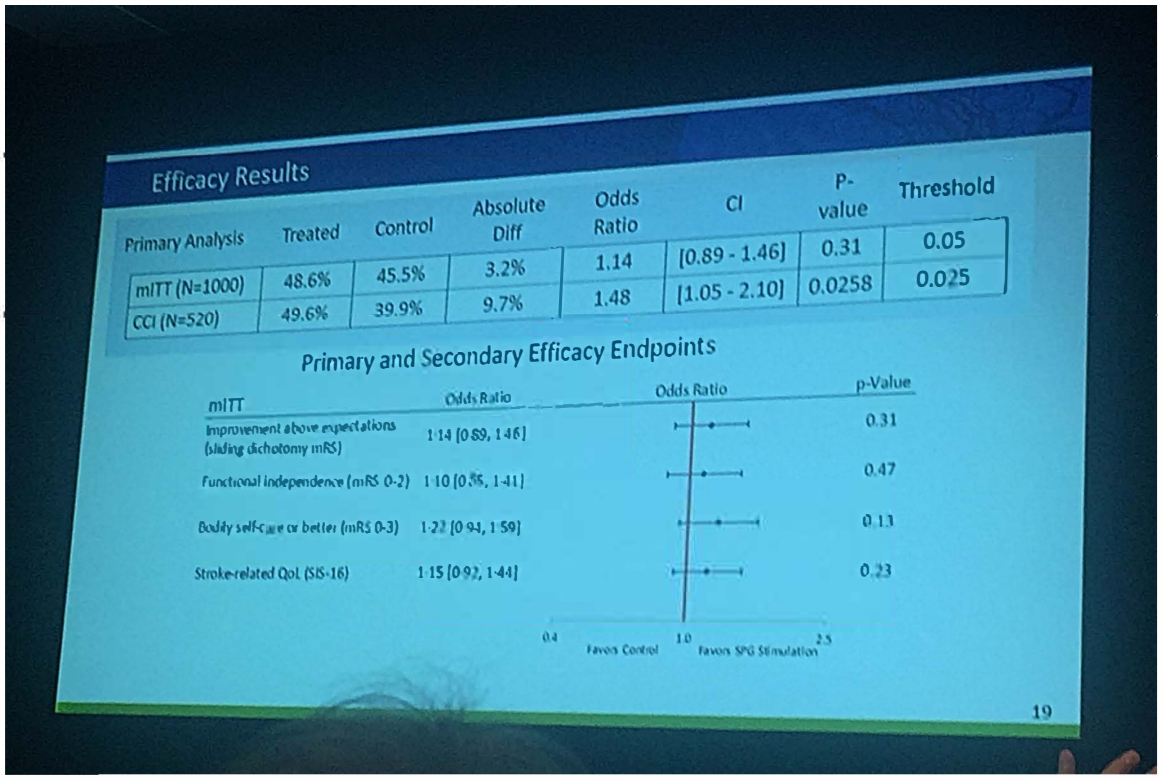

Two Implant Generations
First generation
New
Electrical Control Unit
1st Generation
New
Enrolled (n)
621
379
Active Arm (n)
293
188
Features
• Robust structure
• Easier, faster implantation
• Stimulation intensity visibility
14


Primary Efficacy Endpoint: mRS Improvement Above Expectations at 3 months
Sliding Dichotomy*
Prognostic Model for mRS Outcome
• From 1077 control patients in VISTA
• Predictor
• Age
• NIHSS
• Brain side
Expected mRS
Favorable
Unfavorable
0,1 0 1 2 3 4 5/6
2 0 1 2 3 4 5/6
3 0 1 2 3 4 5/6
4 0 1 2 3 4 5/6
5,6 0 1 2 3 4 5/6
*ESO Acute Stroke Trials Outcomes Consensus Statement – Stroke 2012;43 / Lancet Neurol 2009;8:434-40 / Stroke 2008;39:87-99
15

