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Food and Drug Administration
Department of Health and Human Services
WO 2200
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Dear Drs. Hamburg and Shuren,

Public Citizen, a consumer advocacy group representing more than 225,000 members and supporters nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 360h(e) and 360j(m) and 21 C.F.R. §§ 810 and 814.118, to immediately:

(1) Withdraw approval of the humanitarian device exemption (HDE) application for the Wingspan Stent System with Gateway PTA Balloon Catheter (hereafter referred to as the Wingspan Stent System) that was submitted by Boston Scientific Corp. because the recently completed Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial conclusively demonstrated that treatment of high-risk patients with intracranial artery stenosis with the Wingspan Stent System plus aggressive medical therapy provides substantially less benefit and causes significantly more

harm (i.e., a 2.5-fold higher risk of stroke or death at 30 days post-intervention) in comparison to aggressive medical treatment alone,[1] and as a result:

(a) There is a lack of a showing of reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the labeling thereof;
(b) The device is ineffective under the conditions of use prescribed, recommended, or suggested in the labeling thereof; and
(c) There is not a reasonable basis from which to conclude that the probable benefit to health from the use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available alternative forms of treatment.

(2) Order Stryker, which bought Boston Scientific Neurovascular, to initiate a class I recall of all unused Wingspan Stent Systems because of evidence of significantly increased risk of strokes and death in patients treated with this device, without evidence of any benefit compared to medical treatment without the stent.

## I. BACKGROUND

### A. Intracranial atherosclerotic disease

Each year in the U.S., approximately 700,000 patients experience an ischemic stroke, and 240,000 have a transient ischemic attack (TIA).[2,3] Atherosclerotic intracranial arterial stenosis (narrowing of the blood vessels supplying blood to the brain) is a common cause of these events, accounting for approximately 8% of ischemic strokes and TIAs.[4,5] Patients with 70-99% stenosis are at particularly high risk for recurrent stroke.[6] Medical therapy (combination antiplatelet therapy, blood pressure-lowering medication, and management of other risk factors) has long been available as a standard treatment for this condition and has improved over time.[7,8] Over the past three decades, clinicians in the U.S. and other countries have also experimented with intracranial angioplasty, with and without stent placement, as an alternative or supplement to medical therapy.[9,10,11] For many years, these procedures were performed using balloon catheters and stents that, although approved for treating coronary artery stenosis, were unapproved by the FDA for intracranial use.[12] They were also performed without any published evidence from randomized, controlled clinical trials comparing intracranial angioplasty and stenting to standard medical therapy without the use of such devices.

### B. Regulatory status of the Wingspan Stent System

The Wingspan Stent System combines a percutaneous transluminal angioplasty (PTA) balloon catheter (the Gateway PTA Balloon Catheter) with a self-expanding, neurovascular, nitinol stent (the Wingspan Stent) and stent delivery system (the Wingspan Delivery System).[13] This device carries the FDA description of “intracranial neurovascular stent” and the FDA product code NJE, is a class III device, and was

approved by the FDA under an HDE application, number H050001, on August 3, 2005.[14,15]

The HDE provides an exemption from the ordinary approval requirements for medical devices, meaning the sponsor need not submit a premarket approval application demonstrating effectiveness through scientifically valid clinical investigations (or gain approval by demonstrating substantial equivalence to a previously approved predicate device).[16,17] By utilizing the HDE process, Boston Scientific was able to gain marketing approval for the Wingspan Stent System on the basis of a single, uncontrolled, 45-subject trial that was not designed to demonstrate whether treatment with the device was safer or more effective than medical therapy alone.[18]

The Wingspan Stent System is approved by the FDA for the following indication:

> The Wingspan Stent System … is indicated for use in improving cerebral artery lumen diameter in patients with intracranial atherosclerotic disease, refractory to medical therapy, in intracranial vessels with ≥50% stenosis that are accessible to the system.[19]

## II. STATEMENT OF GROUNDS

### A. Clinical study presented with HDE application for the Wingspan Stent System provided no evidence that the device is safer or more effective than medical therapy alone

The only clinical study data submitted to the FDA in 2005 to support Boston Scientific's HDE application for the Wingspan Stent System came from a small, prospective, uncontrolled, multicenter, single-arm study of 45 subjects conducted in 12 academic medical centers in Europe and Asia (the Wingspan safety study).[20,21] Subject enrollment criteria included a history of stroke more than seven days prior to enrollment, with recurrent symptoms attributable to intracranial stenosis≥50% that were refractory to medical therapy. Forty-four subjects underwent intervention with the Wingspan Stent System and were considered evaluable at 30 days post-stent placement; 42 subjects were evaluated at six months post-stent placement. The composite ipsilateral stroke (a stroke occurring on the side of the brain supplied by the stented intracranial artery) or death rate at 30 days post-procedure, the primary safety end point of the study, was 4.5% at 30 days (two subjects had ipsilateral strokes, one of whom died). The composite ipsilateral stroke or death rate at six months post-procedure was 7.1% (three subjects had ipsilateral strokes, one of whom died).

