Sphenopalatine Ganglion Stimulation to Augment Cerebral Blood Flow

A Randomized, Sham-Controlled Trial

Natan M. Bornstein, MD*; Jeffrey L. Saver, MD*; Hans-Christoph Diener, MD; Philip B. Gorelick, MD; Ashfaq Shuaib, MD; Yoram Solberg, MD; Thomas Devlin, MD, PhD; Thomas Leung, MD; Carlos A. Molina, MD; for the ImpACT-24A Investigators†

Background and Purpose—Many patients with acute ischemic stroke are not eligible for thrombolysis or mechanical reperfusion therapies due to contraindications, inaccessible vascular occlusions, late presentation, or large infarct core. Sphenopalatine ganglion (SPG) stimulation to enhance collateral flow and stabilize the blood-brain barrier offers an alternative, potentially more widely deliverable, therapy.

Methods—In a randomized, sham-controlled, double-masked trial at 41 centers in 7 countries, patients with anterior circulation ischemic stroke not treated with reperfusion therapies within 24 hours of onset were randomly allocated to active SPG stimulation or sham control. The primary efficacy outcome was improvement beyond expectations on the modified Rankin Scale of global disability at 90 days (sliding dichotomy), assessed in the modified intention-to-treat population. The initial planned sample size was 660 patients, but the trial was stopped early when technical improvements in device placement occurred, so that analysis of accumulated experience could be conducted to inform a successor trial.

Results—Among 303 enrolled patients, 253 received at least one active SPG or sham stimulation, constituting the modified intention-to-treat population (153 SPG stimulation and 100 sham control). Age was median 73 years (interquartile range, 64–79), 52.6% were female, deficit severity on the National Institutes of Health Stroke Scale was median 11 (interquartile range, 9–15), and time from last known well median 18.6 hours (interquartile range, 14.5–22.5). For the primary outcome, improved 3-month disability beyond expectations, rates in the SPG versus sham treatment groups were 49.7% versus 40.0%; odds ratio, 1.48 (95% CI, 0.89–2.47); P=0.13. A significant treatment interaction with stroke location (cortical versus noncortical) was noted, P=0.04. In the 87 patients with confirmed cortical involvement, rates of improvement beyond expectations were 50.0% versus 27.0%; odds ratio, 2.70 (95% CI, 1.08–6.73); P=0.03. Similar response patterns were observed for all prespecified secondary efficacy outcomes. No differences in mortality or serious adverse event safety end points were observed.

Conclusions—SPG stimulation within 24 hours of onset is safe in acute ischemic stroke. SPG stimulation was not shown to statistically significantly improve 3-month disability above expectations, though favorable outcomes were nominally higher with SPG stimulation. Beneficial effects may distinctively be conferred in patients with confirmed cortical involvement. The results of this study need to be confirmed in a larger pivotal study.

Clinical Trial Registration—URL:https://www.clinicaltrials.gov.Uniqueidentifier:NCT03767192. **(*Stroke*.2019;50:2108-2117. DOI: 10.1161/STROKEAHA.118.024582.)**

Key Words: blood-brain barrier ■ caregivers ■ collateral circulation ■ thrombectomy ■ vasodilatation

See related article, p 1954

In patients with acute ischemic stroke (AIS), reperfusion is associated with better neurological outcomes and anterograde reperfusion is the goal of current therapeutic strategies. Two direct reperfusion therapies have shown benefit in randomized trials and are recommended in guidelines for the management of eligible patients with AIS[1] but both have limitations. Intravenous thrombolysis use is limited by

Received December 10, 2018; final revision received March 19, 2019; accepted March 28, 2019.

From the Brain Division, Shaarei Zedek Medical Center, Jerusalem and Tel Aviv Sourasky Medical School, Tel Aviv University (N.M.B.); Department of Neurology and Comprehensive Stroke Center, David Geffen School of Medicine at UCLA, Los Angeles CA (J.L.S.); Faculty of Medicine, University of Duisburg-Essen (H.-C.D.); Davee Department of Neurology, Northwestern University, Chicago, IL (P.B.G.); Department of Medicine (Neurology), University of Alberta, Edmonton (A.S.); BrainsGate Ltd, Caesarea, Israel (Y.S.); Department of Neurology, University of Tennessee College of Medicine, Chattanooga (T.D.); Division of Neurology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong (T.L.); and Stroke Unit, Department of Neurology, Vall d'Hebron University Hospital, Barcelona (C.A.M.).

Guest Editor for this article was Markku Kaste, MD, PhD.

*Drs Bornstein and Saver contributed equally.

†A list of all ImpACT-24A Investigators is given in the Appendix.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.118.024582.

Correspondence to Jeffrey Saver, MD, Reed Neurologic Research Center, UCLA, 710 Westwood Plaza, Los Angeles, CA 90095. Email jsaver@mednet.ucla.edu

contraindications to lytic exposure in many patients, increased rates of hemorrhagic transformation compared with untreated patients, and low recanalization rates (30% of visualized artery occlusions).[2] Endovascular thrombectomy is constrained by being limited to large vessel occlusions accessible by thrombectomy devices, available only at advanced thrombectomy-capable stroke centers, and risks of subarachnoid hemorrhage and infarcts in new territories.[3,4] Therefore, there is a need for a therapy that is safe and efficacious in an extended time window, can be administered in frontline hospitals, does not require advanced imaging for patient selection, and is not associated with hemorrhagic transformation.

Enhancement of blood flow through collateral vessels is an attractive alternative or complementary therapeutic approach, yielding reperfusion of ischemic tissues via routes other than recanalization of the directly supplying artery. Patients with AIS with good collateral flow have been shown to have lower rates of infarct expansion and improved functional outcomes.[3–8]

The sphenopalatine ganglion (SPG) is the source of parasympathetic innervation to the anterior cerebral circulation.[9] In preclinical studies, SPG stimulation led to arterial vasodilatation, increased ipsilateral cerebral blood flow, and augmentation of cortical tissue perfusion.[10] In preclinical models of anterior circulation stroke, SPG stimulation reduced infarct volume,[11,12] increased neuronal survival,[13] reduced damage to the blood-brain barrier,[10] and improved neurological outcome[10,13] when started at various time points, including up to 24 hours from stroke onset.[10,13]

In a single-arm feasibility study, SPG stimulation in 98 patients with AIS was safe and demonstrated potential efficacy compared with historical controls, with nominally lower disability levels and a higher rate of functional independence at 3 months. A greater benefit was observed in patients with aphasia, suggesting potential enhanced efficacy among patients with cortical involvement.[14]

The goal of the ImpACT-24A trial (Implant Augmenting Cerebral blood flow Trial-24A) was further assessment of the safety of neurostimulator implantation, and of the safety and efficacy of SPG stimulation to enhance outcome in anterior circulation patients with AIS up to 24 hours from onset.

Methods

Study Data Availability

The authors will deposit the control group data, analytic methods, and study materials, one year after publication, in the VISTA (Virtual International Stroke Trial Archive; http://www.virtualtrialsarchives.org/vista/), to be maintained by VISTA as available for use by other researchers; and additionally will make all their data, analytic methods, and study materials available to regulatory agency researchers for purposes of reproducing the results.

Study Design and Participants

ImpACT-24A was a prospective, multinational, randomized, sham-control, double-blind, adjunctive to standard of care, and parallel arm trial. The study was performed in 41 centers in 7 countries. A list of participating sites, investigators, and DSMB members is shown in Tables I and II in the online-only Data Supplement.