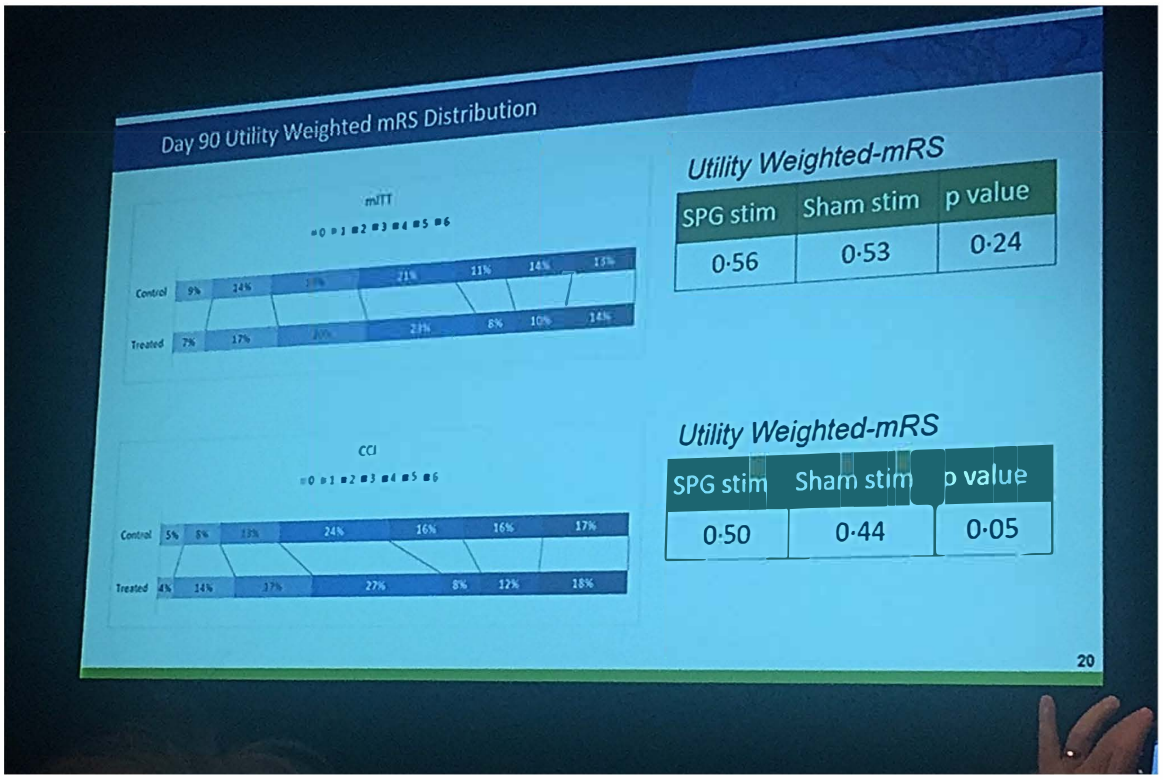

Patient Features
mITT Population
CCI Population
Treated
Sham
Treated
Sham
N 481 519 244 276
Age, years 70 71 70 72
Sex (female) 50% 52% 48% 49%
NIHSS 12 (9 - 14) 12 (9 - 14) 13 (12 - 15) 13 (11 - 15)
Stroke side (left brain) 57% 50% 57% 52%
Pre-stroke mRS > 0 8·5% 5·6% 8·6% 6·2%
Hypertension 87% 84% 87% 85%
Diabetes 24% 27% 22% 24%
Atrial Fibrillation 25% 26% 34% 31%
ASPECTS 8 (6 - 9) 8 (6 - 9) 7 (5 - 8) 7 (5 - 8)
Onset (LKW) to 1st Tx 19·9 (16·0 - 22·6) 18·7 (15·6 - 21·8) 19·7 (15·8 - 22·5) 18·5 (15·5 - 21·1)
Time from LKW (Implantation longer than Sham) p<0.0001, mITT: Side randomization imbalance p=0.04; CCI: No other differences with p<0.1
17