Eighteen adverse events occurred in 12 subjects during performance of the procedure, including the following:

- Vasospasm (N=5)
- Hematoma (N=3)
- Hypertension (N=3)

- Asymptomatic frontal medial branch occlusion (N=1)
- Respiratory failure due to epiglottis edema (N=1)
- Arrhythmia (N=1)
- Neurological symptoms (nystagmus) (N=1)
- Fever (N=1)
- Hypervolemia (N=1)
- Hyperglycemia (N=1)[22,23]

In its assessment of the Wingspan safety study, the FDA stated that the "the study did not include a control group because no alternative standard therapy was readily available for this disease state."[24] However, an appropriate control group would have been a group of subjects treated with medical therapy (i.e., antiplatelet therapy, blood pressure-lowering medication, and management of risk factors) alone. Given the lack of an appropriate control group, the Wingspan safety study provided no evidence that treatment with the Wingspan Stent System was safer or more effective than medical therapy alone. Furthermore, the data suggested that treatment with the device caused post-procedural strokes in some subjects, leading to death in at least one subject, as well as a variety of other serious periprocedural adverse events.

**B. Uncontrolled and nonrandomized controlled clinical studies published before and after the FDA's approval of the HDE application for the Wingspan Stent System provided no evidence that the device is safer or more effective than medical therapy alone**

Several uncontrolled or nonrandomized clinical studies of the Wingspan Stent System were published in the scientific literature either immediately before or after the FDA's approval of the HDE application for this device. The results of these studies are summarized here.

*Prospective, uncontrolled, single-site, single-arm study*

Henkes et al reported preliminary results of a prospective, uncontrolled, single-site, single-arm study involving 15 subjects treated with the Wingspan Stent System at an academic medical center in Germany.[25] These 15 subjects were a subset of the 45 subjects enrolled in the Wingspan safety study submitted with the HDE application and described above.[26] Therefore, the results of the Henkes et al study will not be discussed further.

*Prospective, uncontrolled, multicenter, single-arm study*

Bose et al published results of the Wingspan safety study in 2007.[27] The investigators reported six-month follow-up data for 43 subjects (one more than the number presented in the HDE application submitted to the FDA). The six-month composite ipsilateral stroke or death rate was 7.0% (three subjects had ipsilateral strokes, one of whom died).

Bose et al also reported nonadjudicated, physician-reported follow-up conducted outside the study protocol for these 43 subjects, ranging from seven to 22 months (average of 13 months). One additional subject had an ipsilateral stroke, resulting in a one-year ipsilateral stroke rate of 9.3%, and there were no additional neurologic deaths.

*The U.S. Wingspan Registry: a prospective, uncontrolled, multicenter, single-arm registry study*

Following the FDA's approval of its HDE application for the Wingspan Stent System, Boston Scientific established and funded a registry study, known as the U.S. Wingspan Registry, initially involving four academic medical centers in the U.S., with subsequent expansion to a fifth center.

Fiorella et al initially reported periprocedural results in 78 consecutive patients enrolled in the U.S. Wingspan Registry who underwent treatment of 82 intracranial artery stenoses ≥50% with the Wingspan Stent System between November 2005 and July 2006 at the initial four academic medical centers.[28] Forty-eight patients presented with a history of stroke and 28 with a history of TIA. Fifty-four of the 82 intracranial artery stenoses (65.8%) in these patients were ≥70%.

Eighty-one of the 82 intracranial artery stenoses were treated with both the Gateway balloon and Wingspan Stent (98.8% technical success rate for stent deployment across the stenotic lesion; for one lesion, tortuous carotid artery anatomy prevented deployment of the stent). The mean±standard deviation (SD) percent stenosis of the 82 intracranial artery lesions was 74.6±13.9% pretreatment and 27.2±16.7% post-stent placement.

Five patients (6.4%) had major procedural complications with the following outcomes:

- Vessel perforation after angioplasty (death on post-procedure day 5)
- Reperfusion hemorrhage (aphasia and hemiparesis)
- Multiple posterior circulation strokes (death on post-procedure day 16)
- Guidewire perforation of the basilar apex (death during the procedure)
- Contralateral (right hemisphere) embolic infarction (death on post-procedure day 15)

The rate of fatal periprocedural complications was 4.9%.

One patient experienced transient visual symptoms that completely resolved within 36 hours after the procedure. Five extracranial parent-vessel dissections related to the guide catheter manipulation occurred, two of which were flow limiting and required stenting. One flow-limiting intracranial dissection occurred after Gateway angioplasty, but resolved after Wingspan Stent placement and did not result in any neurologic sequelae.

Magnetic resonance imaging was performed on 38 patients within 72 hours of the procedure. Thirteen of the 38 patients (34.2%) had new ischemic lesions after the procedure. Ten of these 13 patients were asymptomatic, but the other three had major periprocedural complications.

