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Testimony Before the Food and Drug Administration's Neurological Devices Advisory Committee Meeting Regarding the PMA for Ischemic Stroke System (ISS500) Submitted by BrainGate LTD

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I am Michael Abrams, a health researcher at Public Citizen's Health Research Group. I have no financial conflicts of interest.

Public Citizen strongly opposes approval of the premarket approval application (PMA) for BrainGate's Ischemic Stroke System (ISS500) because data from clinical trials of the device fail to provide a reasonable assurance that the device is effective.

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Here are the primary effectiveness outcome results for the one pivotal phase 3 trial of the ISS500.[1]

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

[1] Food and Drug Administration. FDA executive summary. Ischemic Stroke System (ISS500). Neurological Devices Advisory Committee meeting. December 10, 2021. https://www.fda.gov/media/154693/download. Accessed December 9, 2021. PDF page 3.

The top row shows the modified intent-to-treat (mITT) analysis, which only included subjects who received at least one active or sham treatment session.[2] A statistically significant effect was not seen (p=0. 31).[3]

The bottom row of the table shows *post-hoc* analyses with just 520 subjects with confirmed cortical involvement (CCI).[4] Those results tend toward significance, but notably were not, as the p-value was prespecified at 0.025.[5]

A key question before the committee today is whether this data supports effectiveness. We believe it does not, and the Food and Drug Administration (FDA) technical review of this PMA seems to concur with that assessment.

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In fact, not only is the *post-hoc* subpopulation analysis statistically suspect, there is also clear imbalance in the exclusions used to yield that final analytic subpopulation.

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

Twelve percent of the CCI patients were excluded from the final ITT population of the ISS500 treatment group because they did not receive the stimulation therapy compared with 0% of the sham therapy group.[6] In the words of the FDA reviewers: "This imbalance between the cohorts raises serious doubts about the results of the study."[7]

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Moreover, the primary efficacy outcome used— improvement beyond expectation on the 3-month mean Rankin score (mRS) of global disability, according to the sliding dichotomy approach — is suspect in its derivation. Historic VISTA data is used to predict the 3-month-post-stroke disability score based on NIH stroke scale score, age and hemisphere effected, but that

[2] *Ibid*. PDF page 2.
[3] *Ibid.* PDF page 3.
[4] *Ibid*. PDF page 2.
[5] *Ibid*. PDF page 16.
[6] *Ibid*. PDF page 4.
[7] *Ibid.* PDF page 4.

prediction model only proved accurate 22.2% of the time (the diagonal orangish numbers in the center of this grid).[8]

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

The Y-axis of the table is the predicted mRS score using the Original VISTA model, and the X-axis is the actual mRS score. The numbers in orange represent correct predictions where the model prediction matches the actual mRS outcome. The numbers in blue and green are all erroneous predictions. From these data, the model demonstrates 22.2% accuracy (the sum of all orange numbers divided by the number of sham 519 patients, or 115/519).

Table 3 Accuracy of Original Vista Sliding Scale in Sham Group of ImpACT 24-B Trial

Note, for example, that 20 people died (Rankin score=6), even as the model predicted they would have moderate or lower disability. In the words of the FDA reviewers: "…the imperfect performance of the VISTA model [represents] a serious confounder of the sliding responder analysis results."[9] This clearly raises concern about the validity of the trial's main effectiveness outcome measure.

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The FDA review further noted significant protocol changes late in the trial that the sponsor relied upon to alter the results in their favor.[10] And note, overt or unconscious biases plausibly had a role in these changes because the treating investigators for this device trial were not blinded.[11]

Changes implemented late in the trial included focus on the CCI subpopulation, unplanned interim analyses, revisions to the statistical plan, and the addition of several analyses including

[8] *Ibid*. PDF page 4.
[9] *Ibid*. PDF page 5.
[10] *Ibid*. PDF page 6.
[11] *Ibid*. PDF page 6.

alternative implantation inclusion criteria, alternative endpoints, and multiple changes to the device design.[12] Regarding the latter point, FDA reviewers wrote this: "FDA generally considers that the device used in a pivotal clinical study should be the final device."[13] That was not the case here. The device changed over time.

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Data here shows that the device was tested in only 31 U.S. patients, and the results from those patients were not supportive of effectiveness.[14]

	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]

Moreover, between-country heterogeneity regarding effectiveness of this device, as noted by the FDA, suggests great uncertainty regarding the device's true effects.[15]

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Regarding safety issues, the FDA notes that the implantation (puncture insertion through the upper palate) and stimulation procedures both likely carry latent risks, especially the concern that sphenopalatine ganglion stimulation might yield a reperfusion injury at the ischemic core or penumbra.[16]

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Lastly the FDA has expressed concern that the definition of CCI is not clear enough to reliably identify patients who might benefit from the said device.[17]

Accordingly, Public Citizen, consistent with many of the concerns expressed by the FDA reviewers, urges this advisory committee to vote "no" on all three voting questions about the ISS500.

[12] *Ibid*. PDF page 6.
[13] *Ibid*. PDF page 6.
[14] *Ibid*. PDF page 7.
[15] *Ibid*. PDF pages 116-7.
[16] *Ibid*. PDF pages 7, 37-8.
[17] *Ibid*. PDF page 8.