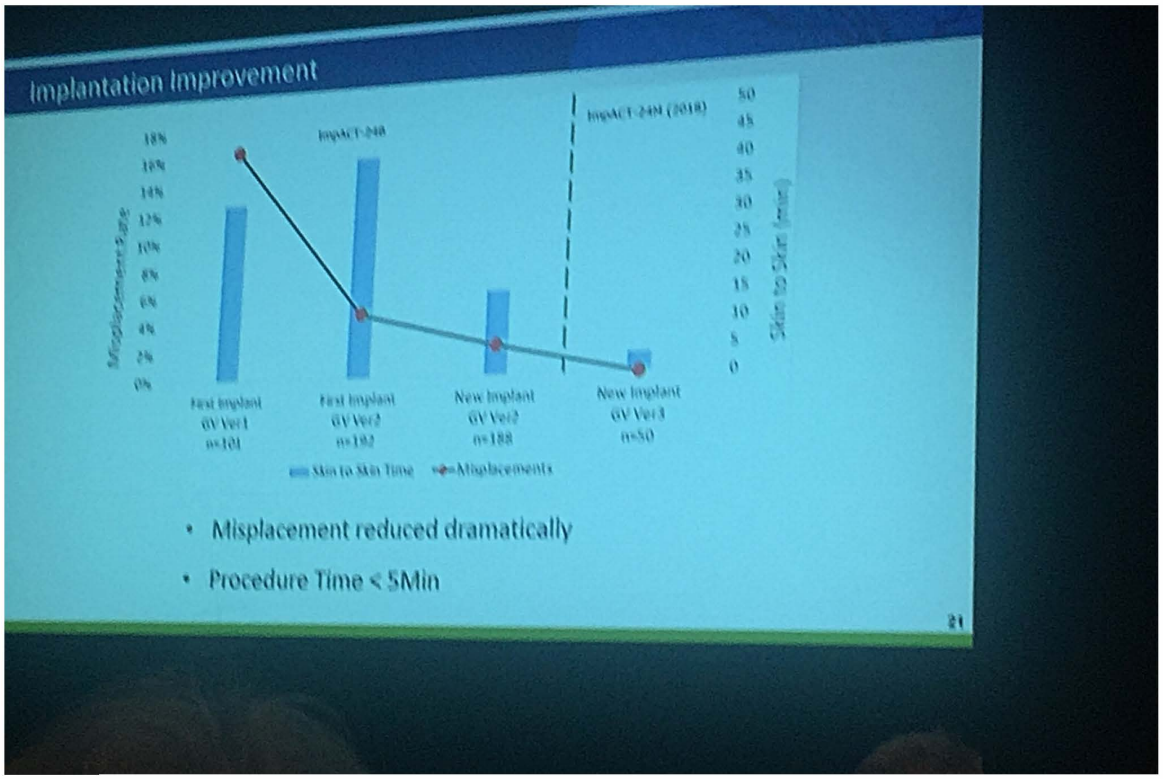


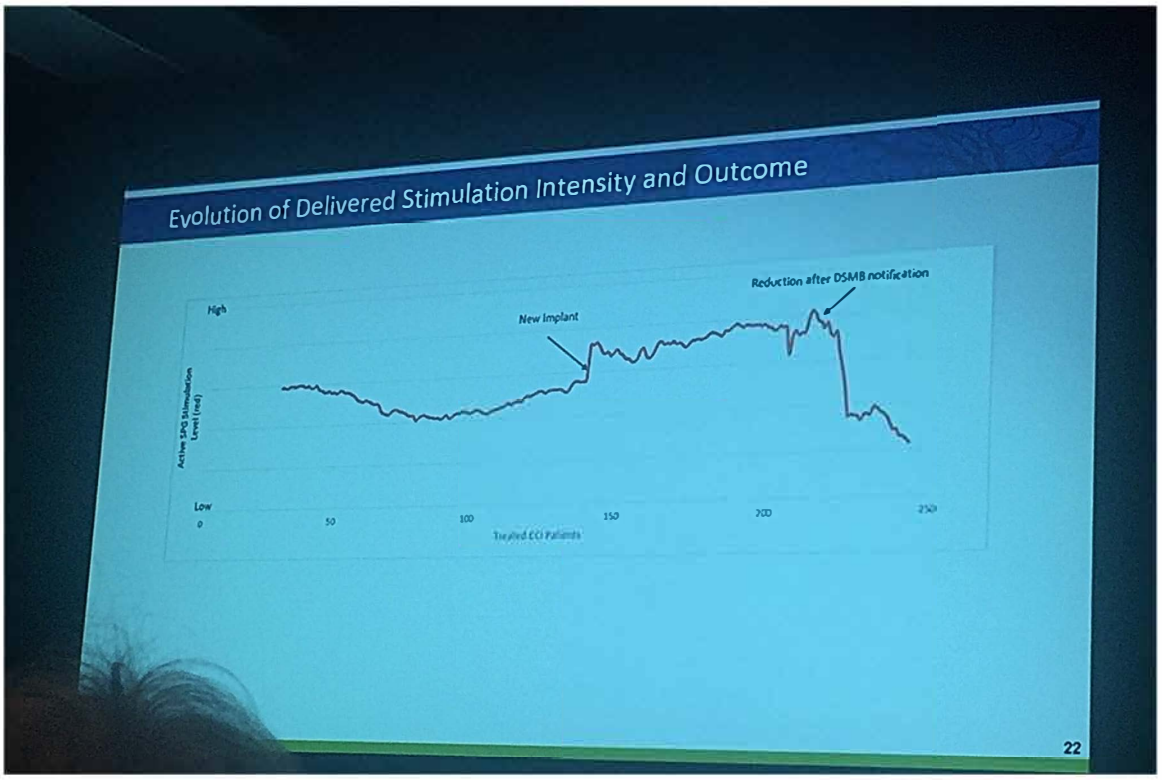
	CCI (n=520)	Non-CCI (n=480)	All (n=1000)	p
Age, years	70	69	70	0·10
Sex (female)	48.7%	53.3%	50.9%	0·14
NIHSS	13 (11 - 15)	9 (8 - 12)	12 (9 - 14)	<0·0001
Stroke side (left brain)	54.6%	51.7%	53.2%	0·35
Pre-stroke mRS > 0	7.3%	6.7%	7.0%	0·69
Hypertension	86.2%	85.2%	85.7%	0·67
Diabetes	23.1%	28.3%	25.6%	0·06
ASPECTS	7 (5 - 8)	9 (7 - 9)	8 (6 - 9)	<0·0001
Atrial Fibrillation	32%	18%	25%	<0·0001
Onset (LKW) to 1st Tx	19.2	19.4	19.3	0·53

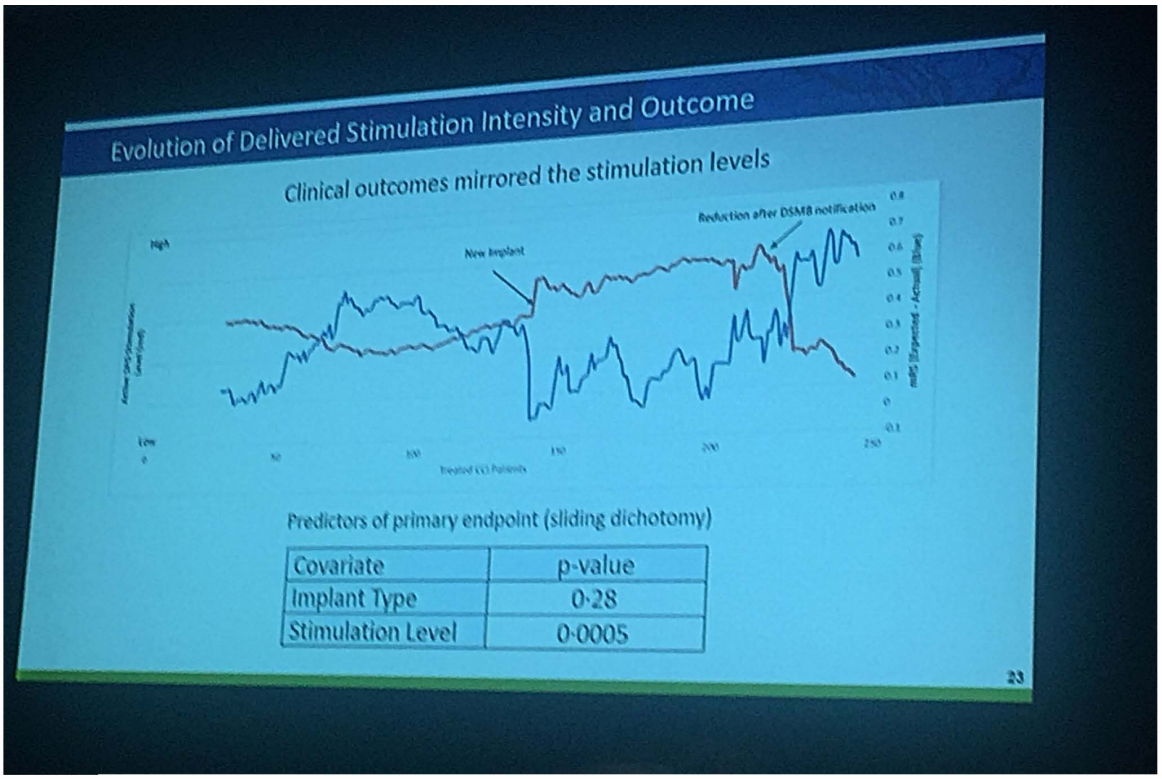


Primary Analysis	Treated	Control	Absolute Diff	Odds Ratio	CI	P-value	Threshold
mITT (N=1000)	48.6%	45.5%	3.2%	1.14	[0.89 - 1.46]	0.31	0.05
CCI (N=520)	49.6%	39.9%	9.7%	1.48	[1.05 - 2.10]	0.0258	0.025