In commenting on the limitations of the initial analysis of their registry data, Fiorella et al noted the following:

> Complications were tracked by the primary operators involved in the procedures. As such, it is possible that neurological morbidity in these patients could have been underestimated in the absence of independent neurological adjudication … The current series represents an initial experience in a relatively small population of patients. Until large numbers of patients are treated, the actual complication profile of the procedure remains an approximation. Equally important, no longitudinal follow-up of these patients is available at this time. Correspondingly, the efficacy of [the] Wingspan [Stent System] for the prevention of recurrent ischemic events cannot be assessed at this point. Until these data are better understood, the precise role of the Wingspan [Stent] system for the treatment of symptomatic [intracranial atheromatous disease] remains poorly defined.

Levy et al subsequently reported data on the observed incidence of in-stent stenosis and thrombosis on angiographic follow-up of 84 intracranial stenotic lesions in 78 patients enrolled at five academic centers participating in the U.S. Wingspan Registry for whom follow-up imaging was available.[29] At the time of their report, 129 patients with 137 lesions treated with the Wingspan Stent System had been enrolled in the registry. The average time between the stenting procedure and follow-up imaging was 5.9 months, with a range of 1.5 to 15.5 months. In-stent stenosis was defined as a lesion demonstrating stenosis greater than 50% and absolute luminal loss greater than 20% on follow-up imaging versus baseline immediately post-stent placement. Twenty-five of the 84 stented lesions (29.7%) were found to have in-stent stenosis upon follow-up imaging, and four (4.8%) had complete thrombosis. Of the 29 patients with in-stent stenosis or thrombosis, eight were symptomatic, including four with stroke (one of whom died) and four with TIAs.

Finally, in the most recently published report by the U.S. Wingspan Registry investigators, Fiorella et al presented 12-month follow-up results on 158 patients who underwent treatment of 168 intracranial artery stenoses ≥50% with the Wingspan Stent System.[30] The average degree of pre-treatment stenosis was 75.2%, and 115 of the treated lesions (68.4%) were ≥70%. The primary end point was any stroke or death within 30 days of the stenting procedure or any ipsilateral stroke after 30 days. The average duration of follow-up was 14.2 months, with 143 patients followed for at least three months and 110 for at least 12 months. Periprocedural strokes occurred in nine patients (5.7%), and four patients (2.5%) died from these strokes. The cumulative rate for the primary end point was 15.7% for all patients and 13.9% for patients with high-grade (≥70%) stenosis. Of the 13 ipsilateral strokes occurring after 30 days, three resulted in death. In commenting on the limitations of their study, the investigators noted

that 13% of patients were lost to follow-up at the 12-month time period, which may have resulted in bias with respect to the reported one-year event rates.

*The National Institutes of Health (NIH) Wingspan Intracranial Stent Registry Study (the NIH Wingspan registry study): a prospective, uncontrolled, multicenter, single-arm registry study*

The National Institute of Neurological Disorders and Stroke (NINDS, part of the NIH) funded the NIH Wingspan registry study, which involved 16 U.S. academic medical centers. Nahab et al reported clinical outcomes in 158 registry patients who presented with an ischemic stroke, TIA, or other cerebral ischemic event (e.g., vertebrobasilar insufficiency) in the territory of an angiographically confirmed 50-99% stenosis of a major intracranial artery while on antithrombotic therapy and underwent treatment with the Wingspan Stent System between November 2005 and October 2006.[31] Of the 158 patients, 129 (81.6%) had a stenosis ≥70%. The mean±SD percent stenosis of the intracranial artery lesions was 77±13% pretreatment and 21±15% post-stent placement. The primary end point was any stroke or death within 30 days of the stenting procedure or stroke in the territory of the stented artery more than 30 days after stenting. Median follow-up was 5.4 months.

The primary end point at six months occurred in 13.9% of patients (95% confidence interval [CI] 5.9% to 21.1%). Any stroke or death occurred in 5.0% (95% CI 2.5% to 9.7%) of patients within 24 hours of the procedure and in 9.2% (95% CI 5.6% to 15.1%) of patients within 30 days. Factors associated with the primary end point on univariate and multivariate analyses were posterior circulation stenosis (versus anterior circulation), stenting at low-enrollment sites (versus high-enrollment sites), stenting 10 or fewer days from the qualifying event (versus more than 10 days), and stroke as the qualifying event (versus TIA or other event). There was no significant difference in the primary end point based on age, gender, race, or degree of baseline stenosis.

In commenting on the limitations of their study, Nahab et al noted the following:

> Limitations of our study include the lack of central adjudication of events and cerebral angiograms and the lack of prospective follow-up of study patients. Because in-person follow-up was not required and relied on patient self-report, the risk of stroke may have been underestimated.

