PUBLICCITIZEN

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

Testimony to the Food and Drug Administration's Neurological Devices Panel of the Medical Devices Advisory Committee on the Wingspan Stent System with Gateway PTA Balloon Catheter for the Treatment of Intracranial Artery Stenosis

Michael A. Carome, M.D., and Sidney Wolfe, M.D.
Public Citizen's Health Research Group
March 23, 2012

I am Dr. Michael Carome, Deputy Director of the Health Research Group at Public Citizen, testifying on behalf of myself and Dr. Sidney Wolfe, Director of the group. We have no financial conflicts of interest.

In December, we petitioned the Food and Drug Administration (FDA) to withdraw approval of the humanitarian device exemption (HDE) application for the Wingspan Stent System because the 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 causes significantly more harm (i.e., a 2.5-fold higher risk of stroke or death at 30 days post-intervention) and is no more effective in comparison to aggressive medical treatment alone.[1] Thus, criteria for withdrawal of HDE approval under FDA regulations at 21 C.F.R. § 814.118(a)(1)-(3) had been met:

(1) 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;
(2) The device is ineffective under the conditions of use prescribed, recommended, or suggested in the labeling thereof; and
(3) 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.

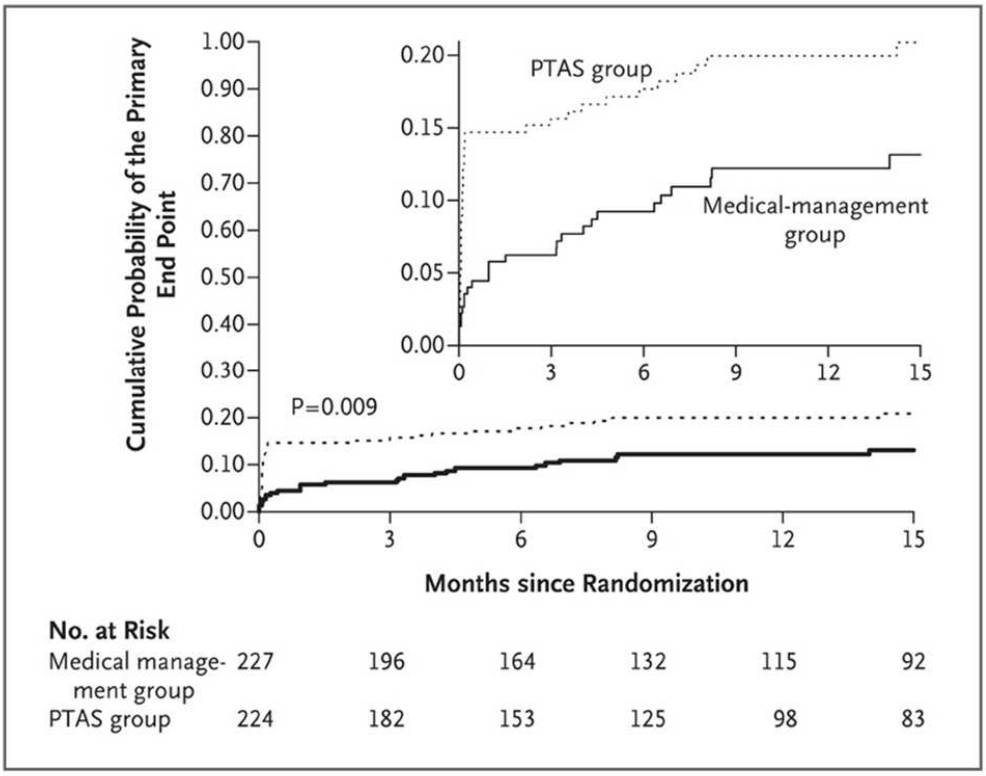
The key SAMMPRIS results are presented in Table 1 and Figure 1 below and have already been reviewed in detail by this panel.[2]

Table 1: Key Results of the SAMMPRIS Trial

Outcome Measure	Wingspan Stent Group N=224	Control Group – Aggressive Medical Therapy Alone N=227	P-value
30-day stroke or death	14.7%	5.8%	P=0.002**
One-year primary endpoints*	20.0%	12.2%	P=0.009***

*Primary endpoints: Stroke or death within 30 days, or stroke in the territory of a qualifying intracranial artery stenosis beyond 30 days.
**z test
***Two-sided log-rank test

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.