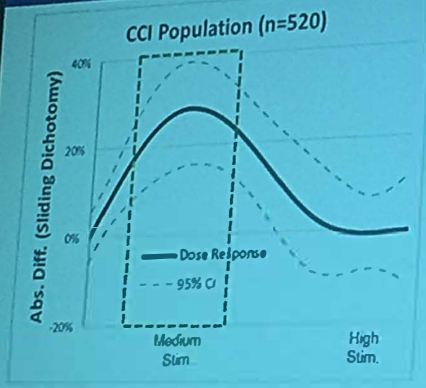

Day 90 Utility Weighted mRS Distribution
mITT
Control
Treated
CCI
Control
Treated
Utility Weighted-mRS
SPG stim | Sham stim | p value
0·56 | 0·53 | 0·24
Utility Weighted-mRS
SPG stim | Sham stim | p value
0·50 | 0·44 | 0·05
20


Implantation Improvement
ImpACT-24M (2018)
First Implant GV Ver1 n=101
First Implant GV Ver2 n=192
New Implant GV Ver2 n=188
New Implant GV Ver3 n=50
Skin to Skin Time
Misplacements
• Misplacement reduced dramatically
• Procedure Time < 5Min
21


Evolution of Delivered Stimulation Intensity and Outcome
Reduction after DSMB notification
New Implant
High
Low
0
50
100
150
200
250
22


Evolution of Delivered Stimulation Intensity and Outcome
Clinical outcomes mirrored the stimulation levels
Reduction after DSMB notification
New Implant
High
Low
Predictors of primary endpoint (sliding dichotomy)
Covariate
p-value
Implant Type
0·28
Stimulation Level
0·0005
23

Relation Between Stimulation Level and Clinical Outcomes



Endpoint	Dose Response p-value
Improved Above Expected (mRS Sliding Dichotomy)	0.0006
Independence (mRS 0-2)	0.0007
Self-Care or Better (mRS 0-3)	0.0006
SIS-16 QoL	<0.0001

- Inverted U-Shaped Dose Effect Curve (IUSDEC)
- Medium stim (25% of SPG pts): Absolute diff 29%, OR 3.34 [1.84-6.04], p<0.0001