In an earlier report, Zaidat et al presented data on the subset of 129 patients enrolled in the NIH Wingspan registry study who had 70-99% intracranial artery stenosis.[32] Any stroke (ischemic or hemorrhagic) occurred in eight patients (6.2%), resulting in two deaths, within 24 hours of the procedure. Other periprocedural complications included the following:

- Stent thrombosis (N=4) that was successfully treated with thrombolysis in three cases

- Cerebral infarcts on magnetic resonance imaging (MRI), with neurologic signs lasting less than 24 hours (N=2)
- TIAs (N=2)
- Asymptomatic artery dissection (N=2)
- Transient vasospasm (N=2)

Two additional ischemic strokes and two additional deaths occurred during days 2 to 30 post-stenting. The event rate for any stroke or death at 30 days and six months was 9.6% (95% CI 5.6% to 16.3%) and 14.0% (95% CI 8.7% to 22.1%), respectively.

Zaidat et al,[33] in a post hoc analysis, also compared the outcomes of patients with 70-99% stenosis and TIA or stroke within 30 days prior to stenting in the NIH Wingspan registry study (N=86) to high-risk subjects enrolled in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial[34] who had 70-99% intracranial artery stenosis and TIA or stroke within 30 days prior to enrollment (N=122) and received medical therapy alone. The Kaplan-Meier curves for cumulative probability of an event (i.e., any stroke or death within 30 days or any stroke in the territory of the stenotic artery beyond 30 days from initiation of treatment) were similar in the two groups up to three months but diverged beyond that point (lower rates in the stented NIH registry study patients). However, given the small sample size in the registry, the 95% CI for the stented patients was wide, and the upper 95% CI curve for the stented patients was higher than the curve observed for the WASID high-risk subjects. The investigators concluded the following:

> Whether stenting with Wingspan provides any benefit compared with medical therapy in these patients can only be established in a randomized trial which we are planning.

We agree with the investigators' assessment. Attempts at comparisons to historical controls are fraught with potential bias because of differences in subject populations, enrollment criteria, adjudication of end points, and changes in medical care over time, among other factors.

*Prospective, randomized, single-center study comparing two types of Wingspan Stent System procedures, without a control group receiving medical therapy alone*

Yu J et al conducted a prospective, randomized study comparing two different sizes of Gateway PTA Balloon Catheters in 72 subjects with symptomatic 50-99% intracranial stenosis documented by cerebral angiography who were undergoing intervention with the Wingspan Stent System at a single university hospital in China between April 2007 and September 2009.[35] Thirty-four subjects underwent angioplasty of 36 stenoses prior to stent placement with a catheter that had a balloon diameter sized to 80% of the normal parent-vessel diameter, which is the recommended balloon size in the operating manual for the Wingspan Stent System (standard group). Thirty-eight subjects underwent balloon angioplasty of 41 stenoses prior to stent placement with a catheter that had a balloon diameter sized to 100% of the normal parent-vessel diameter

(experimental group). The in-stent restenosis rate was significantly lower in the experimental group than in the standard group (22.0% versus 33.3%, P<0.05). Periprocedural complications included three stenosis-related ischemic strokes (two in the experimental group and one in the standard group), one intracranial artery dissection (experimental group), one arterial perforation (experimental group), and one stent migration (standard group). No deaths were reported in the perioperative phase.

*Prospective, single-center case series study with comparison to a historical control group that received medical therapy alone*

Jiang et al presented data from a prospective case series study involving 100 patients with 105 angiographically verified ≥70% intracranial artery stenosis who underwent treatment with the Wingspan Stent System within 90 days of a TIA or minor ischemic stroke at a single academic medical center in China between January 2007 and February 2009.[36] All patients were treated with aggressive medical therapy, including dual antiplatelet agents and management of modifiable atherosclerotic risk factors. The primary end point was any stroke or death within 30 days post-stenting or ipsilateral stroke after 30 days. The ≥70% stenosis sub-group in the previously referenced WASID trial[37] was used as a historical control group as part of the analysis of the primary end-point data.

The stent-placement success rate was 99%. All patients but one had clinical follow-up of at least 12 months. One patient died of ipsilateral stroke eight months after stenting. Other key results were as follows:

- Five patients (5.0%) had a primary end point within 30 days post-stenting (three ischemic strokes and two intracerebral hemorrhages) without fatality.
- Four patients (4.0%) had an ipsilateral stroke more than 30 days post-stenting.
- The cumulative probability of a primary end point at one year was 7.3% (95% CI 2.0% to 12.5%), which was lower than the 18% risk (95% CI 13% to 24%) of ipsilateral stroke at one year in the historical control group from the WASID study (P<0.05).
- Forty-five stented vessels in 44 patients were evaluated by follow-up angiography at a mean of 8.6 months. The in-stent restenosis rate was 26.7% (12 of 45) and the symptomatic restenosis rate was 11.1% (5 of 45).

In commenting on these results, the investigators noted the following limitations of their study:

> There are some limitations to this study. First, the WASID data were used as a historical control to estimate the stenting benefit. Despite the fact that the WASID was a well-done randomized trial, using the WASID data as a control may import additional variability. In addition, the medical treatment of [intracranial artery stenosis] in our days is not the same as it was in the WASID trial, especially regarding the use of antiplatelets, statins, and blood pressure control.

