Appendix 1: Eligibility Criteria (Protocol Revision 4)

Inclusion Criteria

Subjects met ALL of the criteria listed below:

Age ≥ 22 and ≤ 75 years;

Subject had a single target aneurysm located in the following zones:

- Zone 1 - Petrous through superior hypophyseal segments of the ICA
- Zone 2 - Communicating segment of the ICA through A1 or M1 segment
- Zone 3 - Posterior Circulation
  - Basilar artery (not including the basilar bifurcation)
  - Vertebral artery (distal to the PICA)
  - Vertebral artery (proximal to the PICA)

As well as any of the following criteria:

Subject for whom existing endovascular options (coiling, stent-assisted coiling) would had been ineffective because the aneurysm was predisposed to recurrence due to having any of the following characteristics:

a) Aneurysm had a maximum fundus diameter less than 10mm but ≥2mm.

i. To mitigate the risk for the treatment of subjects with small stable aneurysms that may not require treatment with respect to the possible risks and benefits associated with treatment, the treating clinician had to record a treatment

justification (such as increased risk of rupture) for the aneurysms < 7mm that were selected for treatment.

b) Aneurysm had any of the following morphologies:

i. No discernible neck.

ii. Segmental parent artery dysplasia.

iii. Aneurysm neck involving > 180 degrees of parent artery circumference.

iv. Complex lobulations limiting stent/coiling as a treatment option

v. Neck > 4mm or dome/neck ratio ≤2.

OR

Subject had a fusiform aneurysm of any size requiring treatment.

OR

Subject was a poor candidate for open surgical treatment because of prior surgical procedures, comorbidities or location limiting conventional surgical options.

Additionally, the subjects met the following criteria:

The parent artery diameter was 2.0 - 5.0mm distal and/or proximal to the target intracranial aneurysm;

Subject fulfilled study requirements, and the subject or his/her Legally Authorized Representative provided a signed informed consent form;

Negative pregnancy test (serum or urine) in a female subject who has had menses in the last 18 months;

Subject committed to return to the investigational site for the 30-day, 180-day, and 12-month follow-up evaluations.

Exclusion Criteria

Subjects were excluded from the study if ANY of the following conditions existed:

Subject who suffered from a subarachnoid hemorrhage in the last 60 days;

Subject who suffered from any intracranial hemorrhage in the last 30 days;

Subject who presented with an intracranial mass or was currently undergoing radiation therapy for carcinoma or sarcoma of the head or neck region;

Subject with symptomatic extracranial or intracranial stenosis of the parent artery (>50%) proximal to the target aneurysm;

Subject with an irreversible bleeding disorder, a platelet count of less than 100,000/ml < 100 $x10^3$ cells/mm^3 or known platelet dysfunction or a contraindication to or inability to tolerate anticoagulants/antiplatelet agents;

Active peptic ulcer disease, major systemic hemorrhage within 30 days, active bleeding diathesis, platelet < 100,000 or known platelet dysfunction, INR ≥ 1.5, clotting factor abnormality, current alcohol or substance abuse, uncontrolled severe hypertension

(systolic pressure >180 mm Hg or diastolic pressure >115 mmHg), creatinine ≥ 3.0 mg/dL (unless on dialysis);

Subject with contraindications or known allergies to anticoagulants or antiplatelets (aspirin, heparin, ticlopidine, clopidogrel, prasugrel or ticagrelor);

Subject with known hypersensitivity to metal, such as nickel-titanium and metal jewelry;

Subject with documented contrast allergy, or other condition, that prohibits imaging;

Evidence of active infection at the time of treatment;

Presence of any of the following unequivocal cardiac sources of embolism; chronic or paroxysmal atrial fibrillation, mitral stenosis, mechanical valve, endocarditis, intracardiac clot or vegetation, myocardial infarction within three months, dilated cardiomyopathy, left atrial spontaneous echo contrast, ejection fraction less than 30%;

Subject who had a previous intracranial stenting procedure associated with the target aneurysm;

Subject who was unable to complete the required follow-ups;

Subject with life-threatening diseases;

Subject who was pregnant or breastfeeding;

Subject of childbearing potential, and unwilling to prevent pregnancy during their participation in the study.