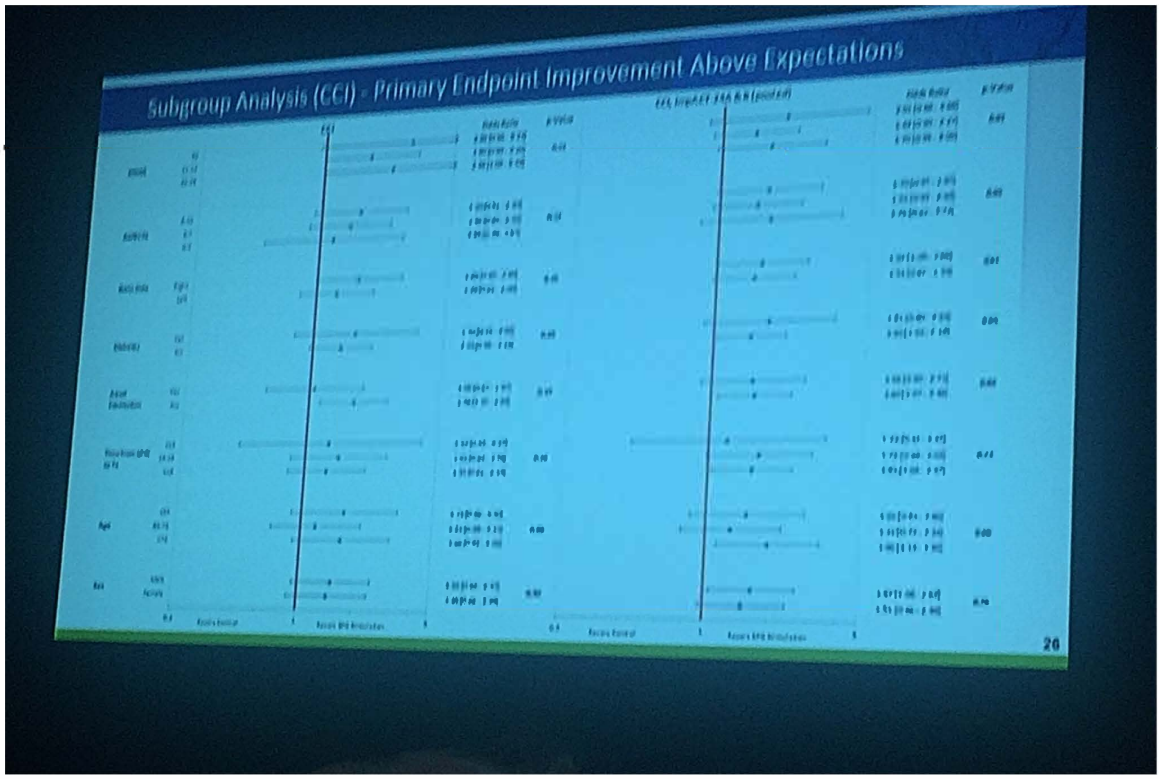
24

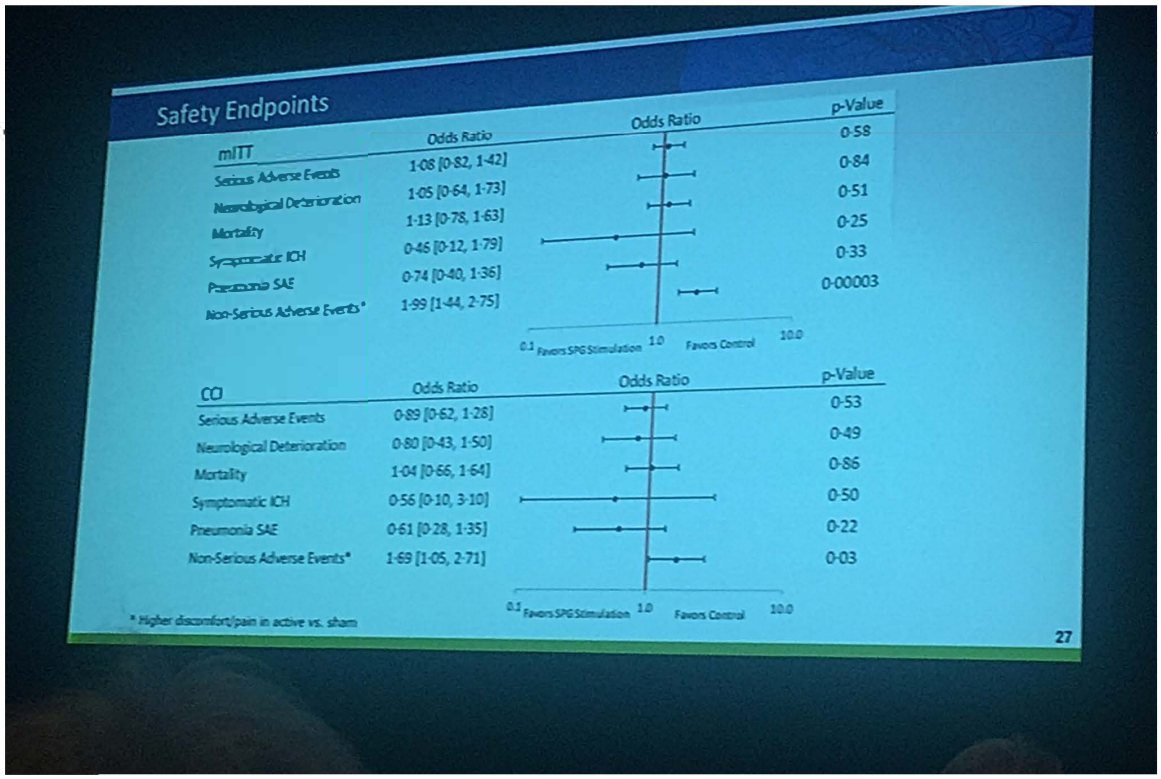
Independent Predictors of Primary Endpoint - CCI

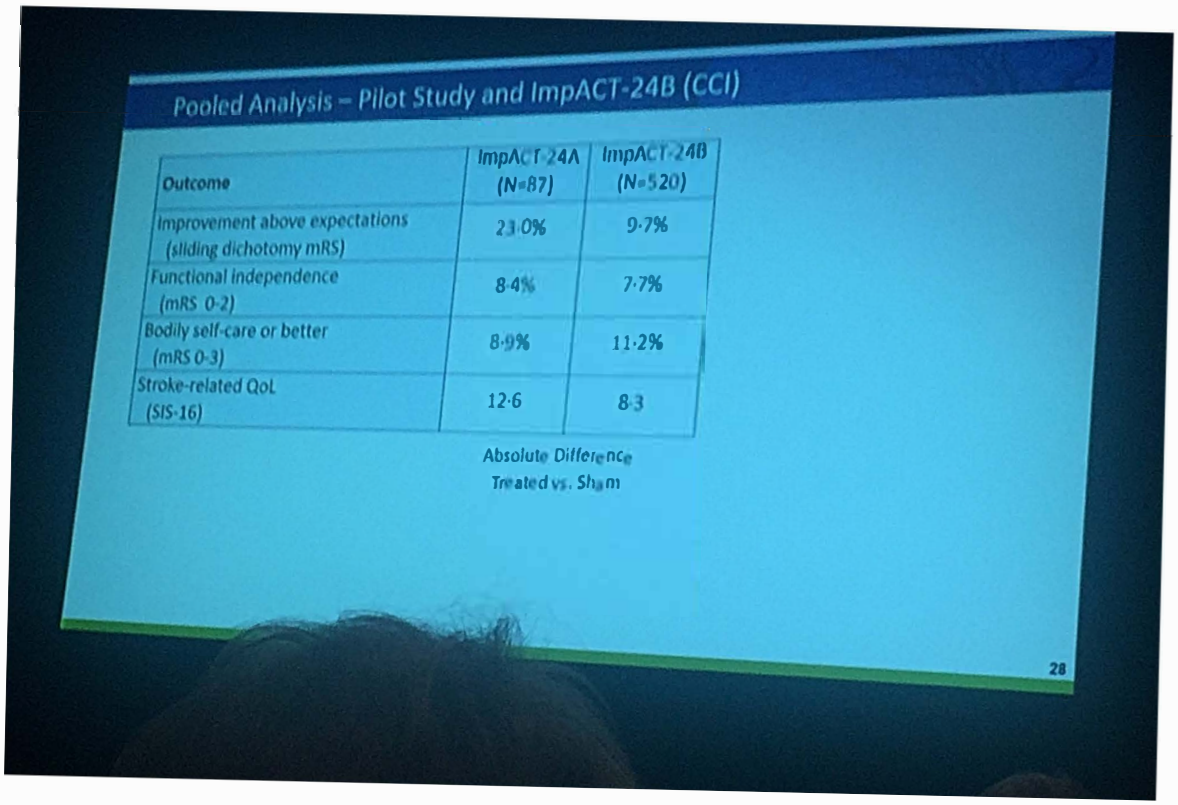
Variables	p-value
Stimulation Level	0·004
Brain side	0·001
Diabetes	0·001
ASPECTS	0·002
NIHSS	0·003