The study included patients aged 18 to 85 years, with National Institutes of Health Stroke Scale (NIHSS) scores between 7 and 18, clinical evidence of stroke in the anterior circulation, and ability to start treatment up to 24 hours from stroke onset (time last known well). Patients were excluded if they had radiological evidence of intracranial hemorrhage, massive (>2/3 of middle cerebral artery territory), lacunar or posterior circulation acute infarcts, or were eligible for treatment with intravenous thrombolysis or endovascular thrombectomy per national and institutional standard of care. Presence of likely lacunar or posterior circulation infarcts was assessed based on pattern of clinical deficits and location of early infarct signs, if present, on initial computed tomography (CT) or magnetic resonance imaging.

The protocol was approved by health authorities and institutional review boards in all participating countries and centers, and written informed consent was obtained from all participants or their legally authorized representatives. The study was registered at clinicaltrials.gov (URL: https://www.clinicaltrials.gov. Unique identifier: NCT00826059).

Randomization and Masking

The study design included an implantation phase and a randomized treatment phase. All enrolled patients first underwent the neurostimulator implantation procedure. Then, subjects in whom an implant was placed proceeded to randomization in a 2:1 ratio to active SPG stimulation arm or to sham stimulation. Patients in both groups received medical therapy according to the standard of care for AIS throughout their study participation.

Randomization was performed by the participating centers through an Interactive Web-Based Randomization System using block randomization with variable block size, stratified by stroke severity (NIHSS strata). Patients, implanters, caregivers, outcome assessors, and the sponsor were all blinded to treatment allocation.

Procedures

Implantation was a bedside, minimally invasive procedure in which the neurostimulator electrode (23 mm long and 2 mm in diameter) was implanted into the pterygopalatine canal near the SPG (Figure I in the online-only Data Supplement). The procedure included 3 parts: (1) locating the canal foramen; (2) preparing the canal for the insertion of the neurostimulator using a set of rigid trocars (diameters, 1.0–2.0 mm); and (3) implanting the neurostimulator. An optic navigation system was introduced after 143 implantations, aiming to improve the rate of on-target neurostimulator placement. Certification to perform implantations using this system included half-day training on a model.

After implantation, active/sham stimulation was administered in daily 4-hour sessions, beginning immediately following the placement procedure and continuing for 5 consecutive days. Active/sham stimulation was induced by a transmitter placed on the patient's face over the pterygoid canal.[15] To ensure treatment tolerability, actual/sham stimulation parameters started at a low level and were incrementally advanced until minor symptoms, such as tingling or discomfort occurred. If discomfort occurred before reaching the maximum level, the stimulation level was reduced to reach each patient's comfortable tolerance level. For blinding purposes, active and sham treatments also included identical beeping and transmitter vibrations at variable intensities. Zero current was delivered in the sham stimulation in a masked manner.

After the last treatment on day 5, CT or magnetic resonance imaging neuroimaging was performed to assess infarct lesion size and detect potential hemorrhagic transformation. Also, the scan was used to assess the attained implant position, rated by a central positioning evaluator, blinded to treatment group assignment. A neurostimulator was rated as well-placed if it was within 5 mm of the pterygopalatine fossa. After the day 5 imaging, the implant was removed with fine forceps.

Outcomes

The primary outcome was final global disability level on the modified Rankin Scale (mRS) at 3 months better than expectation (sliding dichotomy analysis), assessed by each site's masked evaluator.[16,17] Success in achieving improvement beyond expectation was defined as an mRS score one or more points better (lower) than expected based

on a prognostic model incorporating baseline NIHSS score, age, and stroke side (Table III in the online-only Data Supplement). The model was derived from outcomes of 1077 pooled individual patients in control arms of 8 clinical trials in the VISTA repository.[18] The proportion of patients with better than expected disability outcomes were compared in the SPG stimulation and sham-control groups (sliding dichotomy analysis).

Prespecified secondary clinical efficacy outcomes were (1) improvement above expectations (sliding dichotomy mRS) at 3 months specifically among patients with aphasia at entry and (2) substantial neurological recovery at 3 months (defined as NIHSS score ≤1 or improved by ≥9 from baseline). Prespecified additional efficacy outcomes were (1) stroke-related quality of life at 3 months according to the Stroke Impact Scale-16 and (2) self-reported functional outcome assessed with the Riks-Stroke (Swedish Stroke Register) assessment questions at 6 and 12 months. In addition, 2 commonly analyzed outcomes in acute stroke trials were assessed as post hoc, exploratory efficacy end points: (1) functional independence (mRS, 0–2) at 3 months and (2) the distribution of disability outcomes at 3 months across all 7 mRS levels.

For safety analysis, adverse events were classified by the investigators as related or unrelated to the implantation/treatment. Safety end points included a 3-month comparison between the active and sham stimulation groups of (1) all serious adverse events; (2) neurological deterioration, defined as an increase of 4 or more points on the NIHSS related to any neurological event within the first 10 days after stroke onset; (3) implantation complications; (4) stimulation-related adverse events; and (5) mortality.

Statistical Analysis

The primary efficacy analysis was conducted in the modified intention to treat (mITT) population, which included all patients who received at least one full active or sham treatment session during the trial. Dichotomous end points were assessed using a χ^2 test, and the Stroke Impact Scale-16 efficacy end point was assessed using a *t* test. The safety analysis population consisted of all subjects who had a neurostimulator implanted.

Sample size projections assumed a true difference between the treatment groups of 11.5% on the proportion of success in mRS score outcomes, so that 390 patients in the SPG stimulation group and 195 patients in the Sham stimulation group would provide 80% power to detect a statistically significant group difference group at a 2-way alpha level of significance of 0.05. To adjust for interim analyses, the total number of patients at the final analysis was 660. Power and sample size calculations were performed by simulation, assuming analysis with the χ^2 test. Interim analyses were planned when 200, 295, and 585 patients completed their 90-day follow-up. An independent data and safety monitoring board monitored the overall study.

Heterogeneity of treatment effect was assessed in 6 prespecified subgroups: presenting deficit severity (NIHSS), lesion extent Alberta Stroke Program Early CT Score (ASPECTS), time from stroke onset, sex, side, and stroke location (cortical versus noncortical). ASPECTS assessment was done centrally by a neuroradiologist masked to treatment group assignment. The confirmed cortical involvement (CCI) subgroup was defined as patients with NIHSS score ≥10 and signs of hypodensity or tissue swelling in at least one cortical region on initial imaging according to the ASPECTS map (M1-M6 or insular cortex).[19] For the secondary efficacy end point analysis in aphasic patients, aphasia was considered present at entry if the NIHSS language subitem score was ≥1. Additional sensitivity analyses were conducted in the full ITT population; the on-target placement (OTP) population, consisting of all patients with on-target neurostimulator placement and at least one stimulation session; and the population with confirmed anterior circulation infarcts on final imaging (excluding patients with posterior circulation infarcts or no visualized infarcts).

Results

The study was conducted between first enrollment in February 2009 and final study visit in January 2011, with patient flow as shown in Figure 1. Of the 327 patients enrolled in the implantation phase, 6 exited before the implantation procedure started, 18 had incomplete implantations without passage of the neurostimulator into tissue, and 303 had implantations completed and advanced to the randomized phase. Among these 303 patients, 202 were randomized to SPG stimulation group and 101 to sham stimulation. Of the 303 implantations, 229 (75.6%) were rated as well-placed. The correct placement rate improved during the study, in part reflecting the introduction of the optic navigation system, from 66% among the first 100 placements to 88% among the last 100 placements (Figure II in the online-only Data Supplement). Overall, 177 (58%) of implantations were by surgeons and anesthesiologists and 126 (42%) by neurologists. The rate of implantation by neurologists increased with the introduction of the optic navigation system from 24% before optic guidance to 57% after optic guidance (Table IV in the online-only Data Supplement). Given the improving rate of OTPs, the trial Steering Committee, with the agreement of the trial Data Safety and Monitoring Board, stopped enrollment in the trial at the time of the first interim analysis, so that open evaluation of accumulated patients could be conducted, and a subsequent trial be launched with anticipated homogenously higher OTP rates.