Arguments opposing our petition

Various arguments opposing our petition have been made by Stryker, numerous neuro-interventionists, or and the FDA. All are seriously flawed.

Argument 1 (Stryker, the FDA, and others): The SAMMPRIS trial did not follow the current HDE indication for use (i.e., it focused on studying the treatment of severe intracranial atherosclerotic disease, early in the treatment life cycle and with an aggressive treatment regimen and rigorous oversight of medication compliance).[3] Also, the patient population studied for the trial that led to the Wingspan HDE approval is different than the one studied in the SAMMPRIS trial (e.g., SAMMPRIS subjects were younger and had more stenosis and the lesions were in different locations, and not all had a prior history of stroke).[4]

Counterarguments

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.[5]

This first argument should be rejected for the following reasons, discussed in the January 12 supplement to our petition:[6]

(1) The FDA-approved indication for the Wingspan Stent System does not stipulate a time interval between (a) when a patient experiences a neurologic event, such as a stroke or TIA, attributed to intracranial atherosclerotic disease and (b) when the patient is treated with the stent. It does not restrict use of the stent to patients who had a stroke, patients above a certain age, or patients who have stenoses in specific intracranial artery locations. The FDA-approved HDE indication also does not specify the clinical parameters under which intracranial atherosclerotic disease is considered "refractory to medical therapy." Therefore, a large group of patients matching the profile of the SAMMPRIS trial subjects are eligible for treatment with this device under the FDA-approved HDE indication and will remain at risk as long as the device remains on the market.
(2) Subjects enrolled in the SAMMPRIS trial — with ≥70% stenosis of an intracranial artery, and having had a recent stroke or TIA in the distribution of the stenotic lesion — were considered to have the highest risk of suffering additional neurologic injury from a stroke and thus thought to be the subgroup of patients *most* likely to benefit from a stent using the Wingspan Stent System in the sclerotic intracranial artery.
(3) The pre-market approval Wingspan HDE safety study was very small, and it was reasonable to expect that the patient population subsequently treated under the HDE post-approval would encompass a broader range of clinical characteristics. The language of the FDA-approved HDE indication clearly allowed for this.
(4) There was significant overlap in the clinical characteristics profile of (a) subjects in the SAMMPRIS trial and (b) subjects in the Wingspan HDE safety study, and the several hundred patients considered eligible for treatment with the Wingspan Stent System under the FDA-approved HDE indication and enrolled in the two registry studies, the U.S. Wingspan Registry[7,8,9] and NIH Wingspan Registry Study.[10,11]

Argument 2 (Society of NeuroInterventional Surgery [SNIS],[12] Stryker, and others): Many SAMMPRIS subjects were not on antithrombotic therapy at the time of their qualifying event, and this deviation from the indication in the FDA-approved label may have accounted for the worse clinical outcomes in SAMMPRIS compared to prior studies.

Counterarguments:

Contrary to this argument, the absolute and relative increase in the risk of stroke or death at 30 days in SAMMPRIS subjects receiving the Wingspan stent versus medical therapy alone was actually higher in the subgroup of subjects on antithrombotic therapy at the time of their qualifying event than that seen in the subgroup of subjects who were not on antithrombotic therapy at that time (see Tables 2 and 3 and Figures 2 and 3).[13]

