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Safety and efficacy results of the Flow Redirection Endoluminal Device (FRED) stent system in the treatment of intracranial aneurysms: US pivotal trial

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ABSTRACT

Objective To evaluate the safety and effectiveness of the Flow Redirection Endoluminal Device (FRED) flow diverter in support of an application for Food and Drug Administration approval in the USA.

Methods 145 patients were enrolled in a prospective, single-arm multicenter trial. Patients with aneurysms of unfavorable morphology for traditional endovascular therapies (large, wide-necked, fusiform, etc) were included. The trial was designed to demonstrate non-inferiority in both safety and effectiveness, comparing trial results with performance goals (PGs) established from peer-reviewed published literature. The primary safety endpoint was death or major stroke (National Institutes of Health Stroke Scale score ≥4 points) within 30 days of the procedure, or any major ipsilateral stroke or neurological death within the first year. The primary effectiveness endpoint was complete occlusion of the target aneurysm with ≤50% stenosis of the parent artery at 12 months after treatment, and in which an alternative treatment of the target intracranial aneurysm had not been performed.

Results 145 patients underwent attempted placement of a FRED device, and one or more devices were placed in all 145 patients. 135/145 (93%) had a single device placed. Core laboratory adjudication deemed 106 (73.1%) of the aneurysms large or giant. A safety endpoint was experienced by 9/145 (6.2%) patients, successfully achieving the safety PG of <15%. The effectiveness PG of >46% aneurysm occlusion was also achieved, with the effectiveness endpoint being met in 80/139 (57.6%)

Conclusion As compared with historically derived performance benchmarks, the FRED flow diverter is both safe and effective for the treatment of appropriately selected intracranial aneurysms.

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INTRODUCTION

Flow diverters have had a major impact on the treatment of intracranial aneurysms. Multiple flow diverters are approved outside the United States, but until recently only two such devices have been approved for use within the United States. The Flow Redirection Endoluminal Device (FRED) system received regulatory approval for use in Europe in 2013 and detailed descriptions of the device have been previously published.[1–3] The flow-diverting portion of the system is a self-expanding nitinol stent comprising two integrated layers, with the inner layer being composed of a low porosity, 36 or 48 nitinol wire braid.

This paper reports the results of the US pivotal trial of the FRED Stent System in the Treatment of Intracranial Aneurysms, a multicenter, prospective, single arm, investigational device exemption clinical study conducted to evaluate the safety and efficacy of the FRED system. Based on the results of this trial the US Food and Drug Administration (FDA) recently granted premarket approval of the FRED system.

METHODS

Study design

The US pivotal trial of the FRED Stent System in the Treatment of Intracranial Aneurysms was a prospective, multicenter, single-arm study initiated in 25 US centers and one additional Japanese site. One hundred and forty-five patients were treated at 23 centers with enrollment taking place between July 2013 and December 2016. The last subject visit was in January 2018. The study protocol was approved by each center's institutional review board, and all patients submitted written informed consent prior to enrollment. The study was conducted under good clinical practices and included independent adjudication of all adverse events. An independent core laboratory evaluated all angiographic data and adjudicated effectiveness outcomes. An independent Clinical Events Committee (CEC) adjudicated all endpoints. An independent Data Safety Monitoring Board conducted study safety reviews. Funding for this study was provided by Microvention Inc.

A detailed set of inclusion and exclusion criteria are included in the online supplementary materials (online supplemental appendix 1). Key inclusion criteria stipulated that the target aneurysm arise proximal to the anterior communicating segment, the middle cerebral artery M1/M2 junction, or the basilar artery bifurcation, that the parent artery be 2.0–5.0 mm in diameter, and that the aneurysm be wide necked or otherwise unfavorable in morphology as defined in online supplemental appendix 1. For the purposes of enrollment, the location of the aneurysm was determined by the

enrolling investigator, but ultimately adjudicated by the core laboratory. Discrepancies—for example, an aneurysm enrolled as an A1 segment aneurysm but later adjudicated as an anterior communicating artery aneurysm, were not considered to be major protocol violations. Exclusion criteria included recent (<60 days) subarachnoid hemorrhage, proximal arterial stenosis >50%, dolichoectatic aneurysms, bifurcation aneurysms, and prior stenting of the target aneurysm.