In the SPG stimulation group, 153/202 (75.7%) of patients received at least one active SPG stimulation session and were included in the mITT population, including 145 who completed at least 4 treatment sessions and 8 who completed <4, while 49 patients had off-target placements and consequently did not receive actual SPG stimulation. Sham treatment was considered to have been delivered regardless of implant position. Accordingly, in the sham stimulation group, 100/101 (99.0%) of patients received at least one sham stimulation session and were included in the mITT population, including 76 who had OTP and 24 who had off-target placements, while 1 patient did not receive any sham treatment. The resulting total number of patients in the mITT population was 253 (153 in the SPG stimulation group and 100 in the sham stimulation group).

Patient baseline characteristics are shown in Table 1. Overall, in the mITT population, age was median 73 years (interquartile range [IQR], 64–79), 52% were female, baseline deficit severity on the NIHSS was median 11 (IQR, 9–15), and time from last known well to first stimulation was median 18.6 hours (IQR, 14.6–22.4). Patient features were generally well balanced, although a higher rate of atrial fibrillation and lesser extent of ASPECTS early ischemic changes were noted in the sham group. Day 5 imaging revealed that 12 mITT patients (4.7%) had posterior circulation infarcts (rather than anterior) and additional 12 (4.7%) had no final visualized infarct. Baseline patient features in the full-ITT and the full-OTP populations were similar to the mITT population (Table V in the online-only Data Supplement).

Among the overall 303 randomized subjects, 298 completed the 90-day primary outcome follow-up assessment: 200/202 (99.0%) in the SPG stimulation group and 98/101 (97.0%) in the sham stimulation group. Among the 253 patients in the mITT population, in the SPG stimulation group, 152 (99.3%) of 153 completed the 90-day follow-up, and 1 (0.7%) had worst case mRS 6 imputed as no follow-up available; in the sham stimulation group, 97 (97.0%) of 100 patients completed the 90-day follow-up, 2 (2.0%) had last

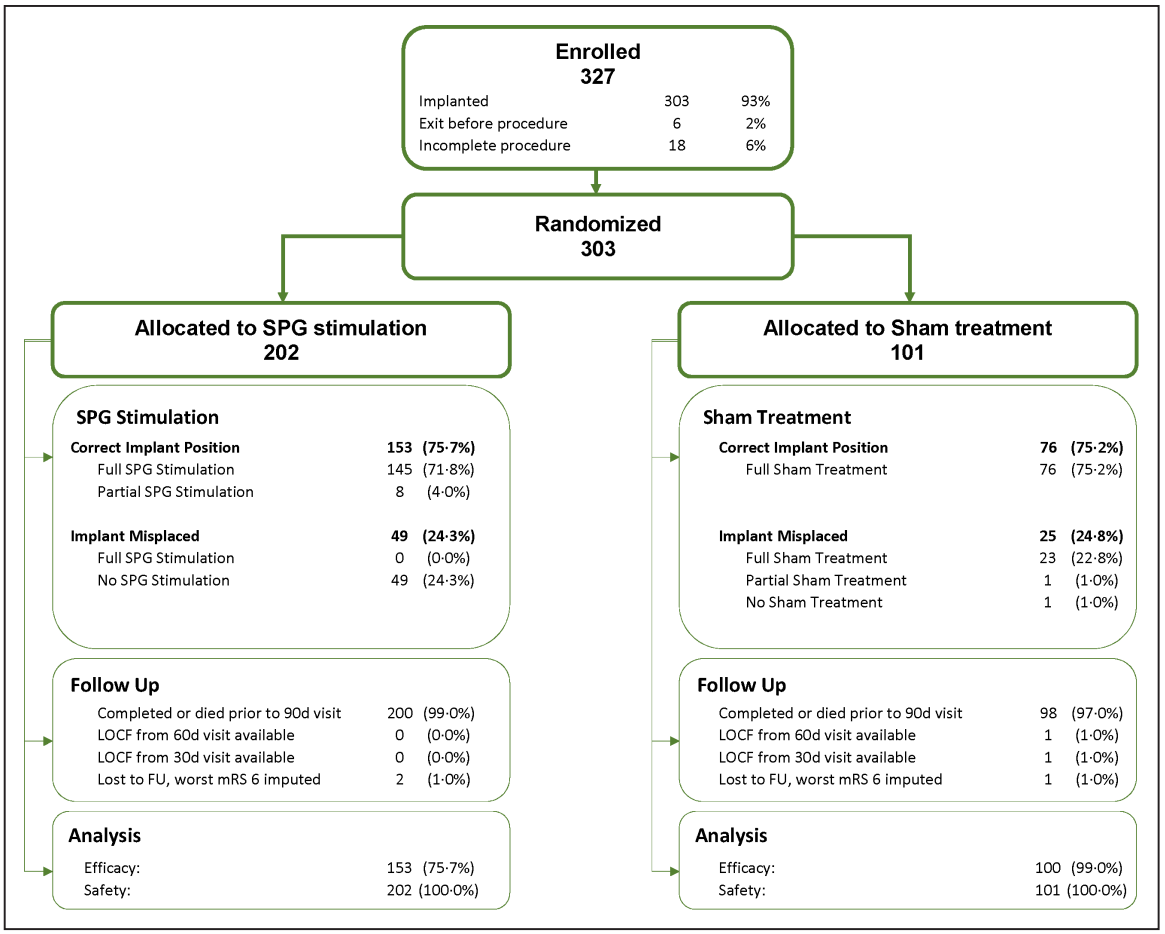

Figure 1. Patient study flow diagram (CONSORT [Consolidated Standards of Reporting Trials] chart). SPG indicates sphenopalatine ganglion.

observation carried forward, and 1 (1.0%) had worst case mRS 6 imputed when no follow-up available (Figure 1). Rates of completion for the longer term, 6 and 12 months, assessments were lower (<75%), so the additional Riks-Stroke end point was not formally analyzed. End of treatment patient blinding assessment questionnaires indicated excellent maintenance of patient blinding with regard to exposure to SPG or sham stimulation (Table VI in the online-only Data Supplement).