Angiographic exclusion criteria:

Subject had a cerebral diagnostic angiogram that demonstrated an aneurysm that was not appropriate for endovascular treatment;

Subject had an extracranial stenosis greater than 50% in the carotid artery of the target aneurysm;

Subject had an intracranial stenosis greater than 50% in the treated vessel;

Subject had a mycotic or dissecting aneurysm;

Subject had a bifurcation aneurysm for example at the bifurcation of the internal carotid artery, the middle cerebral artery or at the anterior communicating artery such that placement of the device would fail to satisfactorily cover the entire neck of the aneurysm or a major cerebral artery would be put at risk through "jailing";

Subject had a posterior circulation aneurysm with the following morphology:

Placement of the device would include the basilar artery bifurcation

Large or giant dolichoectatic aneurysm;

Subjects aneurysm had significant branch exiting from dome of aneurysm (for example, ophthalmic artery);

Subject was harboring more than one aneurysm with both aneurysms requiring treatment at the same time;

Subject had an arteriovenous malformation (AVM) in the area of the target aneurysm.

Appendix 2: Derivation of Performance Goals (PG)

A search of the published literature on flow diverters for the endovascular treatment of intracranial aneurysms was conducted to establish clinical study performance goals for safety and effectiveness. The focus of the safety performance goal was the rates major complications and the focus of the effectiveness performance goal was the rates complete angiographic occlusion within the first year of treatment.

The search criteria are outlined below:

Inclusion criteria	
Condition	Intracranial aneurysm OR cerebral aneurysm OR brain aneurysm In-stent stenosis
Time period	2007 or later
Treatment	flow diverter OR flow diversion, Pipeline, Silk, Surpass
Available data	Published results in full (i.e. not only in abstract) and in a peer reviewed journal, book or online publication Aneurysm location 12-month follow-up and angiographic data Safety outcomes peri-procedurally, within 30 days, or within 12 months Reports of death, ischemic safety events, non-ischemic events
Population	identifiable population or sub-population of aneurysms consistent with the target populations defined in the FRED protocol
Exclusion criteria	
Types of studies	Animal, pediatric, imaging techniques, reviews/meta-analyses, overlapping cohorts, psycho/social outcomes, economic/cost analysis outcomes, long-term follow-up only
Anatomical	Non-cerebral OR non-intracranial Aneurysms not intended for treatment with FRED
Treatment	FRED device, liquid embolic agents, clipping, coiling, stent assisted coiling

The search yielded 15 articles for reference for effectiveness, with an additional 21 for reference for additional in-stent stenosis information and 14 articles for safety. The rates obtained from the publications were stratified by anatomical location (anterior or posterior). Results were combined across studies, within anatomic location, to obtain estimates of the applicable event rates using inverse variance weighting, as described by Fleiss[1].

The combined estimates obtained for each anatomic location were then combined using the proportion of subjects treated in each of the two anatomic locations in order to obtain a single comparator rate for the endpoint. A target performance goal rate was subsequently obtained by applying separate offsets for the primary safety and efficacy endpoints reflecting weighting estimates for anterior and posterior distributions.

Effectiveness endpoint

The primary efficacy endpoint for the FRED study is based on a core lab's assessment of occlusion. In order to account for this, success rates were adjusted down by 12% in publications that did not report results from a core lab assessment. The FRED endpoint also includes as a failure any in-stent stenosis greater than or equal to 50% within one year of treatment. Not all publications reported on in-stent stenosis. A 3.8% downward adjustment was applied to those publications that did not report their own rate.

There were 15 publications included in the analysis that reported data for aneurysms located anterior circulation. The sample sizes ranged from 11 to 108 treated aneurysms and the resulting 100% occlusion rates ranged from 30.8% to 100%. The Fleiss method was applied to the rates of total occlusion of aneurysms with adjustment for core laboratory and in stent stenosis resulting in a combined estimate for effectiveness for the anterior location of 56.2%.