The study was designed to demonstrate non-inferiority in safety and effectiveness results as compared with performance goals (PGs) identified from a comprehensive analysis of the peer-reviewed published literature. The PGs were based on the results of prior studies reporting the safety and effectiveness of endovascular treatment of intracranial aneurysms with flow-diverter devices for patient populations that are directly comparable to this study's subject population (online supplemental appendix 2).

The safety and efficacy goals were a priori determined and prespecified at <15% and >46%, respectively.

Patients were evaluated clinically, including National Institutes of Health Stroke Scale (NIHSS) score and modified Rankin Scale (mRS) score preprocedure, and then re-evaluated after treatment at the time of discharge, and subsequently at follow-up around 30 days, 180 days, and 1 year. Ophthalmic evaluations were done at baseline and as needed subsequently for any patients with new visual symptoms. Mandatory 6-month and 1-year follow-up digital subtraction angiographic studies were core laboratory adjudicated.

Device characteristics

FRED stents are available in diameters 2.5 to 5.5 mm, with the 2.5 and 3.0 mm devices being deliverable through a Headway 21, 0.021" internal diameter microcatheter, and the larger sizes requiring a Headway 27, 0.027" internal diameter microcatheter. The flow diverting or 'working length' of the devices available are from 7 to 39 mm.

Procedures

All treated patients underwent a standard neuroendovascular procedure with the intention of delivering and implanting a FRED device across the aneurysm neck. Patients were treated with both aspirin and clopidogrel prior to the procedure with either a loading dose the day before or daily doses for 7 days before. All patients were treated with two antiplatelet agents for a minimum of 6 months after the procedure and then were maintained on monotherapy (American Stroke Association recommended) for the remainder of the study period (if no contraindication). Testing of antiplatelet medication effectiveness was not required.

Safety assessment

The primary safety endpoint of the study was the proportion of subjects who experienced death or major stroke (≥4 more points on the NIHSS) within 30 days of the procedure, or had any major ipsilateral stroke or neurological death within 12 months of the procedure. All adverse events reported by the investigational sites were adjudicated by an independent blinded CEC. In addition, a blinded independent Data Safety Monitoring Board provided oversight. Study site visits by clinical monitors were conducted, as needed, to achieve 100% verification of source data. Patient evaluations including, mRS and NIHSS scores, were conducted at baseline and hospital discharge and then within defined follow-up windows at the 30-, 90-, 180-day, and 12-month time points. Screening for adverse events occurred at each time point from the procedure forward.

Effectiveness assessment

The study primary effectiveness endpoint was the proportion of subjects with complete occlusion of the target aneurysm and ≤50% stenosis of the parent artery at the target intracranial aneurysm at 12 months after treatment as assessed by angiography, and without re-treatment of the target intracranial aneurysm within 1 year post-FRED placement. Any re-treatment was considered an endpoint failure for effectiveness. An independent core laboratory adjudicated the angiographic occlusion of the aneurysms using the Raymond scale,[4] reviewing images that were obtained immediately after the procedure, at 180 days and at 12 months. Parent artery stenosis was assessed by the core laboratory, with significant stenosis being defined as greater than 50% luminal loss using the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) method.[5] Multiple additional secondary safety and efficacy endpoints were also studied as noted in the results section.

Statistical methods

The study was designed to compare primary effectiveness success with an independently derived performance goal (a summary of the derivation and literature supporting the performance goals used as developed by Microvention and agreed to by the FDA is provided in online supplemental appendix 2). The trial is considered successful if the two-sided 95% credible interval, lower bound of the effectiveness rate exceeds the 46% PG and the two-sided 95% credible interval upper bound of the safety rate is below the 15% PG. The use of two-sided testing is consistent with the Pipeline premarket approval and FDA guidance.

Three patient populations were used for statistical analysis. The intention-to-treat (ITT) population, which consisted of all patients for whom the FRED system had been introduced into the bloodstream, was used for all effectiveness analyses to test the effectiveness hypothesis for the performance goal. The safety population consisted of all subjects in whom the investigational device was implanted as well as deaths due to technical failure during the index procedure, and was used to test the safety hypothesis of the performance goal. The third population was the per protocol population, consisting of all subjects in the ITT population for whom there were no major protocol deviations.