Table 1. Baseline Demographic and Clinical Characteristics of Patients

	mITT Population				CCI Population			
	SPG Group	Sham Group	All	*P* Value	SPG Group	Sham Group	All	*P* Value
N	153	100	253		50	37	87	
Age, y (IQR)	73 (64–79)	74 (64–79)	73 (64–79)	0.22	74 (65–81)	74 (63–80)	74 (64–80)	0.90
Sex (female)	53.6%	51.0%	52.6%	0.69	62.0%	56.8%	59.8%	0.62
NIHSS (IQR)	11 (8–15)	11 (9–14)	11 (9–15)	0.50	14 (11–17)	14 (11–17)	14 (11–17)	0.45
Stroke side (left brain)	43.1%	52.0%	46.6%	0.17	46.0%	43.2%	44.8%	0.80
Prestroke mRS=1	9.8%	15.0%	11.9%	0.21	14.0%	13.5%	13.8%	0.95
Hypertension	75.2%	74.0%	74.7%	0.84	76.0%	78.4%	77.0%	0.79
Diabetes mellitus	32.0%	33.0%	32.4%	0.87	32.0%	51.4%	40.2%	0.07
Atrial fibrillation	26.1%	39.0%	31.2%	0.03	34.0%	64.9%	47.1%	0.004
ASPECTS (IQR)	7 (5–10)	8 (7–10)	8 (5–10)	0.01	5 (3–6)	7 (3–8)	5 (3–7)	0.36
Time from LKW to first stimulation, h (IQR)	18.3 (14.7–22.4)	18.9 (14.4–22.5)	18.6 (14.6–22.4)	0.70	20.0 (15.8–23.3)	19.1 (14.8–21.9)	19.5 (15.3–23.0)	0.19

ASPECTS indicates Alberta Stroke Program Early CT Score; CCI, confirmed cortical involvement; IQR, interquartile range; LKW, last known well; mITT, modified intention to treat; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

In the mITT population, rates of the primary efficacy end point of improvement beyond expectations at 90 days for SPG versus sham stimulation were 49.7% versus 40.0%; odds ratio (OR, 1.48 [95% CI, 0.89–2.47]; *P*=0.13). A similar response pattern was seen in the mITT population for all secondary and additional/exploratory efficacy outcomes, as well as the full mRS distribution at 90 days (Table 2, Figure 2, Table VII and Figure IIIA in the online-only Data Supplement). In the full ITT, OTP, and confirmed anterior circulation infarct mITT sensitivity populations, results were directionally similar, with mildly lower between-group differences in nominal rates of the primary end point for the full ITT and OTP populations (Tables VIII and IX in the online-only Data Supplement) and mildly higher between-group differences for the confirmed anterior circulation infarct mITT population (Table X in the online-only Data Supplement).

Evidence of heterogeneity of treatment effect was detected in 1 of the 6 prespecified subgroup analyses (Figure 3). While no significant differences were noted for presenting deficit severity (NIHSS), lesion extent (ASPECTS), time from stroke onset, sex, brain side, a significant treatment interaction was noted with cortical versus noncortical infarct location (interaction, *P*=0.04). Benefit on the primary end point was enhanced in the CCI population, with rates of improvement beyond expectations for SPG versus sham stimulation 50.0% versus 27.0%; OR, 2.70 (95% CI, 1.08–6.73); *P*=0.03. A similar response pattern, though with mildly smaller absolute differences in outcomes, was seen for all secondary and additional/exploratory efficacy outcomes in the CCI population, as well as the full mRS distribution at 90 days (Table 2, Figure 2, Table VI and Figure IIIB in the online-only Data Supplement). No treatment benefit was observed in the complementary non-CCI group, which showed improvement beyond expectations in SPG versus sham stimulation 49.5% versus 47.6%; OR, 1.08 (95% CI, 0.58–2.02); *P*=0.81 and functional independence (mRS, 0–2) 46.6% versus 50.8%; OR, 0.85 (95% CI, 0.45–1.58); *P*=0.60. The CCI population, compared with non-CCI patients, had more severe neurological deficits (median NIHSS score, 14 versus 9; *P*<0.0001) and more extensive infarct signs on imaging (median ASPECTS 5 versus 10; *P*<0.0001). Baseline features in the CCI population were well balanced across treatment groups except for more frequent atrial fibrillation in the sham group (Table 1).

Evaluable CT or MR day-5 imaging in the mITT population were available for 141/153 (92.1%) of SPG stimulation patients and 92/100 (92.0%) of sham stimulation patients. Day 5 ASPECTS scores in both treatment arms were median 6 IQR (3–8), despite smaller infarcts at baseline in the sham arm (median, 8 versus 7 and IQR, 7–10 versus 5–10). ASPECTS infarct growth scores from baseline to day 5 in SPG versus sham stimulation patients were median 0 (IQR, 0–3) versus median 1 (IQR, 0–2); *P*=0.78. In the CCI population, ASPECTS infarct growth scores from baseline to day 5 in SPG versus sham stimulation were median 0 (IQR, 0–2) versus median 1 (IQR, 0–4); *P*=0.02.

Safety outcomes in the lead safety population, comprising the 303 patients who had a neurostimulator implanted, are shown in Table 3. Serious adverse events with SPG versus sham stimulation were 30.2% versus 35.6%; OR, 0.78 (95% CI 0.47–1.30); *P*=0.34. Mortality rates were 12.9% versus 15.8%; OR, 0.78 (95% CI 0.40–1.54); *P*=0.48. There were no serious adverse events related to stimulation, and no symptomatic intracranial hemorrhages were reported in the SPG stimulation arm. Rates of neurological deterioration were identical in both groups (9.9%). Two serious adverse events (0.6%) were classified as related or possibly related to the implantation—one epistaxis and one torn extraction thread resulting in a surgical procedure to remove the implant. In both, the patients recovered fully. Mechanical implant failures occurred in 13/303 (4.3%), including implant cracks/breaks/sealing breach in 7 (2.3%) and torn threads in 6 (2.0%).

Table 2. Primary, Secondary, and Additional/Exploratory Efficacy Outcomes at 90 Days

Outcomes	mITT Population (N=253)					CCI Population (N=87)				
	SPG Stimulation	Sham Stimulation	Abs. Diff.	Odds Ratio (95% CI)	*P* Value	SPG Stimulation	Sham Stimulation	Abs. Diff.	Odds Ratio (95% CI)	*P* Value
Primary end point										
Improvement above expectations (sliding dichotomy mRS)	49.7%	40.0%	9.7%	1.48 (0.89–2.47)	0.13	50.0%	27.0%	23.0%	2.70 (1.08–6.73)	0.03
Secondary end points										
Substantial neurological recovery (NIHSS score ≤1 or improved ≥9)	41.1%	33.7%	7.4%	1.37 (0.81–2.33)	0.24	46.0%	25.0%	21.0%	2.56 (1.00–6.52)	0.047
Improvement above expectations (in patients with aphasia)	58.3%	43.8%	14.6%	1.80 (0.84–3.88)	0.13	64.0%	29.4%	34.6%	4.27 (1.13–16.05)	0.03
Additional/exploratory end points*										
Stroke-related qualify of life (SIS-16)	52.8	49.6	3.2	1.16 (0.74–1.83)	0.52	43.6	31.0	12.6	1.83 (0.84–3.89)	0.13
Functional independence (mRS, 0–2)	41.2%	40.0%	1.2%	1.05 (0.63–1.75)	0.85	30.0%	21.6%	8.4%	1.55 (0.58–4.18)	0.38

Abs. Diff. indicates absolute difference; CCI, confirmed cortical involvement; mITT, modified intention to treat; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SIS-16, Stroke Impact Scale-16; and SPG, sphenopalatine ganglion.

*Stroke-related quality of life was a prespecified additional efficacy end point; functional independence was a post hoc, exploratory end point.