The investigators concluded that a "randomized trial comparing medical therapy alone with medical therapy plus Wingspan stenting, conducted at high-volume centers, is needed to confirm the additional benefit of stenting."

*Prospective, single-center case series studies*

Lanfranconi et al presented outcome data for 16 patients who underwent treatment of 17 severe (>70%) atherosclerotic intracranial artery stenosis with the Wingspan Stent System at a single academic medical center in Italy between March 2006 and July 2008.[38] Nearly all of the patients had neurologic symptoms in the distribution of the stenotic artery prior to treatment. Within one day of the procedure, three patients had periprocedural complications, which included two strokes and one intracerebral hemorrhage (17.6% post-procedural complication rate). There was no control group in this study.

Yu SC et al presented outcome data for a prospective case series of 60 patients with either symptomatic ≥70% intracranial stenosis or symptomatic ≥50% intracranial stenosis with recurrent ischemia despite medical therapy who underwent treatment with the Wingspan Stent System at a single academic medical center in Hong Kong, China, between February 2006 and November 2008.[39] The mean±SD percent stenosis was 78±11% for patients with middle cerebral artery stenosis (N=35) and 73±11% for patients with stenosis of other intracranial arteries. Major outcomes for this series included the following:

- Periprocedural complications: two patients (3.3%)
- Ipsilateral stroke at 30 days: three patients (5.0%)
- Death or ipsilateral stroke at 30 days: five patients (8.3%)
- Ipsilateral stroke at one year: six patients (10.0%)
- Death or ipsilateral stroke at one year: eight patients (13.3%)
- In-stent restenosis at one year: five patients (8.3%)

Again, there was no control group in this study.

*Retrospective, single-center case series studies*

Two small, retrospective case series studies evaluating the outcomes of patients treated with the Wingspan Stent System have been published.

Samaniego et al conducted a retrospective, single-center chart-review study of patients treated for symptomatic intracranial atherosclerotic disease at an academic medical center in the U.S. from July 2004 to September 2007.[40] Patients were either treated with "best medical therapy" (undefined) (N=58) or percutaneous transluminal angioplasty and stenting (PTAS) plus antiplatelet agents (N=53). PTAS was performed on 31 lesions using the Wingspan Stent System, and the remaining 26 procedures were performed with other stent devices. The occurrence of transient ischemic attack, stroke, and vascular death following treatment was higher in the PTAS group, with 28.3%

events in the PTAS group versus 24.1% events in the medical therapy group (time frame unspecified).

However, for several reasons, no meaningful conclusions regarding treatment with the Wingspan Stent System relative to medical therapy alone can be drawn from the study by Samaniego et al. First, the study was not randomized. Second, there were large imbalances between the two patient groups with respect to many important clinical variables, including prior TIAs, presence of diffuse intracranial atherosclerosis, stroke or TIA as the presenting condition, and severity score for stroke at presentation. Third, the outcomes for all PTAS-treated patients were pooled together, and outcome data for the subset of patients treated with the Wingspan Stent System were not presented.

Zhao et al presented data from a retrospective review of medical records for 27 patients with ≥50% intracranial artery stenosis who underwent treatment of 29 stenotic lesions with the Wingspan Stent System from May to October 2007 at a single university hospital in China.[41] Patients presented with TIAs (N=14), recent acute stroke (N=9), or transient or persistent dizziness (N=4). The mean degree of stenosis was 72% (range 56-88%) at baseline and 25% (range 0-45%) immediately post-stenting. Four patients (14.8%) suffered periprocedural strokes, three of which were ipsilateral. No patient deaths occurred. There was no control group in this study.

*Summary conclusions regarding the studies preceding the SAMMPRIS trial*

All of the studies described above have significant methodological weaknesses that prevent any valid conclusions from being drawn regarding the relative risks and benefits of treatment of intracranial arterial stenosis with the Wingspan Stent System versus treatment with medical therapy alone. In particular, the studies either had no comparator control group that received medical therapy alone or involved a comparison to either a historical control group (the post hoc analysis of the NIH Wingspan registry study by Zaidat et al[42] and the prospective case series study by Jiang et al[43]) or a nonrandomized contemporaneous control group (the retrospective case series study by Samaniego et al[44]). The studies with these control groups, such as the study by Zaidat et al, thus had significant potential for bias in favor of the subjects treated with the Wingspan Stent System. Furthermore, most of the studies discussed above had small numbers of subjects or involved a single study site, resulting in limited generalizability.