Study analyses for primary effectiveness and safety endpoints were conducted using Bayesian methods, consistent with other medical device submissions to the FDA's Center for Devices and Radiological Health to allow the computation of equitail 95% credible limits for assessment of the statistical hypotheses. This decision was made in advance of any data assessments for either effectiveness or safety. Other outcomes, including secondary endpoints for which formal hypothesis testing was not prespecified, are presented descriptively.

RESULTS

One hundred and sixty-seven patients consented to take part in the study, of whom 145 underwent attempted treatment with a FRED system. All these 145 patients had a FRED device implanted, and thus the same 145 patients comprised both the ITT and safety analysis populations. Subject and aneurysm characteristics are summarized in table 1 and subject accountability is presented in figure 1.

Table 1 Subject and aneurysm baseline characteristics

Characteristics	Mean±SD or N (%) (n=145)	(Median) (min, max)	
Age (years)	59.1±11.5	(60.1) (23.9, 82.9)	
Female	129 (89%)		
Race			
White	104 (71.7%)		
Black	24 (16.6%)		
Asian	7 (4.8%)		
Native American	1 (0.7%)		
Other	9 (6.2%)		
Prior Stroke	5 (3.4%)		
Hypertension	90 (62.1%)		
Hyperlipidemia	64 (44.1%)		
Diabetes mellitus	14 (9.7%)		
Multiple aneurysms	36 (24.8%)		
Family history of aneurysm	34 (23.4%)		
Tobacco use	48 (33.1%)		
mRS score			
0	103 (71.0%)		
1	31 (21.4%)		
2	9 (6.2%)		
3	2 (1.4%)		
Aneurysm location	Total	Fusiform	Saccular
Cavernous carotid	41 (28.3%)	10	31
Ophthalmic	50 (34.5%)	2	48
Supraclinoid carotid	10 (6.9%)	2	8
Superior hypophyseal	14 (9.7%)	1	13
PComA segment	20 (13.8%)	20	0
Anterior cerebral	2 (1.4%)	1	1
Anterior communicating	2 (1.4%)	0	2
Vertebral	2 (1.4%)	1	1
PICA	2 (1.4%)	1	1
Basilar	2 (1.4%)	0	2
Previously ruptured	8 (5.5%)		
Prior treatment			
Clipped	2 (1.4%)		
Coiled	23 (15.9%)		
Aneurysm dome height	11.5±4.7	(10.2)(3.7, 29.0)	
No >10 mm	106 (73.1%)		

mRS, modified Rankin Scale; PComA, posterior communicating artery; PICA, posterior inferior cerebellar artery.

The majority of subjects (135/145, 93.1%) had a single device deployed at the index aneurysm, while nine subjects (6.2%) had two devices deployed, and one subject (0.7%) had three FRED devices deployed. Of the total 155 devices implanted to deal with the target aneurysm in 145 patients, three were placed during reintervention procedures. These reinterventions were considered as treatment failures for the purposes of the study. Aneurysm sizes were reported by the sites: 102 aneurysms were large (>10 mm) and four were giant (≥25 mm), yielding a total of 73.1% large or giant aneurysms (table 1). Twenty-five aneurysms had undergone prior treatment with clips or coils, and eight of these had a history of rupture 76–2396 days prior to FRED treatment.

Protocol deviations

There were 10 major protocol deviations resulting in a per protocol population that consisted of 135 patients. Major deviations were adjudicated by the CEC and included five patients who missed a follow-up visit, two patients who did not have the required imaging performed, and one each of assessment not completed per protocol, stent used in addition to the FRED system, and enrollment of a patient with atrial fibrillation, which was an exclusion criterion.