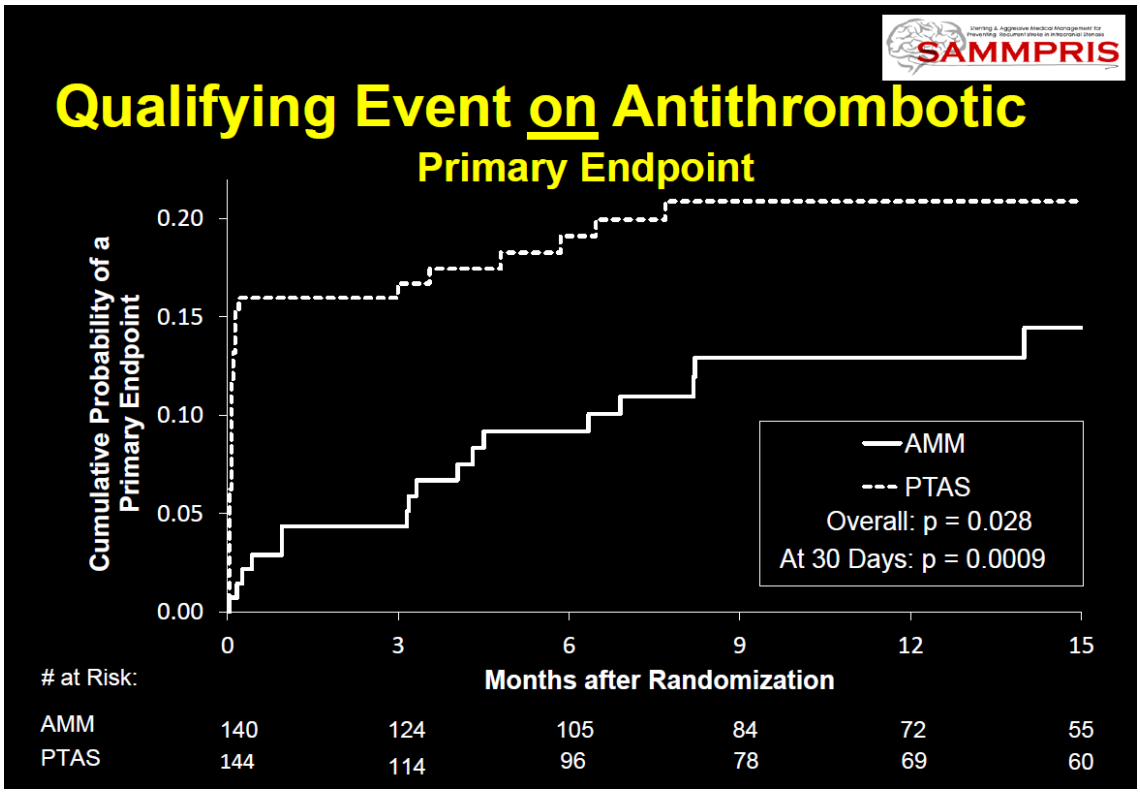
Table 2: Occurrence of Primary Endpoint in SAMMPRIS Subjects with a Qualifying Event ON Antithrombotic Therapy

	Wingspan Stent Group N=144	Control Group – Aggressive Medical Therapy Alone N=140
Stroke or death at 30 days	16.0% (23/144)	4.3% (6/140)
Primary endpoint at any time	21.5% (31/144)	12.1% (17/140)

Table 3: Occurrence of Primary Endpoint in SAMMPRIS Subjects with a Qualifying Event NOT ON Antithrombotic Therapy