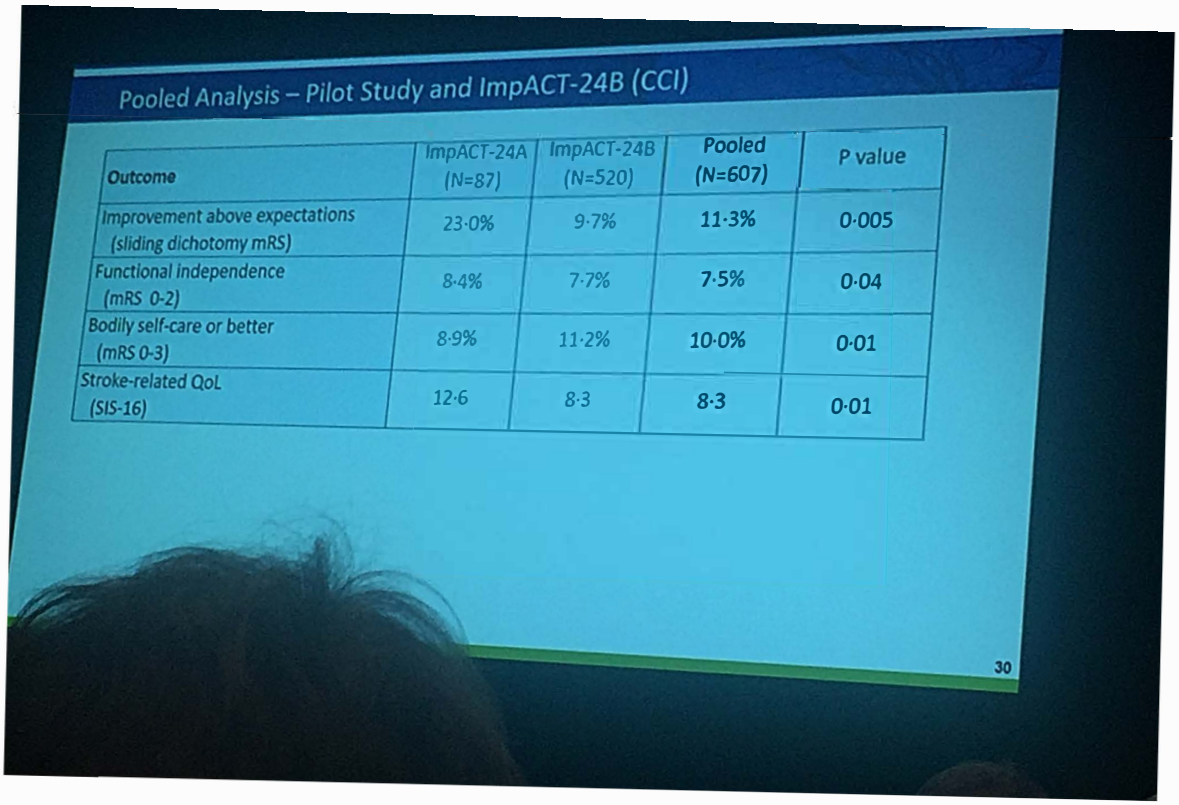
Notes:
(1) Predictors of improvement beyond expectation (sliding dichotomy) using LRT
(2) Non-significant covariates: Time from onset, Atrial Fibrillation, Sex, Age
(3) Sliding dichotomy partially adjusts for NIHSS, Side, Age