Safety

After 1-year of follow-up (within 425 days), 9/145 (6.2%) patients met the composite primary safety endpoint of major stroke/death within 30 days or major ipsilateral stroke/neurological death after 30 days. The performance goal of <15% was therefore met. These nine events resulted in death or disabling stroke in four patients. Six had a major stroke within 30 days of treatment (four of these strokes occurred between 3 and 24 hours after the procedure, and the remaining two on postprocedure days 18 and 27). Two had a major ipsilateral stroke after 30 days and one patient fell at day 235 post treatment, sustaining an ipsilateral subdural hematoma (adjudicated as an ipsilateral stroke), which resulted in death. Enrollment of this patient was a protocol violation because of the pre-existing condition of atrial fibrillation, and at the time of the fall, the patient was taking warfarin in addition to aspirin and clopidogrel. The components of the primary safety endpoint and summary of events resulting in disabling stroke or death are given in table 2.

At last follow-up, among the nine patients who had met the safety endpoint, five had recovered to mRS score ≤2, leaving four patients who were dead or disabled defined as mRS score >2. The mean of the posterior distribution of the primary safety endpoint at 12 months after treatment is 6.8% with an equitailed 95% CI of 3.3% to 11.3%, meaning the safety endpoint performance goal of less than 15% was successfully met. The posterior probability of the alternative hypothesis is 0.999 therefore exceeding the predefined one-sided threshold of 0.975 (0.95 equitailed). Disabling strokes (including the patient that experience the subdural hematoma resulting in the sole neurological death in the series) occurred in 4/145 (2.8%) patients. In all, 11 patients had a deterioration in their mRS score as of their last follow-up, with two of these patients deteriorating for reasons unrelated to their aneurysm.

Safety outcomes were analyzed by prespecified subgroups, including study site, gender, ruptured versus unruptured, aneurysm size, aneurysm site, age, and comorbidities. With respect to the safety outcome across sites, no difference was seen between the pooled high volume (>4) versus low volume (<5) enrollers. Similarly, there was no difference in the safety endpoint events for anterior versus posterior circulation aneurysms, but a higher rate of major stroke was seen in the posterior communicating artery segment of the internal carotid artery—that is, 5/6 of the major strokes that occurred within 30 days of treatment ($p<0.001$) and 5/9 of the primary safety outcome endpoints overall ($p<0.005$) occurred in patients with the target aneurysm at this location. These adverse events were multifactorial in origin and no features specific to this location appeared to explain the higher rate of safety events at this site.

No significant differences in the rate of primary safety endpoint (or safety subcomponent) events were noted in relation