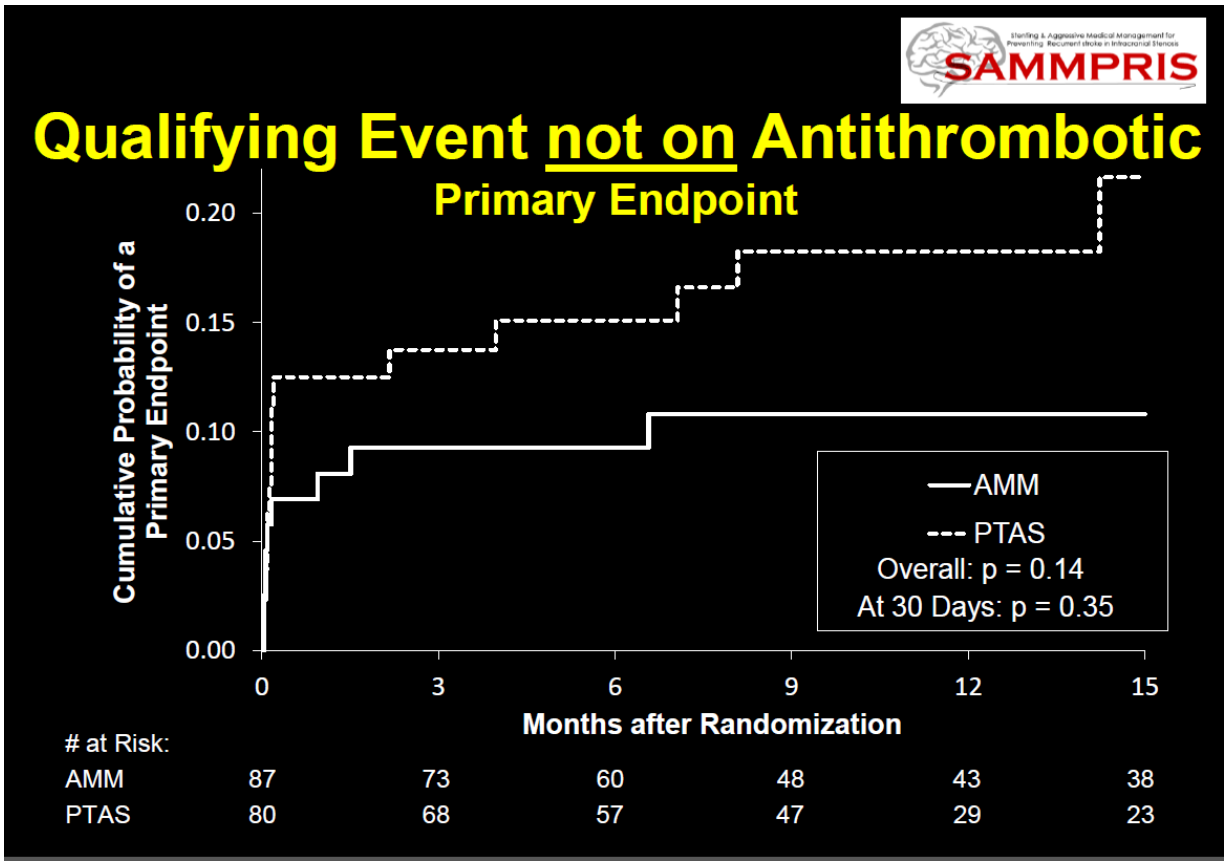
	Wingspan Stent Group N=80	Control Group – Aggressive Medical Therapy Alone N=87
Stroke or death at 30 days	12.5% (10/80)	8.0% (7/87)
Primary endpoint at any time	18.8% (15/80)	10.3% (9/87)

Figure 2: Cumulative Probability of a Primary Endpoint in SAMMPRIS Subjects with a Qualifying Event ON Antithrombotic Therapy



AMM: Control group receiving aggressive medical management
PTAS: Experimental group receiving Wingspan stent and aggressive medical management

Figure 3: Cumulative Probability of a Primary Endpoint in SAMMPRIS Subjects with a Qualifying Event NOT ON Antithrombotic Therapy



AMM: Control group receiving aggressive medical management
PTAS: Experimental group receiving Wingspan stent and aggressive medical management

The FDA reported numerous other subgroup analyses for the SAMMPRIS trial and noted the following:[14]

> ***With the many resulting subgroups, the presence by chance of contradictory or spurious results would not be unexpected. In this context, it is notable that all of the subgroup results point in the same direction of no added benefit, and in some cases, significantly worse outcomes associated with the PTAS treatment in the SAMMPRIS trial*** [emphasis in original].

This included the subgroup of subjects most comparable to the subjects in the HDE safety study (i.e., medically refractory with a history of stroke and a qualifying event of stroke).

Argument 3 (SNIS[15]): "Despite these early disappointing results [from the SAMMPRIS trial], there is no evidence from this trial that the Wingspan Stent itself is unsafe. There were apparently no recorded device failures or vessel ruptures due to use of the stent in the trial."

Counterarguments:

This nonsensical argument implies that the Wingspan stent can be looked at in isolation from the entire procedure used to insert the stent when used to treat patients with intracranial stenosis, which it cannot. In SAMMPRIS, 10 of the 33 strokes in the stent group (30.3%), but none of the 12 strokes in the control group (0%), within 30 days of enrollment were symptomatic brain hemorrhages (P=0.04). The remarkably high number of hemorrhagic strokes in the stent group clearly resulted from using the stent, and many were likely due to perforations or tears in the vessel walls.