On the other hand, these studies all demonstrated that treatment with the Wingspan Stent System carries substantial risk of grave harm, especially in the short term, including the risk of death and stroke. Of particular concern is the significant number of periprocedural adverse events that can be caused by placement of the Wingspan Stent, including the following:

- Ischemic or hemorrhagic stroke (periprocedural stroke rates ranged from 5.7% to 17.6%)
- Death (periprocedural mortality rates ranged from 0% to 2.5%)
- TIAs

- Intracranial artery dissection
- Intracranial artery perforation
- Stent thrombosis

In addition, the risk of any stroke or death within 30 days post-stenting ranged from 5.0% to 9.6%.

Furthermore, it is also important to recognize that the neurological morbidity in patients across these studies was likely underestimated for a variety of reasons, including a lack of independent neurological adjudication of events, inadequately defined study end points, and incomplete patient follow-up.

**C. The SAMMPRIS trial:[45] a well-designed, randomized, controlled, multicenter clinical trial demonstrating that aggressive medical therapy alone is safer and more effective than aggressive medical therapy plus treatment with the Wingspan Stent System**

*SAMMPRIS trial methods*

The SAMMPRIS trial was an investigator-initiated, randomized, controlled, multicenter clinical trial funded by the NINDS and conducted at 50 U.S. sites. Patients were eligible for the trial if they had a TIA or nondisabling stroke within 30 days before enrollment, attributed to angiographically verified stenosis of 70-99% of the diameter of a major intracranial artery. Additional inclusion criteria included the following:[46]

- A modified Rankin score of ≤ 3
- Target area of stenosis in an intracranial artery that has a normal diameter of 2.00 millimeters (mm) to 4.50 mm
- Target area of stenosis is less than or equal to 14 mm in length
- Age ≥ 30 years and ≤ 80 years (potential subjects age 30-49 had to meet additional inclusion criteria)

Subjects were randomly assigned to receive aggressive medical management alone (medical-management group) or aggressive medical management plus PTAS with the Wingspan Stent System (PTAS group). Aggressive medical management consisted of aspirin (325 milligrams [mg] per day) and clopidogrel (75 mg per day) for 90 days after enrollment, as well as management of primary and secondary risk factors (elevated systolic blood pressure, elevated low-density lipoprotein and non-high-density lipoprotein cholesterol levels, diabetes, smoking, excess weight, and insufficient exercise). In addition to aspirin and clopidogrel, one drug from each major class of antihypertensive agents, rosuvastatin, and the lifestyle program were also provided to manage primary and secondary risk factors.

The PTAS was performed by neurointerventionists who were selected by a committee of experienced neurointerventionists on the basis of procedure notes and outcomes of the 20 most recent consecutive cases of intracranial stenting or angioplasty performed

by the neurointerventionists under consideration. Subjects who were randomly assigned to PTAS were required to undergo the procedure within three business days after randomization.

Subjects were evaluated at the time of study entry, at four days, and at 30 days, and have continued to be evaluated every four months. Subjects were to undergo assessment until 90 days after a primary end point occurs, the subject dies, three years of follow-up have been completed, or the close-out visit for the trial is held. The close-out visit would occur when the last subject enrolled has been followed for one year. At follow-up visits, subjects were examined by study neurologists who also managed the subjects' vascular risk factors. If a stroke was suspected during the follow-up period, the subject was examined by the study neurologist, and MRI or computed tomography (CT) of the brain was typically performed. Because study group assignment was known to the study neurologist, there was a protocol requirement for a second site neurologist who was not aware of the study group assignment to evaluate any subject who has a hard-to-classify event (a TIA lasting more than one hour or mild ischemic stroke).

The primary end point was stroke or death within 30 days after enrollment or after a revascularization procedure for the qualifying lesion during the follow-up period (i.e., angioplasty for symptomatic restenosis in a subject in the PTAS group or placement of a stent in a subject in the aggressive medical-management group), or ischemic stroke in the vicinity of the qualifying artery beyond 30 days. Ischemic stroke was defined as a new focal neurological deficit of sudden onset, lasting at least 24 hours, that was not associated with hemorrhage on CT or MRI of the brain. All end points were adjudicated by an independent panel of neurologists and cardiologists who were not informed of study group assignments.

*SAMMPRIS trial results*

Enrollment in the SAMMPRIS trial began in November 2008 and ended in April 2011, after the trial's independent data and safety monitoring board recommended that enrollment be stopped because of safety concerns regarding the increased risk of periprocedural stroke or death in the PTAS group and because the futility analysis indicated that there was virtually no chance that a benefit from PTAS would be shown by the end of the follow-up period if enrollment continued.

A total of 451 subjects underwent randomization (medical-management group N=227, PTAS group N=224). ). Data published by the SAMMPRIS trial investigators included all adverse events as of the date that the last subject enrolled had completed the 30-day evaluation. There were no significant differences between the two study groups with respect to any of the baseline demographic and clinical characteristics of the subjects.