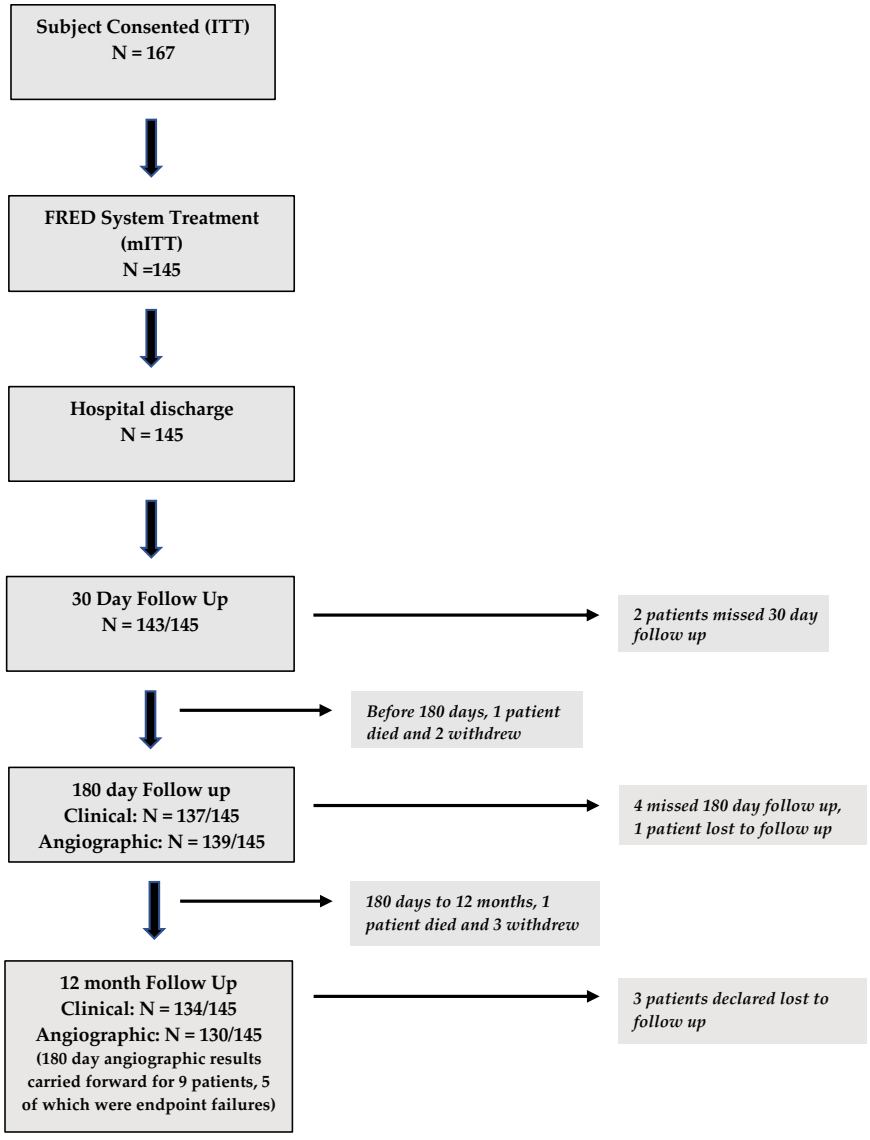

Figure 1 Patient accountability. FRED, Flow Redirection Endoluminal Device; ITT, intention-to-treat; mITT, modified intention-to-treat.

to patient age or gender, nor in relation to aneurysm size or rupture status. There were no unexpected adverse device effects during this trial.

As detailed above, a total of nine primary safety endpoint events occurred, resulting in death or permanent disability in four patients. An additional nine neurological events were adjudicated as minor strokes, for a total of 18 strokes occurring in 15 patients. The severity, timing, baseline mRS score, and mRS score at last follow-up of the patients with a stroke are shown in table 3.

As listed in table 2, four subjects experienced hemorrhagic events. Three of the events were adjudicated as primary safety endpoints, one of these, as described above, the result of a subdural hematoma secondary to a fall 235 days after treatment. The fourth event, 12 months after treatment of a small cavernous segment aneurysm, was a small sylvian fissure subarachnoid hemorrhage. This was adjudicated as a minor stroke but resulted in no new neurological deficit. The remaining two hemorrhagic events were adjudicated as primary safety endpoints secondary to delayed target aneurysmal hemorrhage. One of the delayed hemorrhages resulted from a previously unruptured 17 mm right carotid supraclinoid sidewall aneurysm. A second FRED was placed, and complete aneurysm occlusion was achieved. Twelve-month NIHSS and mRS scores were unchanged from their baseline values of 1 and 0, respectively. The final hemorrhagic event resulted from a previously unruptured 16 mm left posterior communicating segment aneurysm with a subarachnoid hemorrhage 18 days after treatment. A second FRED device was placed as was a ventricular drain. At the 12-month follow-up the aneurysm was completely occluded and mRS and NIHSS scores were 0. Although both of these patients achieved excellent outcomes, their treatment is reported as a failure with respect to both safety and efficacy. In total 9/145 (6.2%) patients experienced a device-related serious adverse event as adjudicated by the CEC (six strokes, one aneurysm rupture, two transient ischemic attacks).

Device thrombosis

There were 12 (8.3%) reports of 'device thrombosis'. Eight of these thrombosis events occurred on the day of the index procedure, and all eight were successfully treated with various

Table 2 Primary safety endpoint events through 12 months and primary safety analysis of neurological death and disabling stroke (CEC-adjudicated safety population)

Analysis using prespecified primary safety endpoint definition	n=145 n (%)	Posterior Mean (95% CI)	Posterior probability*
Primary safety†	9 (6.2%)	6.8% (3.3% to 11.3%)	0.999
Primary safety components:			
Major stroke within 30 days	6 (4.1%)	4.8% (1.9% to 8.7%)	
Death within 30 days	0	0.7% (0.0% to 2.5%)	
Major ipsilateral stroke 31–425 days	3 (2.1%)	2.7% (0.7% to 5.8%)	
Neurological death 31–425 days‡	1 (0.7%)	1.4% (0.2% to 3.7%)	
Additional primary safety analysis using composite rate of neurological death and any disabling stroke (mRS score ≥3)			
Primary safety	4 (2.8%)		
Primary safety components:			
Major stroke within 30 days	2 (1.4%)		
Death within 30 days	0		
Major ipsilateral stroke 31–425 days	2 (1.4%)		
Neurological death 31–425 days‡	1 (0.7%)		