Moreover, the FDA's preliminary review of medical device reports (MDRs) in the Manufacturer and User Facility Device Experience database revealed a significant number of Wingspan stent failures. Stent deployment issues were reported in 81 MDRs, including reports of premature deployment, unsuccessful deployment, and problems with stent expansion, associated with complications including vessel perforation and damage, and pieces of the device (Guidewire/catheter segment) being left behind.[16]

Argument 4 (SNIS[17]): The benefits of the Wingspan Stent System can be seen in comparisons of one of the SAMMPRIS subject groups to groups in other studies. For example:

> "[I]n patients with [symptomatic] 70-99% stenosis [in intracranial arteries in the WASID trial], the one- and two-year risk of stroke was 23% and 25% respectively, which is a higher … risk of stroke than patients treated in the Wingspan arm of the SAMMPRIS trial."
>
> "[I]t is worth noting that one recent study [i.e., Jiang et al, 2011[18]] demonstrated a one-year 7.3% stroke and death rate in a cohort of patients treated with the Wingspan stent for greater than 70% symptomatic stenosis. These results are superior to the results from the medical arm of SAMMPRIS at 12.2%"

Counterarguments:

Such comparisons of the outcomes in one group of SAMMPRIS subjects to outcomes in groups from other studies are seriously flawed, are inconsistent with evidence-based medicine, and deserve no further consideration. Randomized, controlled trials are the gold standard evidence, and the only valid comparisons are those between the experimental arm and control arm in the SAMMPRIS trial.

Argument 5 (SNIS[19]): "For patients randomized to aggressive medical therapy in SAMMPRIS, there was still a 12.2% one-year risk of stroke or death. This bespeaks the terrible natural history of [intracranial atherosclerotic disease (ICAD)] and a poor prognosis for patients, despite best medical management. For patients who abruptly fail medical therapy, the Wingspan stent procedure is potentially life and disability-saving."

Counterarguments:

This argument ignores the fact that SAMMPRIS subjects randomized to intervention with the Wingspan stent did significantly worse at one year. Thus, treatment with the Wingspan stent worsens, rather than improves, the "terrible natural history of ICAD" and the "poor prognosis" for patients, causing more "abrupt failures" of treatment. Furthermore, there is no valid scientific evidence to support the wishful thinking that treatment with the Wingspan stent will improve morbidity and mortality outcomes in patients who abruptly fail medical therapy. It is highly unlikely that any patient subgroup would have better outcomes when treated with the Wingspan stent in comparison to aggressive medical therapy alone, thereby reversing the direction of the relative risk seen in the high-risk patients enrolled in the SAMMPRIS trial.

Conclusions

The credibility of the FDA is on the line. The SAMMPRIS trial provides overwhelming evidence that the Wingspan stent is much more dangerous but no more effective than aggressive medical therapy alone, evidence that cannot be refuted by any of the prior uncontrolled case series and cohort studies. Such studies are subject to significant bias and routinely report better results than randomized, controlled studies.

Unlike the SAMMPRIS trial, the very small Wingspan HDE safety study provided no data on the relative safety and efficacy of treatment with the Wingspan Stent System, in comparison to medical treatment only, in any patient population. It is inconceivable that the FDA would have approved the HDE application for the Wingspan Stent System if the data from the SAMMPRIS trial had been submitted as part of the HDE application.

The FDA's failure to withdraw approval of the HDE application for the Wingspan Stent System upon learning, almost a year ago, of the early termination of enrollment in the SAMMPRIS trial because of the higher risk of periprocedural stroke or death in the group receiving the stent shows the agency's unwillingness to fulfill its legal obligation under FDA regulations at 21 C.F.R. § 814.118.

Patients will continue to be harmed unless the FDA withdraws its approval of the HDE application for the Wingspan Stent System.

Finally, beyond the FDA's obligation to remove this device from the market, no one would volunteer to participate in further studies of this device if appropriately informed that the best available evidence indicates that the device more than doubles the risk of death or stroke shortly after the procedure and offers no benefit beyond aggressive medical treatment.