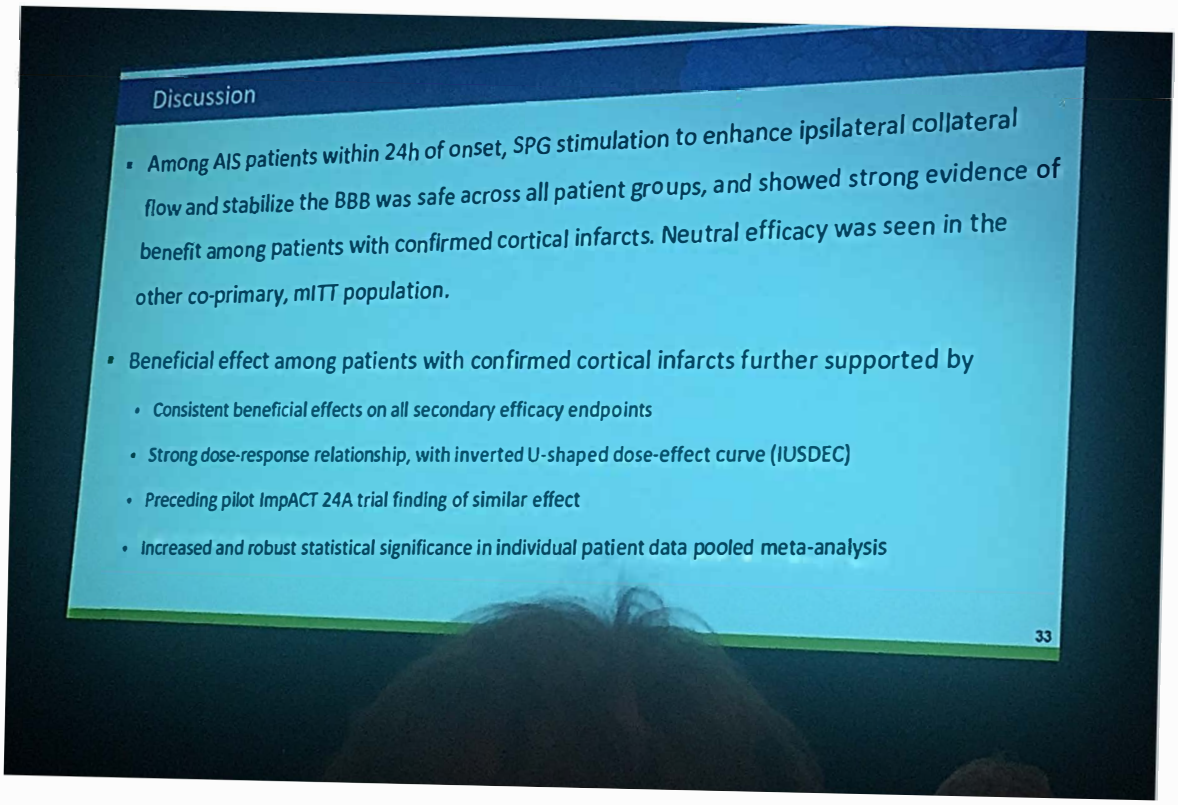
25

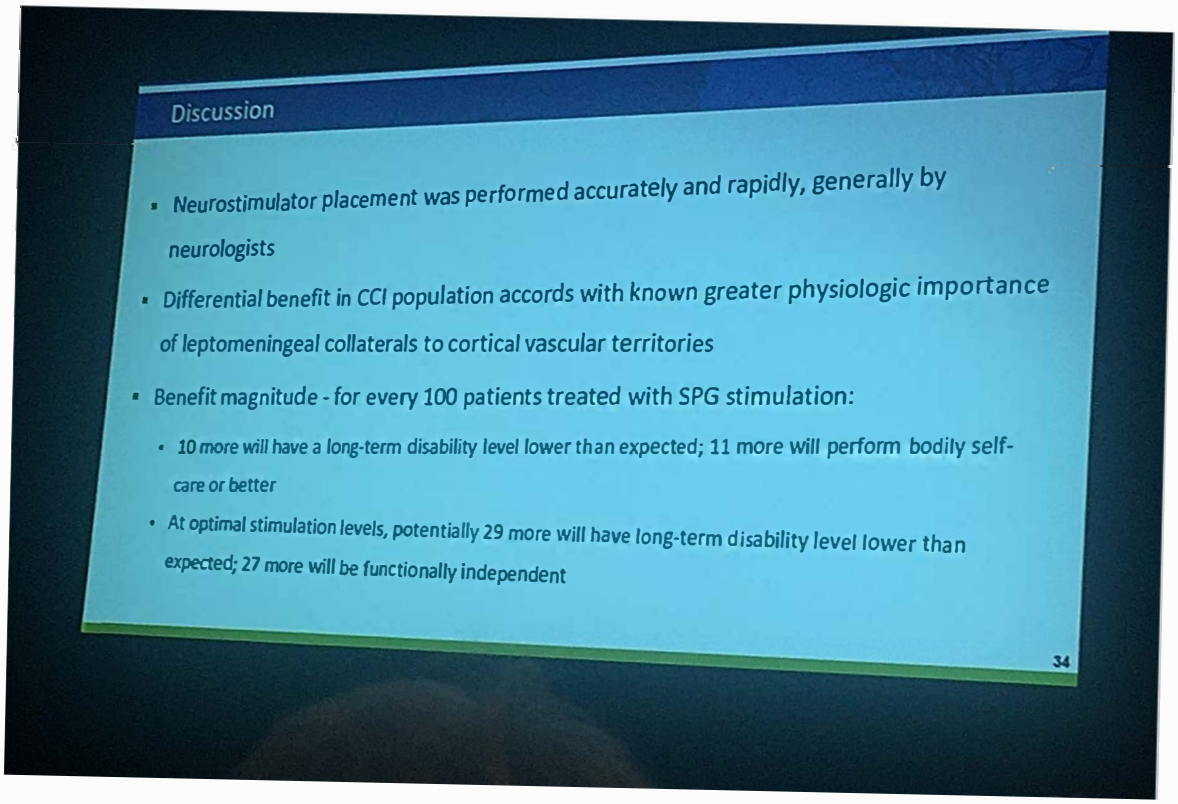

Subgroup Analysis (CCI) - Primary Endpoint Improvement Above Expectations
20

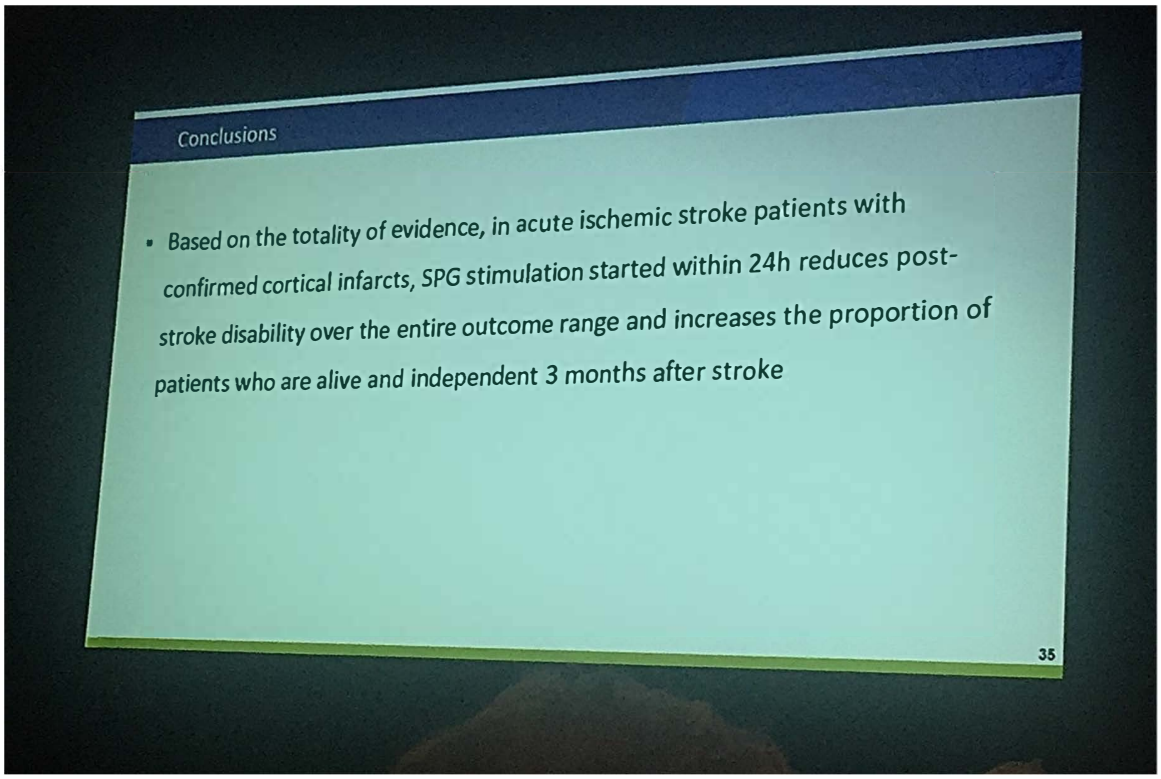

Safety Endpoints
mITT
Odds Ratio
Odds Ratio
p-Value
Serious Adverse Events
1·08 [0·82, 1·42]
0·58
Neurological Deterioration
1·05 [0·64, 1·73]
0·84
Mortality
1·13 [0·78, 1·63]
0·51
Symptomatic ICH
0·46 [0·12, 1·79]
0·25
Pneumonia SAE
0·74 [0·40, 1·36]
0·33
Non-Serious Adverse Events*
1·99 [1·44, 2·75]
0·00003
0.1
Favors SPG Stimulation
1.0
Favors Control
10.0
CCI
Odds Ratio
Odds Ratio
p-Value
Serious Adverse Events
0·89 [0·62, 1·28]
0·53
Neurological Deterioration
0·80 [0·43, 1·50]
0·49
Mortality
1·04 [0·66, 1·64]
0·86
Symptomatic ICH
0·56 [0·10, 3·10]
0·50
Pneumonia SAE
0·61 [0·28, 1·35]
0·22
Non-Serious Adverse Events*
1·69 [1·05, 2·71]
0·03
0.1
Favors SPG Stimulation
1.0
Favors Control
10.0
* Higher discomfort/pain in active vs. sham
27


Pooled Analysis – Pilot Study and ImpACT-24B (CCI)
Outcome
ImpACT-24A (N=87)
ImpACT-24B (N=520)
Improvement above expectations (sliding dichotomy mRS)
23·0%
9·7%
Functional independence (mRS 0-2)
8·4%
7·7%
Bodily self-care or better (mRS 0-3)
8·9%
11·2%
Stroke-related QoL (SIS-16)
12·6
8·3
Absolute Difference Treated vs. Sham
28


Pooled Analysis – Pilot Study and ImpACT-24B (CCI)
Outcome
ImpACT-24A (N=87)
ImpACT-24B (N=520)
Pooled (N=607)
P value
Improvement above expectations (sliding dichotomy mRS)
23·0%
9·7%
11·3%
0·005
Functional independence (mRS 0-2)
8·4%
7·7%
7·5%
0·04
Bodily self-care or better (mRS 0-3)
8·9%
11·2%
10·0%
0·01
Stroke-related QoL (SIS-16)
12·6