Regarding primary end points within 30 days after enrollment, the 30-day rate of stroke or death was 14.7% in the PTAS group (nonfatal stroke, 12.5%; fatal stroke, 2.2%) and 5.8% in the medical-management group (nonfatal stroke, 5.3%; non-stroke-related death, 0.4%) (P=0.002), constituting a more than 2.5-fold increase in stroke or death

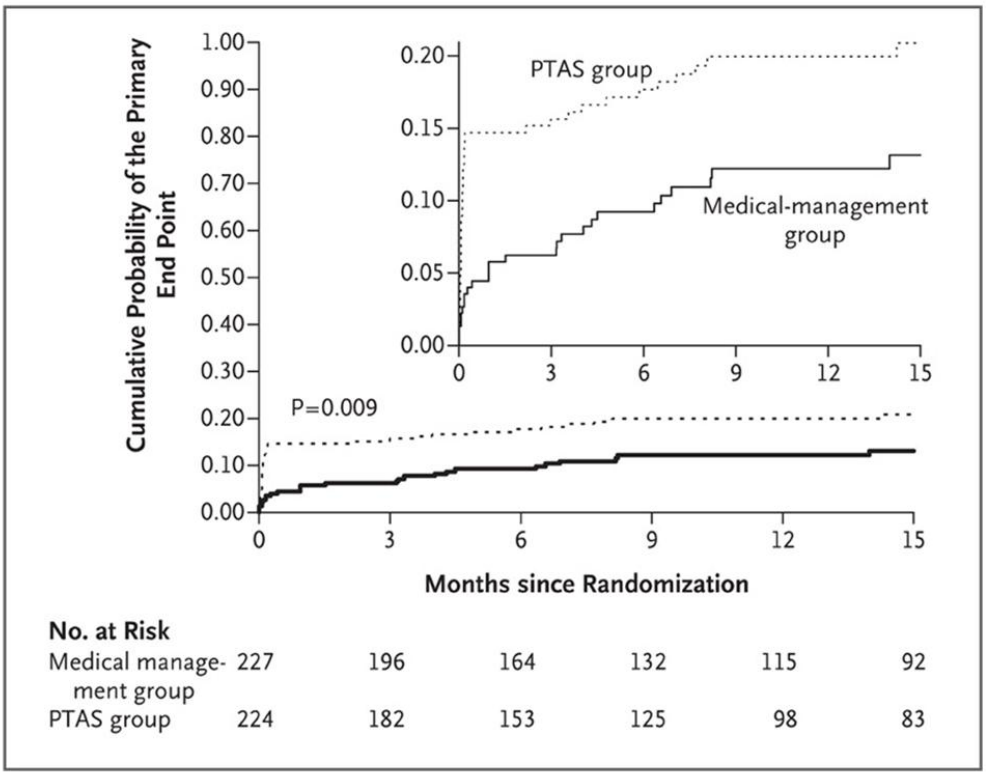
caused by the PTAS. The number needed to harm for PTAS based upon the difference in the rate of stroke or death within 30 days of intervention was only 11 (i.e., for every 11 patients treated with the Wingspan Stent System and medical therapy, one additional patient died or suffered a stroke within 30 days in comparison to patients treated with medical therapy alone).

Ten of the 33 strokes in the PTAS group (30.3%), but none of the 12 strokes in the medical-management group (0%), within 30 days of enrollment were symptomatic brain hemorrhages (P=0.04).

Of the 33 strokes in the PTAS group that occurred within 30 days after enrollment, 25 occurred within one day after the procedure, and eight occurred within two to six days later. The 33 strokes occurred at 25 investigational sites. Of the six sites at which more than one periprocedural stroke occurred, five were among the highest-enrolling sites (i.e., at the 12 sites enrolling half the subjects). The 30-day stroke rate in the PTAS group was 13.5% at the highest-enrolling study sites and 14.7% at the other sites (the 38 sites that enrolled the other half) (P=0.77). The risk of periprocedural stroke did not diminish over the course of the enrollment period.

Regarding primary end points beyond 30 days, nonfatal ischemic strokes in the territory of the qualifying artery occurred in 13 subjects in each group. The probability of the occurrence of a primary end point over the entire follow-up period after enrollment also differed significantly between the two study groups, with one-year rates of the primary end point at 20.0% in the PTAS group and 12.2% in the medical-management group (P=0.009) (see Figure 1).

**Figure 1: Kaplan–Meier Curves for the Cumulative Probability of the Primary End Point, According to Treatment Assignment.**




Chimowitz MI et al. N Engl J Med 2011;365:993-1003.

An as-treated analysis that excluded the 11 subjects in the PTAS group who did not undergo angioplasty or have a stent placed (three of whom had a stroke) and the nine subjects in the medical-management group who underwent PTAS after a TIA during the follow-up period (three of whom had a stroke after PTAS) showed a very similar result that was also highly statistically significant (P=0.009).