Table 1: Listing of anterior effectiveness publications

Author	Year	% w/100% occlusion	# In Stent Stenosis ≥50%
Bescke	2013	86.8%	1
Briganti	2014	89.2%	Not reported
Chalouhi	2014	79.5%	Not reported
Brinjiki	2014	45.5%	Not reported
Chan	2011	69.2%	0
Cinar	2013	92.9%	0
Keskin	2015	100.0%	Not reported
Kim	2014	70.8%	Not reported
Lubicz	2011	75.0%	0
Martinez-Galdamez	2014	40.0%	2
Monteith	2014	30.8%	0
Mpotsaris	2015	50.0%	0
Puffer	2014	61.8%	2
Szikora	2010	94.1%	0
Wagner	2011	72.2%	6

There were 9 publications included in the analysis that reported data for aneurysms located in the posterior location. The sample sizes ranged from 1 to 7 subjects and the resulting 100% occlusion rates ranged from 0% to 100%. There were 7 publications with 100% success rates; these 7 publications had to be combined with other publications in order to facilitate analysis. The Fleiss method was applied to the rates of total occlusion of aneurysms with adjustment for

core laboratory and in stent stenosis resulting in a combined estimate for effectiveness for the posterior location of 45.8%.

Table 2: Listing of posterior effectiveness publications

Analysis Grouping	Author	Year	% w/100 occlusion	# In Stent Stenosis ≥50%
A	Briganti	2014	100.0%	Not reported
A	Cinar	2007	50.0%	0
A	Keskin	2015	100.0%	Not reported
D	Lubicz	2011	66.7%	0
B	Martinez-Galdamez	2014	100.0%	0
C	Monteith	2014	28.6%	0
E	Mpotsaris	2015	33.3%	0
B	Szikora	2010	100.0%	0
B	Wagner	2011	66.7%	0

Applying the weights to the anterior and posterior rates reflecting the natural occurrence, the final combined estimate was 53.8%. Applying the non-inferiority margin, the lower limit of the 95% confidence interval and resulting target performance goal becomes 45.8%.

Safety endpoint

The primary safety endpoint for the FRED study requires freedom from death, stroke and MI w/in 30 days as well as freedom from major ipsilateral stroke and neurological death within 12 months.

There were 13 publications included in the analysis that reported data for aneurysms located in the anterior location. The sample sizes ranged from 9 to 738 treated aneurysms and the resulting composite endpoint rate ranged from 0% to 25%. The Fleiss method was applied to the composite rate resulting in a combined estimate for safety for the anterior location of 5.96%.

Table 3: Listing of anterior safety publications

Author	Year	Composite Endpoint Rate
Becske	2013	5.6%
Briganti	2014	6.1%
Chalouhi	2014	2.5%
Chan	2011	0.0%
Cinar	2013	2.6%
Kallmes	2015	7.0%
Keskin	2015	0.0%

Kim	2014	4.3%
Lubicz	2011	9.1%
Martinez-Galdamez	2014	25.0%
Monteith	2014	5.9%
Mpotsaris	2015	8.3%
Wagner	2011	14.3%

There were 9 publications included in the analysis that reported data for aneurysms located in the posterior location. The sample sizes ranged from 1 to 55 treated aneurysms and the resulting composite endpoint rate ranged from 0% to 100%. The Fleiss method was applied to the composite rate resulting in a combined estimate for safety for the posterior location of 17%.

Table 4: Listing of posterior safety publications

Author	Year	Composite Endpoint Rate
Briganti	2014	0.00%
Cinar	2007	33.33%
Kallmes	2015	18.18%
Lubicz	2011	0.00%
Keskin	2015	100.00%
Martinez-Galdamez	2014	0.00%
Monteith	2014	28.57%
Mpotsaris	2015	33.33%
Wagner	2011	0.00%

Applying the same weights to the anterior and posterior rates, the final combined estimate was 7.5%. Applying the non-inferiority margin, the upper limit of the 95% confidence interval and resulting target performance goal becomes 15%.

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