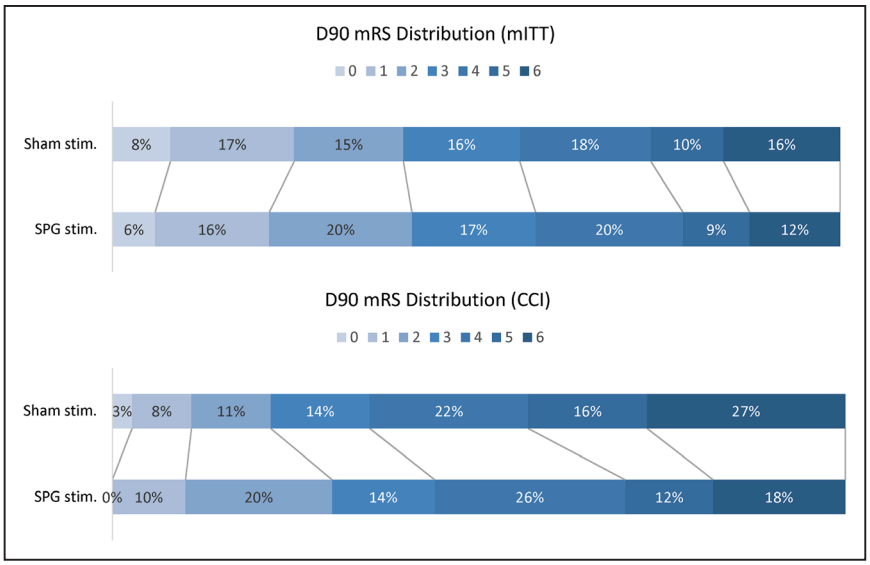

Figure 2. Full distribution of 3-month (90-day) modified Rankin Scale (mRS) outcomes over all 7 levels. **A**, modified intention to treat (mITT) population; and **B**, confirmed cortical involvement (CCI) population. SPG indicates sphenopalatine ganglion.

Discussion

In this sham-controlled, randomized trial, stimulation of the SPG within 24 hours after onset of AIS did not show a statistical difference in increasing the rate of disability improvement beyond expectations at 3 months. There was no evidence of safety concerns. Numerically, outcomes above expectations were 9.7% higher in the SPG stimulation group, and higher rates of favorable outcome did reach nominal statistical significance among patients with confirmed cortical infarcts.

Possible efficacy was further supported by directionally consistent findings across the prespecified secondary efficacy outcomes of functional independence and stroke-related quality of life at 3 months as well as post hoc analyses of bodily self-care or better at 3 months and shift across all 7 mRS levels of disability at 3 months. Additionally, rates of off-target placement of neurostimulators were high initially but improved throughout the study, including after introduction of an optical navigation system. Conversely, while rates were low, device and thread breaks did occur, suggesting fragility of the tested neurostimulator and the desirability of a more robust design.

The findings from this study accord with prior investigations. Observational studies have shown that collateral blood flow is associated with good clinical outcome in patients with AIS.[3–8,14] In addition, smaller prior trials of other collateral enhancement techniques, induced hypertension and partial aortic occlusion, have shown directionally favorable, albeit not statistically significant, effects on functional outcomes.[20–22] Prior

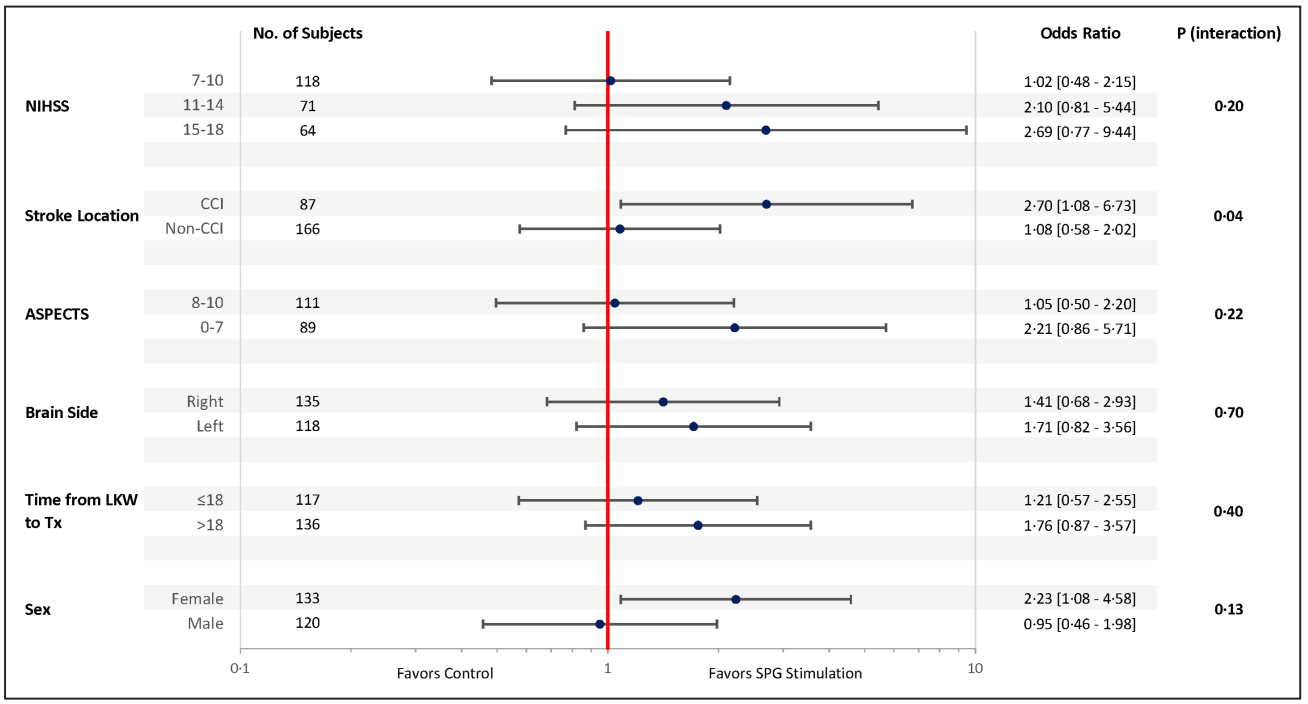

Figure 3. Forest-plot of prespecified subgroups in the modified intention-to-treat population. ASPECTS indicates Alberta Stroke Program Early CT Score; CCI, confirmed cortical involvement; LKW, last known well; and NIHSS, National Institutes of Health Stroke Scale.

Table 3. Safety Outcomes

Outcomes	SPG Group N=202	Sham Group N=101	Odds Ratio (95% CI)	*P* Value
SAEs				
All	61 (30.2%)	36 (35.6%)	0.78 (0.47–1.30)	0.34
Implantation-related	0 (0.0%)	2 (2.0%)	NA	0.21
Treatment-related	0 (0.0%)	3 (3.0%)	NA	0.06
Symptomatic intracranial hemorrhage*	0 (0.0%)	1 (1.0%)	NA	0.72
Neurological deterioration†	20 (9.9%)	10 (9.9%)	1.00 (0.45–2.22)	1.00
Mortality	26 (12.9%)	16 (15.8%)	0.78 (0.40–1.54)	0.48

SAE indicates serious adverse events; and SPG, sphenopalatine ganglion.

*Symptomatic intracranial hemorrhage SAEs were defined as SAEs of neurological worsening of any degree assessed by the local clinician-investigator as causally related to intracranial hemorrhage of any degree.