*Conclusions and comments by SAMMPRIS trial investigators*

In discussing the dramatic results of their study, the SAMMPRIS trial investigators noted the following:

> Contrary to what we hypothesized, the results of this trial showed that aggressive medical therapy was superior to PTAS with the use of the Wingspan system in high-risk patients with intracranial stenosis, because the rate of periprocedural stroke after PTAS was higher than expected and the rate of stroke in the medical-management group was lower than estimated. The 30-day rate of stroke or death in the PTAS group (14.7%) is substantially higher than the rates previously reported with the use of the Wingspan stent in the phase I trial and in

> two registries (rates ranging from 4.4% to 9.6%). The higher rate in the current study does not reflect inexperience of the operators, because most of the interventionists who participated in the registries also participated in this trial, and all the interventionists in this trial were credentialed to participate on the basis of evidence of their experience. In addition, the rates of periprocedural stroke did not decline over the course of the enrollment period and did not differ significantly between high-enrolling sites and low-enrolling sites in this trial …
>
> The rate of stroke in the medical-management group was much lower than expected … Although we expected the rate of stroke to be reduced with intensive management of risk factors — on the basis of post hoc analyses from the WASID trial that suggested that lowering LDL cholesterol and systolic blood pressure could reduce the risk of stroke — we were surprised at the extent and rapidity of the reduction. It is also possible that the combination of aspirin and clopidogrel played an important role in lowering the early risk of stroke. This is supported by the results of a study of transcranial Doppler ultrasonography involving patients with recently symptomatic intracranial stenosis, which showed that aspirin and clopidogrel, as compared with aspirin alone, reduced the frequency of ipsilateral distal microemboli. The effect of the lifestyle modification program on the outcome can be determined only at the end of the follow-up period, but it is unlikely that it contributed to a reduction in the risk of stroke in the medical-management group within 30 days after enrollment …
>
> The difference between the treatment groups in the rate of the primary end point is driven by the early events, since the rates of the primary end point beyond 30 days are currently similar in the two groups.

**D. Overall risk/benefit assessment of the Wingspan Stent System**

The evidence from the SAMMPRIS trial conclusively demonstrated that treatment of high-risk patients with intracranial artery stenosis with the Wingspan Stent System provides substantially less benefit and causes significantly more harm in comparison to aggressive medical treatment alone.

In particular, the SAMMPRIS trial showed that the rate of stroke or death within 30 days after treatment with PTAS in combination with aggressive medical therapy was more than twice as high compared to treatment with aggressive medical therapy alone. Indeed, the number needed to harm for PTAS based upon the difference in the rate of stroke or death within 30 days of intervention was only 11. After 30 days, the Kaplan-Meier curves for the cumulative probability of stroke or death for each study group were parallel. These dramatic results led the SAMMPRIS investigators to terminate enrollment early based on safety concerns (and because futility analysis indicated that there was virtually no chance that a benefit from the stenting procedure would be shown if enrollment continued). These results were achieved even though the PTAS procedures were performed by neurointerventionists in the U.S. who were highly trained and experienced in using the Wingspan Stent System. The message from the trial could

not be clearer: the risks of this intervention substantially outweigh any potential benefit to patients. The study also had strong internal validity and generalizability. It is the only study of the Wingspan Stent System that possesses all of the attributes associated with best scientific evidence, including the following:

- Use of randomization, clear definition of end points, and adjudication of all end points by an independent panel of neurologists and cardiologists who were not informed of study group assignments (to minimize bias)
- Use of contemporaneous controls to ensure comparability between groups
- Use of prospective design to ensure thorough and systematic assessment of factors related to outcomes
- Use of sample sizes large enough to rule out chance as a possible explanation, to ensure statistically and clinically significant outcomes
- Use of multiple centers to ensure generalizability to the broader population

Finally, based on the data from the SAMMPRIS study, enrollment of patients with similar characteristics in future clinical trials involving PTAS with the Wingspan System would be unethical, as the procedure demonstrates no likelihood of benefit to the subjects and would expose them to significant, unnecessary risks when compared to medical therapy alone.

## III. SUMMARY OF REQUESTED ACTIONS

In summary, Public Citizen hereby petitions the FDA, pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 360h(e) and 360j(m) and 21 C.F.R. §§ 810 and 814.118, to immediately:

(1) Withdraw approval of the HDE application for Wingspan Stent System that was submitted by Boston Scientific because the evidence from the SAMMPRIS trial conclusively demonstrated that treatment of high-risk patients with intracranial artery stenosis with the Wingspan Stent System plus aggressive medical therapy provides no additional benefit and causes significantly more harm (i.e., a 2.5-fold higher risk of stroke or death at 30 days post-intervention) in comparison to aggressive medical treatment alone, and as a result:

(a) There is a lack of a showing of reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the labeling thereof;
(b) The device is ineffective under the conditions of use prescribed, recommended, or suggested in the labeling thereof; and
(c) There is not a reasonable basis from which to conclude that the probable benefit to health from the use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available alternative forms of treatment.

(2) Order Stryker, which bought Boston Scientific Neurovascular, to initiate a class I recall of all unused Wingspan Stent Systems because of evidence of significantly increased risk of strokes and death in patients treated with this device, without evidence of any benefit compared to medical treatment without the stent.

## IV. ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

## V. CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

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