*Posterior probability that the primary safety endpoint event rate is <15%.
†Primary safety endpoint defined as rate of death or major stroke within 30 days or neurologic death or major ipsilateral stroke within 12 months.
‡One subject fell and had a major ipsilateral stroke (subdural hematoma) at day 235 postoperatively with subsequent neurological death 1 day later and is listed under both stroke and death 31–425 days for this event.
CEC, Clinical Events Committee; mRS, modified Rankin Scale.

combinations of IIb/IIIa inhibitors and mechanical means. The remaining four events were identified on post-treatment days 1, 3, 5 and 345. Three of these four delayed events were thought to be due to technical problems, including carotid dissection and kinking of the device, and the fourth, noted on day 345, was seen in the setting of multiple territory thrombo-embolic infarcts. Two of these four patients with delayed events had complete occlusion of the parent artery at follow-up (both included as 'stenosis' below) and an additional patient did not undergo follow-up angiography. These 12 events resulted in two subjects experiencing major strokes, three subjects minor strokes, and two subjects with transient ischemic attacks.

Table 3 Listing of all patients with strokes (ischemic and hemorrhagic): CEC-adjudicated, Safety population and outcome by mRS score at last follow-up

Patient	Postoperative day	SAE	mRS at baseline	mRS at last assessment
Deaths (major and minor stroke)				
1	235	SDH (major)	1	6
1	Index	Stroke (minor)		
Major and minor strokes				
2	1	Stroke (major)	0	4
2	311	Visual impairment (minor)	–	
3	27	Stroke (major)	2	6
3	25	Stroke (minor)	–	
Major strokes				
4	345	Stroke (major)	0	3
5	76	Aneurysm rupture (major)	0	0
6	Index	Stroke (major)	0	1
7	1	Stroke (major)	0	0
8	18	Aneurysm rupture (major)	0	0
9	Index	Stroke (major)	1	1
Minor strokes				
10	Index	Stroke (minor)	1	1
11	Index	Stroke (minor)	0	1
12	298	Stroke (minor)	0	0
13	5	Stroke (minor)	0	2
14	1	Stroke (minor)	0	0
15	356	SAH (minor)	0	0

CEC, Clinical Events Committee; mRS, modified Rankin Scale; SAE, serious adverse event; SAH, subarachnoid hemorrhage; SDH, subdural hematoma.

Stenosis

Stenosis of ≥50% at the 12-month follow-up was observed in six patients. Two of the six patients with stenosis were symptomatic, and three of the six had complete parent artery occlusions. The symptomatic patient with complete occlusion was the one described above, who presented at day 345 with multiple territory thromboembolic strokes. The second patient with symptomatic stenosis had embolic strokes on the day of treatment but recovered to NIHSS and mRS scores of 0 by day 30, although kinking and severe stenosis of the device was noted at angiographic follow-up. The four remaining patients were asymptomatic, although two of these patients had complete parent artery occlusions thought to be due to carotid artery dissections.

Effectiveness

Of the 145 patients comprising the ITT population, 139 had follow-up angiograms interpretable by the core laboratory. In nine of these 139 patients angiograms from earlier than 1 year were carried forward as 1-year angiograms were not available. Five of these nine patients were adjudicated as endpoint failures. Eighty of 139 (57.6%) patients met the criteria for primary effectiveness—that is, complete aneurysm occlusion without stenosis >50% and no re-treatment (table 4).