8·3
8·3
0·01
30


Discussion
Among AIS patients within 24h of onset, SPG stimulation to enhance ipsilateral collateral flow and stabilize the BBB was safe across all patient groups, and showed strong evidence of benefit among patients with confirmed cortical infarcts. Neutral efficacy was seen in the other co-primary, mITT population.
Beneficial effect among patients with confirmed cortical infarcts further supported by
Consistent beneficial effects on all secondary efficacy endpoints
Strong dose-response relationship, with inverted U-shaped dose-effect curve (IUSDEC)
Preceding pilot ImpACT 24A trial finding of similar effect
Increased and robust statistical significance in individual patient data pooled meta-analysis
33


Discussion
Neurostimulator placement was performed accurately and rapidly, generally by neurologists
Differential benefit in CCI population accords with known greater physiologic importance of leptomeningeal collaterals to cortical vascular territories
Benefit magnitude - for every 100 patients treated with SPG stimulation:
10 more will have a long-term disability level lower than expected; 11 more will perform bodily self-care or better
At optimal stimulation levels, potentially 29 more will have long-term disability level lower than expected; 27 more will be functionally independent
34


Conclusions
Based on the totality of evidence, in acute ischemic stroke patients with confirmed cortical infarcts, SPG stimulation started within 24h reduces post-stroke disability over the entire outcome range and increases the proportion of patients who are alive and independent 3 months after stroke
35