†An increase of 4 or more points on the National Institutes of Health Stroke Scale related to any neurological event within the first 10 days after the onset of stroke.

preclinical studies have demonstrated that SPG stimulation is a particularly potent method to enhance collateral flow, augmenting cerebral perfusion, stabilizing the blood-brain barrier, reducing infarct size, and improving functional outcome in preclinical stroke models when administered up to 24 hours after stroke onset.[10–13]

This study was the first randomized study assessing the safety and potential benefit of collateral flow augmentation by SPG stimulation for treatment of acute stroke patients. The study was stopped after enrollment of one-half of the originally planned population due to advances in guidance technology that took place over the course of the trial. The optical guidance system, introduced after enrollment of the first 47% of mITT population patients, led to substantial increases in the rate of on-target neurostimulator placement as the trial progressed, making later-enrolled patients increasingly less comparable to early enrolled patients. The ImpACT-24A Steering Committee, therefore, deemed it advisable to end the current study and analyze its results, so that a subsequent study with a uniformly high OTP rate could be conducted to more authoritatively interrogate the efficacy of SPG stimulation. As a result, although initially intended as a definitive pivotal trial, the current study was halted at a moderate sample size and was underpowered to conclusively confirm or disconfirm beneficial effects of SPG stimulation on functional outcome, but adequate to probe for signals of potential benefit. The favorable point estimates for functional outcomes in the current study easily surpass conventional test thresholds for futility,[23] indicating it is desirable for SPG stimulation to proceed to a definitive pivotal trial using advanced placement techniques.

Interpretation of the efficacy findings in the current trial must take into account the different study populations in which analyses were conducted. The mITT lead analytic population was selected to maximize informativeness about treatment effect, containing all patients who received at least one of the planned stimulation sessions in both the SPG and sham stimulation groups. This population showed moderate signals of potential benefit. Two baseline features differed between treatment groups in the mITT population but in a countervailing manner. Atrial fibrillation, which would tend to be associated with worse outcomes, was more common in the sham group; conversely, more extensive ischemic changes on initial brain imaging, which would tend to be associated with worse outcomes, was more common in the SPG stimulation group. The full ITT population includes patients in the SPG arm who did not receive effective SPG stimulation due to suboptimal neurostimulator placement. As expected, signals of treatment benefit are attenuated in this population. The OTP population includes only patients who had correct placement and received at least one of the planned stimulation sessions. As the size of the Sham stimulation group is lower in the OTP than mITT population, analytic power is reduced. However, point estimates suggested effect size magnitudes similar to that observed in the mITT population.

Additional observations from the current trial can usefully inform design of subsequent pivotal trials of SPG stimulation and potentially of collateral enhancement treatments generally. Particularly noteworthy was the presence of modification of treatment effect by stroke location. Beneficial effects of SPG stimulation appeared substantial for patients with confirmed cortical infarcts but attenuated for patients with noncortical infarcts. This observation accords with physiological studies that have demonstrated that collateral enhancement more greatly increases perfusion to cortical and internal border-zone regions than to deep, periventricular arterial territories.[24,25] Collateral arterial networks in the human brain are most robust in the circle of Willis and superficial leptomeningeal arteries supplying the cortical layers than at the level of small penetrating arteries.[5] This potential heterogeneity of treatment effect suggests that subsequent pivotal trials should consider enriching for patients with confirmed cortical infarcts or prespecifying coprimary population analysis in the subset of enrolled patients with cortical strokes.

The relatively late time from onset to treatment start in the current study, a median of over 18 hours from last known well, is noteworthy. In subgroup analysis, there was no heterogeneity of treatment effect between patients treated up to 18 hours and patients treated between 18 and 24 hours, suggesting beneficial effects of SPG stimulation may accrue with treatment start throughout the first 24 hours after onset. This finding accords with preclinical showing benefits of stimulation of the SPG up to 24 hours from stroke onset, including blood-brain barrier stabilization and edema reduction,[10] metabolic normalization,[13] and reduced infarct size.[10] Potential

mechanisms by which SPG stimulation could be beneficial when started in this time window and continued through 5 days including salvage of persistent ischemic penumbra tissue[12,26] and stabilization of the blood-brain barrier deterring vasogenic edema and cerebral herniation.[10]

The safety observations from the current trial were reassuring. Implantation was associated with serious adverse events in only 1 of every 167 patients implanted, and the 2 events that did occur (epistaxis and a minor surgical procedure to remove a stimulator with a torn thread) were not associated with any persisting injury. SPG stimulation was not associated with any increase in serious adverse events, symptomatic intracranial hemorrhage, or mortality. However, the occurrence of device and thread breaks, though infrequent, do indicate the desirability of a structurally more robust neurostimulator design. An implant with stronger mechanical structure extraction thread could better withstand mechanical forces during implantation, and moreover, allow more efficient implantation without the use of trocars.

This study has additional limitations besides those already discussed. First, a small proportion of patients had posterior circulation rather than anterior circulation infarcts on final imaging. Additional patients had no confirmed infarct on final imaging, and a few of these may have actually had nonischemic events. These patient groups introduced noise into the study, and treatment effects increased in magnitude when they were excluded in sensitivity analysis. Second, the absence of vessel imaging to identify presence or absence of large vessel occlusion and of penumbral imaging to identify patients with or without salvageable penumbra constrains insights into physiological characteristics of patients who will or will not respond to SPG stimulation. Advanced vessel and penumbral imaging were not widely employed in routine clinical practice at the time of study conduct. Third, this study evaluated SPG stimulation as a standalone therapy, rather than a treatment delivered concomitantly with intravenous tPA (tissue-type plasminogen activator) or with endovascular thrombectomy. Confining the study population to nonreperfusion therapy patients permitted clear delineation of the safety and efficacy of SPG stimulation alone. Future studies in intravenous thrombolytic and endovascular thrombectomy populations are desirable to explore distinctive efficacy and safety effects in those populations. Fourth, nonplacement and off-target placement of implants complicated study interpretation. The higher rates of on-target implantation with newer guidance technology introduced in latter study stages should reduce this difficulty in future studies. Fifth, the publication of this full report of study results was unduly delayed from the time of the final follow-up visit. Sixth, the accuracy of neurostimulator placement was determined by imaging at end of the treatment course, on day 5, in the current study. In future studies, if techniques to improve rates of correct initial neurostimulator placement are not fully effective, it could be helpful to perform imaging check of placement success at the start of the course, permitting repositioning of off-target devices.

In conclusion, SPG stimulation within 24 hours of onset is safe in AIS. SPG stimulation was not shown to statistically significantly improve 3-month disability above expectations, though favorable outcomes were nominally higher with SPG stimulation beneficial effects may distinctively be conferred in patients with confirmed cortical involvement. The results of this study need to be confirmed in a larger pivotal study.