---

[1] Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011;365:993-1003.
[2] Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011;365:993-1003.
[3] Sarvestani A. Former CDRH director joins Public Citizen in demanding recall of Stryker's brain stent. Mass Device. December 22, 2011. Available at http://www.massdevice.com/news/former-cdrh-director-joins-public-citizen-demanding-recall-strykers-brain-stent. Accessed December 22, 2011.
[4] Barber J. Public Citizen requests recall of the Wingspan stent. Medscape Medical News. January 4, 2011. Available at http://www.medscape.com/viewarticle/756362?sssdmh=dm1.747841&src=nldne. Accessed January 6, 2011.
[5] Food and Drug Administration. Summary of safety and probable benefit: Wingspan Stent System with Gateway PTA Balloon Catheter, HDE Number: H050001. Webpage 1. Available at http://www.accessdata.fda.gov/cdrh_docs/pdf5/H050001b.pdf. Accessed November 28, 2011.
[6] Carome MA, Sorscher S, Wolfe SM. Supplement to citizen's petition – docket number FDA-2011-P-0923. January 12, 2012. Available at http://www.citizen.org/documents/supplement-to-petition-to-fda-to-withdraw-approval-for-wingspan-stent-system-011212.pdf. Accessed March 21, 2012.
[7] Fiorella D, Levy EI, Turk AS, et al. US multicenter experience with the Wingspan stent system for the treatment of intracranial atheromatous disease: periprocedural results. Stroke. 2007;38:881-887.
[8] Levy EI, Turk AS, Albuquerque FC, et al. Wingspan in-stent restenosis and thrombosis: incidence, clinical presentation, and management. Neurosurgery. 2007; 61:644-651.
[9] Fiorella DJ, Turk AS, Levy EI, et al. US Wingspan Registry: 12-month follow-up results. Stroke. 2011;42:1976-1981.
[10] Nahab F, Lynn MJ, Kasner SE, et al. Risk factors associated with major cerebrovascular complications after intracranial stenting. Neurology. 2009;72:2014-2019.
[11] Zaidat OO, Klucznik R, Alexander MJ, et al. The NIH registry on use of the Wingspan stent for symptomatic 70-99% intracranial arterial stenosis. Neurology 2008; 70:1518-1524.

[12] Hirsch JA (on behalf of the Society of NeuroInterventional Surgery). Letter to Dr. Jeffery Shuren regarding Public Citizen's December 21 petition to the FDA to withdraw approval of the Wingspan Stent System. February 17, 2012. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0923-0006. Accessed March 21, 2012.
[13] Lutsep HL, Barnwell SL, Larsen DT, et al. Outcome of patients in the SAMMPRIS trial who had failed antithrombotic therapy at study enrollment. International Stroke Conference 2012. Available at http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_436218.pdf. Accessed March 21, 2012.
[14] Food and Drug Administration. Executive summary prepared for the March 23, 2012 meeting of the Neurological Devices Panel: Current knowledge of the safety and effectiveness of the Wingspan Stent System with Gateway PTA Balloon Catheter for the treatment of intracranial arterial stenosis. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM296664.pdf. Accessed March 21, 2012.
[15] Hirsch JA (on behalf of the Society of NeuroInterventional Surgery). Letter to Dr. Jeffery Shuren regarding Public Citizen's December 21 petition to the FDA to withdraw approval of the Wingspan Stent System. February 17, 2012. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0923-0006. Accessed March 21, 2012.
[16] Food and Drug Administration. Attachment 3 to the executive summary prepared for the March 23, 2012 meeting of the Neurological Devices Panel: Current knowledge of the safety and effectiveness of the Wingspan Stent System with Gateway PTA Balloon Catheter for the treatment of intracranial arterial stenosis. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM296791.pdf. Accessed March 21, 2012.
[17] Hirsch JA (on behalf of the Society of NeuroInterventional Surgery). Letter to Dr. Jeffery Shuren regarding Public Citizen's December 21 petition to the FDA to withdraw approval of the Wingspan Stent System. February 17, 2012. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0923-0006. Accessed March 21, 2012.
[18] Jiang WJ, Yu W, Du B, et al. Outcome of patients with $\geq$ 70% symptomatic intracranial stenosis after Wingspan stenting. Stroke. 2011;42:1971-1975.
[19] Hirsch JA (on behalf of the Society of NeuroInterventional Surgery). Letter to Dr. Jeffery Shuren regarding Public Citizen's December 21 petition to the FDA to withdraw approval of the Wingspan Stent System. February 17, 2012. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0923-0006. Accessed March 21, 2012.