Ischemic Stroke System (ISS500)

Premarket approval application

Sponsor: BrainGate LTD

Neurological Devices Advisory Committee Meeting

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(I have no financial conflicts of interests)

Primary effectiveness outcome not met…

Primary Effectiveness Outcomes for mITT and CCI Responder Groups Modified Rankin Score Less Serious than Expected at 90 Days after Stroke[3]

Analysis Group (n)	Response Rate		Absolute Difference	Odds	p-Value
	ISS	Sham			
mITT (1000)	48.6 % (481)	45.5 % (519)	3.2%	1.14 (0.89–1.46)	0.31
CCI Subset of mITT (520)	49.6 % (244)	39.9 % (276)	9.7%	1.48 (1.05–2.10)	0.0258

Table 1 Primary Effectiveness Outcome for ImpACT-24B Trial

Source: FDA Executive Summary, PDF p. 3

FDA Concern #1: Questionable statistical and clinical significance

- ITT and mITT (fully stimulated or sham treated) differed markedly
- Exclusions only seen in the sphenopalatine ganglion stimulation (SPG) group
  - Excluded: placement of the stimulator failed
  - Excluded: placement was successful, but no stimulation (real or sham) was delivered

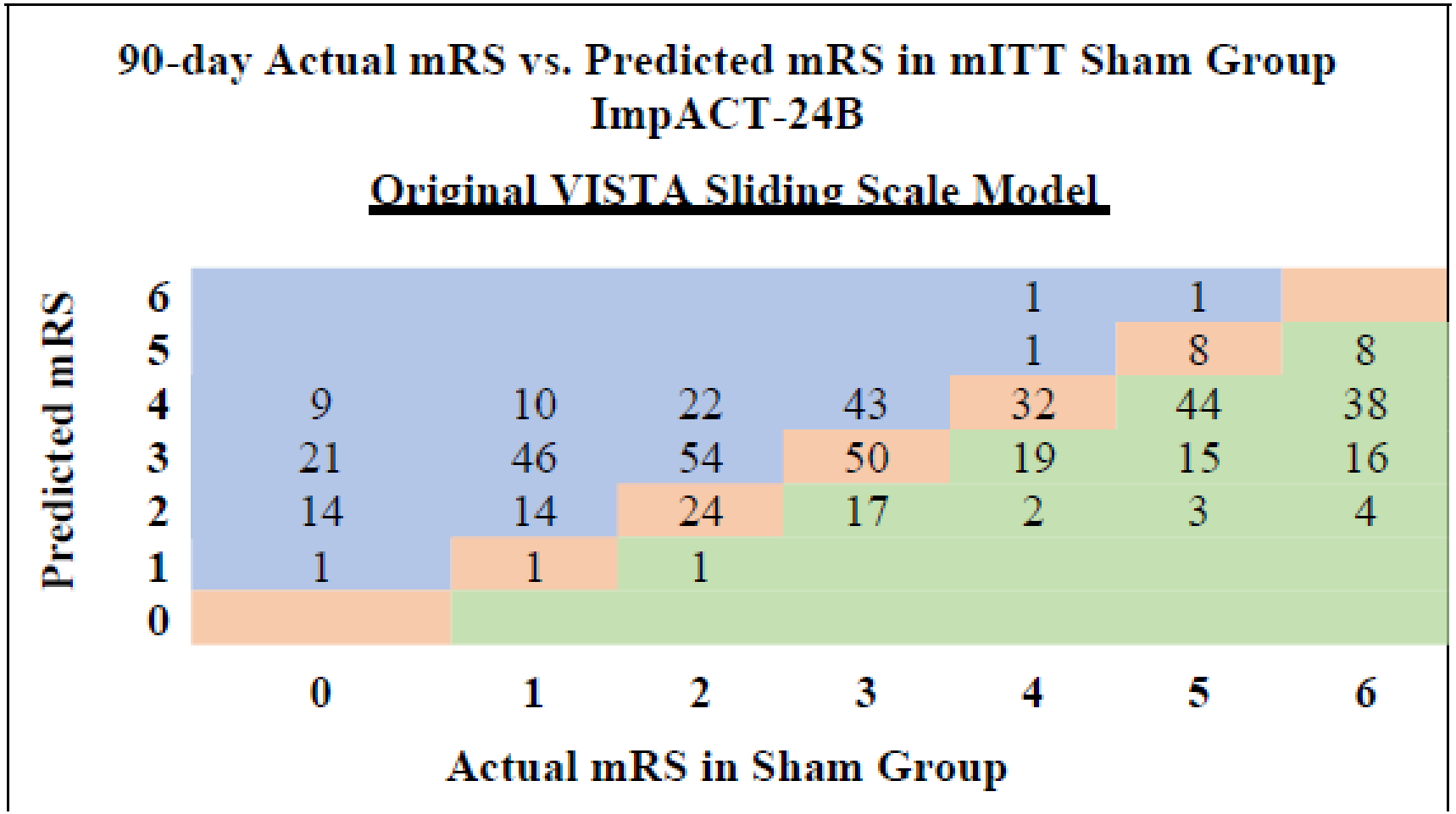
Responder Group in Study ImpACT-24B
CCI Patients Excluded from ITT Population to Form the CCI Population

	SPG	Sham	Total
Randomized Patients with CCI (n)	278	276	554
CCI Patients not in CCI Population(n)	34	0	34
CCI Patients not in CCI Population(n)	12%	0%	6%
CCI Population(n)	244	276	520

Table 2 Imbalance in CCI Population Excluded from ITT Population

Source: FDA Executive Summary, PDF p. 4

FDA Concern #2: sliding dichotomy scale outcome



Source: FDA Executive Summary, Table 3, PDF p. 5

FDA Concern #3: significant protocol changes, late

- Note: the treating investigators were not blinded, and thus their "…communications with the Steering Committee may have introduced bias…" (FDA Execute Summary Document, p. 6)

1. Additional interim analysis not mentioned in initial protocol
2. Revising statistical plan to include only those with implant within 5 mm of the spinal ganglion (rather than within 15 mm).
3. Adding several additional analyses (e.g., Dichotomy mRS 0-2, 0-3)
4. Multiple changes to the device specifications/design

Source: FDA Executive Summary, PDF p. 6

FDA Concern #4: U.S. patient results; heterogeneity internationally

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

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

Source: FDA Executive Summary, PDF p. 7

FDA Concern #5: Safety

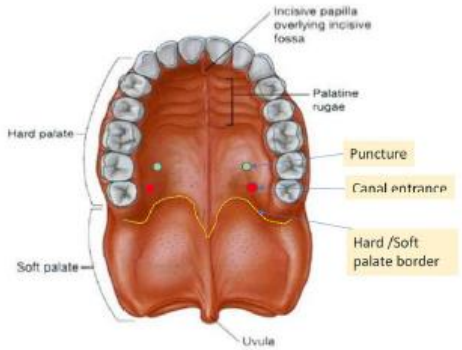


Figure 31 The Upper Palate

"Puncture tool"

Possible adverse events

Upper palate puncture injury, bleeding, swelling, airway enlargement, laryngospasm, microaspiration, chronic neuropathic pain, acute pain; hematoma formation, infection, tachycardia and increased blood pressure.

- Reperfusion injury at the ischemic core and penumbra

Source: FDA Executive Summary, PDF pp. 17, 22, 23

FDA Concern #6: Can physicians select patients who might benefit?

- Pivotal trial selected the CCI subpopulation, after the fact, with criteria that may not be reproducible by clinicians.

- No votes recommended for this device regarding:
  - efficacy
  - safety
  - benefits outweighing risks