Appendix

The ImpACT-24A Investigators include the Site Principal Investigators, DSMB members, and the Site Co-Investigators listed: David Skoloudik, Jan Fiksa, Derk Krieger, Grethe Andersen, Joerg Berrouschot, Carsten Hobohm, Dietmar Schneider, Bernd Griewing, Matthias Endres, Karl-Georg Hausler, Hubert Kimmig, Peter Ringleb, Christian Weimar, Matthias Schilling, Martin Kohrmann, Andreas Hetzel, Manfred Kaps, Raymond Cheung, Piotr Sobolewski,Walenty Nyke, Anna Czlonkowska, Adam Stepien, Brola Waldemar, Agnieszka Słowik, Stelmasiakiem Zbigniewem, Ignacy Lubiński, Pedro Portela, Tomas Segure, Joan Marti-Fabregas, Maria Alonso, Antonio Nunez, Miguel Blanco Miguel, Anna Campello, Joaquin Arenillas, Nash Marshall, David Chiu, Harish Shownkeen, Marilyn Rymer, Souvik Sen; Co-Investigators: Martin Roubec, Martin Kuliha, Ctirad Lakomý, David Tyl, David Kemlink, Ondřej Doležal, Petra Rekova, Veronika Krejčí, Anders Christensen, Bo Belhage, Christian Maschmann, Christian Kruse Larsen, Frank Pott, Hanne Christensen, Jakob Marstrand, Jens Kjellberg Nielsen, Per Meden, Svend Prytz, Sverre Rosenbaum, Jens Christian Hedemann Sorensen, Kaare Stenhoj Meier, Kare Schmift Ettrup, Kristina Dupont Hougaard, Paul Von Wietzel, Anett Stoll, Hans Schwetlick, Hendirk Pradel, Alexander Hemprich, Andreas Schulz, Bernhard Frerich, Carsten Hobohm, Christopher Weise, Dominik Michalski, Felix Schaller, Franziska Schiefke, Jens Helmrich, Johann Pelz, Martin Schnieder, Martin Schneider, Peter Matzen, Rudiger Langos, Stephan Müller-Duerwald, Sven Lukhaup, Ute Bauer, Wolfgang Kloppig, Erich Hiermann, Gregor Mucha, Hassan Soda, Renate Weinhardt, Teresa Mucha, Volker Ziegler, Alexander Abbushi, Benjamin Hotter, Benjamin Winter, Birgit Anthofer, Cornelia Noack, Dinah Laubisch, Gerd Heldge Schneider, Gerhard Jan Jungehulsing, Heiko Mueller, Jens Dreier, Jochen Fiebach, Julia Flechsenhar, Kersten Villringer, Martin Ebinger, Michael Rozanski, Peter Vajkoczy, Randolf Klingebiel, Robert Steinicke, Sandra Pittl, Sarah Hoffmann, Stephan Maul, Thomas Krause, Thomas Liman, Thomas Plath, Tim Nowe, Wolf Schmidt, Carsten Fritzsch, Christopher Haas, Hans-Gerd Will, Katja Haußmann-Betz, Mohsen Bayat, Tomazs Pordzik, Andreas Hug, Christian Jürgen Staff, Christoph Lichy, Georg Eggers, Manja Kloss, Martin Bendszus, Oliver Herrmann, Robin Seeberger, Soenke Schwarting, Stefan Rhode, Timolaos Rizos, Werner Hacke, Benedikt Frank, Bessi Bozkurt, Dagny Holle, Daniel Mueller, Dirk Koch, Hans Christoph Diener, Hind Shanib, Joachim Sudendey, Johannes Brenck, Kolja Busch, Kristina Gartzen, Thomas Gasser, Tim Hagenacker, Boris Buerke, Gudrun Prigge, Jens Minnerup, Johannes Albers, Kai Wermker, Wolfram Schwindt, Ringlestein, Bernd Kallmünzer, Eva Hauer, Lorenz Breuer, Peter Schellinger, Rainer Kollmar, Roland Sauer, Stefan Schwab, Tobias Struffert, Anette Funfack, Anne Stechmann, Axel Schlaeger, Claus Laeppchen, Florian Schuchardt, Jan-Helge Klingler, Janine Reis, Johann Lambeck, Mirko Friedrich, Mona Laible, Philip Wellermeyer, Sandra Beck, Sebastian Rutsch, Wolf-Dirk Niesen, Christian Tanislav, Heidrun Schaaf, Heiko Kerkmann, Ingo Schirotzek, Jens Allendörfer, Stephanie Wolff, Alexander Yuk-Lun Lau, Anne Yin Yan Chan, Deyond Siu, Edward HC Wong, George Kwok Chu Wong, Howan Leung, Lawrence K.S. Wong, Xian Lun Zhu, Yannie Oi Yan Soo, Alan Choi Ting Tse, Gilberto Ka Kit Leung, Kar Ming Leung, Kwan Ngai Hung, May Wai Mei Kwan, Mona Man Yu Tse, Philip Tse, Ping Hon Chan, Raymand Lee, Richard Shek Kwan Chang, Shirley Yin Yu Pang, Sonny Fong Kwong Hon, Tat Sun Cheng, Wai Man Lui, Windsor Wai Wo Mak, Anna Sobota, Baeta Wiater, Barbara Loch, Genowefa Wolak, Irena Łabudzka, Jan Dabal, Marcin Grzesik, Monika Sledzinska, Renata Hatalska-Żerebiec, Wiktor Szczuchniak, Anna Gójska, Dariusz Nałęcz, Dariusz Gasecki, Grzegorz Kozera, Łukasz Dylewicz, Marcin Niekra, Mariusz Kwarciany, Piotr Chomik, Piotr Skowron, Adam Kobayashi, Grzegorz Chabik, Grzegorz Makowicz, Jan Bembenek, Julia Jędrzejewska, Michal Karlinski, Wojciech Czepiel,

Bogdan Brodacki, Jacek Staszewski, Jarosław Kosek, Marcin Jadczak, Marta Durka-Kęsy, Krzysztof Kaluzny, Małgorzata Ziomek, Małgorzata Fudala, Zbigniew Sosnowski, Antoni Ferens, Elżbieta Szczygieł, Krzysztof Banaszkiewicz, Maciej Ziomek, Marcin Wnuk, Anna Szczepańska-Szerej, Ewa Jach, Grazyna Elzbieta Maslanko, Joanna Wojczal, Piotr Luchowski, Andrzej Kowalczyk, Jerzy Jakubiak, Joanna Kopcewicz, Maciej Gajda, Malgorzata Wichlinska-Lubinska, David Rodriguez, Estevo Santamarin, Jorge Pagola, Juan Lorente Guerrero, Marc Ribo, Marta Rubiera, Olga Maisterra, Soccoro Pinero, Valera Catalina Iglesias, Gerard Plans, Helena Quesada, Marco Alberto Aparicio Caballero, Pedro Cardona Portela, Antonio Belinchon De Diego, David Sopelana Garay, Máximo Rafael García Rodriguez, Oscar Ayo Martin, Silvia Crusat Braña, Jorge Garcia, Fernando Munoz Hernandez, Ignasi Catala, Josep Lluis Marti-Vilalta, Rachel Delgado Mederos, Schmid Cristian de Quintana, Sergi Martinez-Ramirez, Jaime Valcarcel Gonzalez, Jaime Masjuan Vallejo, Jorge Diamantopoulus, Marta Del Alamo, Pedro Domingo Poveda, Andres Garcia Pastor, Calros Fernandez Carballal, Fernando Diaz, Roberto Garcia Leal, Ruiz Juretschke, Eduardo Arán Echabe, Jose Castillo Sanchez, Manuel Rodriguez Yanez, Ramon Serramito Garcia, Rogelio Leira Muino, Susana Arias Rivas, Demian Manzano Lopez Gonzalez, Elisa Cuadrado, Eva Giralt, Gloria Villalba, Jaime Roquer, Ois Angel, Maria Jimenez, René Robles Cedeño, Ruy Salinas, Saioa Lejarreta, Yolanda Silva, Adela Fraile, Ana Calleja, Guillermo Arturo Cepeda Landínez, Nieves Tellez, Pablo Garcia Bermejo, Pérez Jaime Santos, Rosa Fernandez Herranz, Peter Hunt, Donald Browning, Michael Violette, Robert Hoddeson, James Rose, Jonathan Zhang, Avi Mazumdar, Henri Echiverri, James Chow, Darren Lovick, Martin Coleman, Naveed Akhtar, Rebecca Sugg, Adam Zanation, Anand Germanwala, Brent Senior, David Huang, Natalie Aucutt-Walter; DSMB: Scott Kasner (Chair), Peter LeRoux, Rüdiger von Kummer, Yuko Palesch.

Acknowledgments

We thank the participating patients and families and the research staff at the participating trial sites.

Sources of Funding

The study was funded by BrainsGate Ltd, Caeserea, Israel.