To account for the six patients without follow-up imaging, a tipping point analysis was done. Assuming a worst-case scenario with none of the six missing patients meeting the effectiveness criteria, the primary effectiveness would be reduced to 80/145 yielding a posterior mean (95% CI) of 55.1% (47.0% to 63.0%). This worst-case scenario exceeds the predefined primary effectiveness endpoint

Table 4 Primary effectiveness (complete aneurysm occlusion with no significant stenosis and no re-treatment) and alternative definition of effectiveness (near-complete aneurysm occlusion with no significant stenosis and no re-treatment) intention-to-treat population

Endpoint	n=139 n (%)	Posterior mean (95% CI)	Posterior probability*
Primary effectiveness	80 (57.6%)	57.4% (49.2% to 65.5%)	0.997
Primary effectiveness components:			
Aneurysm occlusion (Raymond 1) (n=140)†	88 (62.9%)	62.7% (54.6% to 70.4%)	
Absence of clinically significant stenosis of parent artery (≥50%) (n=139)	133 (95.7%)	95.0% (90.9% to 98.0%)	
No re-treatment (n=140)†	132 (94.3%)	93.7% (89.1% to, 97.0%)	
Primary effectiveness, alternative definition	100 (71.9%)	71.6% (63.9% to 78.7%)	>0.999
Primary effectiveness components:			
Aneurysm occlusion (90% occlusion or greater) (n=140)†	112 (80.0%)	79.6% (72.6% to 85.8%)	
Absence of clinically significant stenosis of parent artery (≥50%) (n=139)	133 (95.7%)	95.0% (90.9% to 98.0%)	
No re-treatment (n=140)†	132 (94.3%)	93.7% (89.1% to 97.0%)	

*Posterior probability that the primary efficacy endpoint success rate is >46%.
†One subject was assessed for aneurysm occlusion but not stenosis of the parent artery.

success of >46%, yielding a favorable primary effectiveness result for the trial.

Primary effectiveness of prespecified subgroups of the intention-to-treat population was analyzed by aneurysm site, patient gender, age, aneurysm rupture status, size, and location. No statistically significant differences were seen among these groups for either the composite primary effectiveness measure or any of its subcomponents. There was a trend towards a higher occlusion rate for patients under age 60, but this did not reach statistical significance.

Target aneurysm re-treatment

Re-treatment occurred in eight subjects: four were carried out to deal with complications of aneurysm rupture or thrombosis, and four because of continued aneurysm filling. Three of these treatment failures were due, at least in part, to device migration (or foreshortening). All eight subjects were re-treated by placement of additional flow diverters.

Prespecified secondary endpoints

A summary of the secondary endpoints is included in table 5.

One of the prespecified secondary endpoints was an alternative definition of occlusion, defined as the number of patients with clinically acceptable (90–100%) occlusion, <50% stenosis of the parent artery, and without unplanned alternative treatment. This alternative definition of successful occlusion was seen in 100/139 (71.9%) patients. The subcomponents of this endpoint are shown in table 5.

DISCUSSION

The performance goals of the trial for safety and efficacy were both met, and as a result FDA approval of the FRED system

Table 5 Summary of secondary endpoints

Endpoint	% (n/N)
Proportion of subjects with clinically acceptable (90–100%) occlusion of the target aneurysm, ≤50% stenosis of the parent artery at the target IA at 12 months as assessed by angiography, and in whom an unplanned alternative treatment of the target IA had not been performed within 12 months	71.9% (100/139)
Proportion of subjects in whom an unplanned alternative treatment of the target IA had not been performed within 12 months	94.3% (132/140)
Proportion of subjects with clinically acceptable aneurysm occlusion (90–100%) of the target aneurysm at 12 months	80.0% (112/140)
Incidence of ≥50% in-stent stenosis at the target IA at 12 months as assessed by angiography at the independent core laboratory	4.3% (6/139)
Proportion of subjects with complete occlusion of the target aneurysm on 12 month angiography (Raymond 1)	62.9% (88/140)
Incidence of FRED system procedure-related serious adverse events	27.6% (40/145)
Incidence of FRED system device-related serious adverse events	18.6% (27/145)
Incidence of unsuccessful delivery of the FRED	1.4% (2/145)
Incidence of unsuccessful deployment of the FRED	2.8% (4/145)
Incidence of migration of the FRED system implant at 12 months	2.8% (4/145)
Unplanned alternative treatment on the target IA within 12 months, defined as re-treatment of the target aneurysm with an alternative treatment modality, including open repair, endovascular placement of an additional stent, or treatment of in-stent stenosis observed at the 180-day or 12-month follow-up time-points or at an unscheduled study follow-up visit	5.7% (8/140)
Change in clinical and functional outcomes at 180-day follow-up, as measured by an increase in the modified Rankin Scale score compared with baseline	13.9% (19/137)
Change in clinical and functional outcomes at 1-year follow-up, as measured by an increase in the modified Rankin Scale score compared with baseline	11.9% (16/135)
Incidence of major stroke, as measured by NIHSS score at 12 months (and ophthalmic examination related to the target aneurysm if determined appropriate)	6.2% (9/145)
Incidence of minor stroke, as measured by NIHSS score at 12 months (and ophthalmic examination related to the target aneurysm if determined appropriate)	6.2% (9/145)