Disclosures

Drs Bornstein, Saver, Diener, Gorelick, Shuaib, and Molina received contracted hourly payments from BrainsGate for service on the steering committee, providing guidance on rigorous trial conduct and design. Dr Bornstein also owns stock options in BrainsGate. Dr Diener additionally has research grants from the German Research Council, the German Ministry of Education and Research, the US National Institutes of Health, and the Heinz-Nixdorf Foundation; has had speaking engagements from Abbott, Allergan, Bristol-Myers-Squibb, Pfizer, and Boehringer Ingelheim; has received honoraria from Daicho-Sankyo, Medtronic, and Portola; and has received other remuneration from WebMd. Dr Solberg is an employee of BrainsGate with ownership of stock options; his institution, Brainsgate Ltd is the study sponsor. The institutions of Drs Devlin, Leung, and Molina received payments for study services on the basis of clinical trial contracts with BrainsGate.

References

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al; American Heart Association Stroke Council. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2018;49:e46–e110. doi: 10.1161/STR.0000000000000158
2. Menon BK, Al–Ajlan F, Najm M, Puig J, Castellanos M, Dowlatshahi D, et al; INTERRSeCT Study Investigators. Association of clinical, imaging, and thrombus characteristics with recanalization of visible intracranial occlusion in patients with acute ischemic stroke. *JAMA*. 2018;320:1017–1026. *doi:* 10.1001/jama.2018.12498
3. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al; DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med.* 2018;378:11–21. doi: 10.1056/NEJMoa1706442
4. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708–718. doi:10.1056/NEJMoa1713973.
5. Liebeskind DS. Collateral circulation. *Stroke.* 2003;34:2279–2284. doi: 10.1161/01.STR.0000086465.41263.06
6. Guenego A, Mlynash M, Christensen S, Kemp S, Heit JJ, Lansberg MG, et al. Hypoperfusion ratio predicts infarct growth during transfer for thrombectomy. *Ann Neurol.* 2018;84:616–620. doi: 10.1002/ana.25320
7. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischaemic stroke. *N Engl J Med*. 2015;372:1019–1030. doi:10.1056/NEJMoa1414905.
8. Shuaib A, Butcher K, Mohammad AA, Saqqur M, Liebeskind DS. Collateral blood vessels in acute ischaemic stroke: a potential therapeutic target. *Lancet Neurol.* 2011;10:909–921. doi: 10.1016/S1474-4422(11)70195-8
9. Seylaz J, Hara H, Pinard E, Mraovitch S, MacKenzie ET, Edvinsson L. Effect of stimulation of the sphenopalatine ganglion on cortical blood flow in the rat. *J Cereb Blood Flow Metab.* 1988;8:875–878. doi: 10.1038/jcbfm.1988.145
10. Levi H, Schoknecht K, Prager O, Chassidim Y, Weissberg I, Serlin Y, et al. Stimulation of the sphenopalatine ganglion induces reperfusion and blood-brain barrier protection in the photothrombotic stroke model. *PLoS One.* 2012;7:e39636. doi: 10.1371/journal.pone.0039636
11. Diansan S, Shifen Z, Zhen G, Heming W, Xiangrui W. Resection of the nerves bundle from the sphenopalatine ganglia tend to increase the infarction volume following middle cerebral artery occlusion. *Neurol Sci*. 2010;31:431–435. doi: 10.1007/s10072-010-0238-0
12. Henninger N, Fisher M. Mismatch in experimental stroke stimulating circle of willis nerve fibers preserves the diffusion-perfusion mismatch in experimental stroke. *Stroke* 2007;38:2779–2786.
13. Bar-Shir A, Shemesh N, Nossin-Manor R, Cohen Y. Late stimulation of the sphenopalatine-ganglion in ischemic rats: improvement in N-acetyl-aspartate levels and diffusion weighted imaging characteristics as seen by MR. *J Magn Reson Imaging.* 2010;31:1355–1363. doi: 10.1002/jmri.22110
14. Fisher M. Implant for perfusion augmentation clinical trial -1 (ImPACT-1). A safety and effectiveness evaluation of the Ischemic Stroke System (ISS) in the treatment of Acute Ischemic Stroke—Pilot study report. *Stroke* 2009;40;e154–e155.
15. Khurana D, Kaul S, Bornstein NM; ImpACT-1 Study Group. Implant for augmentation of cerebral blood flow trial 1: a pilot study evaluating the safety and effectiveness of the Ischaemic Stroke System for treatment of acute ischaemic stroke. *Int J Stroke.* 2009;4:480–485. doi: 10.1111/j.1747-4949.2009.00385.x
16. Bath PMW, Lees KR, Schellinger PD, Altman H, Bland M, Hogg C, et al. Statistical analysis of the primary outcome in acute stroke trials. *Stroke*. 2012;43:1171–1178. doi:10.1161/STROKEAHA.111.641456.
17. den Hertog HM, van der Worp HB, van Gemert HM, Algra A, Kappelle LJ, van Gijn J, et al. The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial. *Lancet Neurol*. 2009;8:434–40. doi:10.1016/S1474-4422(09)70051-1.
18. Ali M, Bath PM, Curram J, Davis SM, Diener HC, Donnan GA, et al. The virtual international stroke trials archive. *Stroke.* 2007;38:1905–1910. doi: 10.1161/STROKEAHA.106.473579
19. Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. *AJNR Am J Neuroradiol.* 2001;22:1534–1542.
20. Hillis AE, Ulatowski JA, Barker PB, Torbey M, Ziai W, Beauchamp NJ, et al. A pilot randomized trial of induced blood pressure elevation: effects on function and focal perfusion in acute and subacute stroke. *Cerebrovasc Dis.* 2003;16:236–246. doi: 10.1159/000071122
21. Shuaib A, Bornstein NM, Diener HC, Dillon W, Fisher M, Hammer MD, et al; SENTIS Trial Investigators. Partial aortic occlusion for cerebral perfusion augmentation: safety and efficacy of NeuroFlo in Acute Ischemic Stroke trial. *Stroke.* 2011;42:1680–1690. doi: 10.1161/STROKEAHA.110.609933
22. Chung JW, Kim SK, Kim SJ, Lee MJ, Hwang J. Seo WK, et al. Therapeutic induced hypertension in acute stroke patients with

non-cardioembolic stroke: a multicenter, randomized controlled trial. *Eur Stroke J*. 2018;3(IS):7.
23. Yeatts SD. Novel methodologic approaches to phase I, II, and III trials. *Stroke.* 2013;44(6 suppl 1):S116–S118. doi: 10.1161/STROKEAHA.111.000031
24. Bisschops RH, Klijn CJ, Kappelle LJ, van Huffelen AC, van der Grond J. Collateral flow and ischemic brain lesions in patients with unilateral carotid artery occlusion. *Neurology.* 2003;60:1435–1441.
25. Hillis AE, Wityk RJ, Beauchamp NJ, Ulatowski JA, Jacobs MA, Barker PB. Perfusion-weighted MRI as a marker of response to treatment in acute and subacute stroke. *Neuroradiology.* 2004;46:31–39. doi: 10.1007/s00234-002-0918-4
26. Wheeler HM, Mlynash M, Inoue M, Tipirnini A, Liggins J, Bammer R, et al; DEFUSE 2 Investigators. The growth rate of early DWI lesions is highly variable and associated with penumbral salvage and clinical outcomes following endovascular reperfusion. *Int J Stroke.* 2015;10:723–729. doi: 10.1111/ijs.12436