FRED, Flow Redirection Endoluminal Device; IA, intracranial aneurysm; NIHSS, National Institutes of Health Stroke Scale.

was granted. The primary safety endpoint was met in 9/145 (6.2%) patients and the primary effectiveness endpoint in 80/139 (57.6%) patients. Disabling or fatal neurological events occurred in 4/145 (2.8%) patients. The goal of this trial—that is, to gain regulatory approval with the US FDA, can be compared with the Pipeline for Uncoilable or Failed Aneurysms (PUFS) and Surpass Intracranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide Neck Aneurysms (SCENT) trials, which were similarly carried out to gain US FDA approval for the Pipeline and Surpass devices, respectively.[6 7] With respect to the PUFS trial, major differences from this trial include the larger mean size of the aneurysms included in PUFS, the more restricted locations of aneurysms included (proximal carotid only), and the use of multiple devices in the majority of patients (median three devices per patient). The 6 month safety outcome in PUFS of major stroke or neurological death was met in 5.8% of patients, similar to the rate of 6.2% seen at 1 year in the current study, but the rate of complete aneurysm occlusion seen at 6 months in PUFS was higher at 73.6%. It is possible that the location of aneurysms being primarily within the carotid siphon favored a higher rate of occlusion in PUFS as it has been shown that the straightening effect of a flow diverter in a curved segment of the artery correlates with complete aneurysm occlusion, an effect that would be less frequently seen in straighter segments of the carotid, such as the posterior communicating artery segment.[8] The corresponding safety and efficacy figures for the more recent SCENT trial are 8.3% and 62.8%, not meaningfully different from the current study results. Permanently disabling or fatal stroke events in SCENT were 6.1% vs 2.8% in the FRED Pivotal Trial.

Although the FRED system is a relative newcomer to the flow diversion field, a growing body of high-quality evidence consistently shows it provides satisfactory safety and efficacy results.[9–12] Some caution must be exercised in comparing the results of these trials as they vary in definitions of adverse safety outcome, the proportion of large versus small aneurysms, proportion of anterior versus posterior aneurysm locations, duration of follow-up, and number of aneurysms concomitantly treated with adjuvant devices such as coils. Additionally, the rate of complete aneurysm occlusion in these trials is generally higher than reported in the current study, perhaps, at least in part, because they did not employ the composite endpoint we used in this study where parent artery occlusion, stenosis >50%, use of adjuvant treatment, or re-treatment of target aneurysm would all be adjudicated as failures of efficacy.

Without losing sight of the fact that these differences exist, it is reassuring to note that the very low 2.8% rate of disabling stroke (mRS score >2) or death seen in this trial is consistently reflected in the other recent major trials of the FRED system, where combined permanent morbidity and mortality was reported as ranging from 2.3% to 4.8%.[9–12] As was seen with the Pipeline device,[6 13 14] these same studies of the FRED system report improving rates of complete aneurysm occlusion over time, with occlusion at 1 year ranging from 73.3% to 91.3%.

These results in aggregate are similar to the results reported in prior pooled analyses of treatment with the Pipeline flow diverters, specifically the International Retrospective Study of the Pipeline Embolization Device (IntrePED) study, and the pooled analysis of the PUFS, IntrePED, and ASPIRe data.[15 16] In the pooled analysis the combined major neurologic morbidity and mortality was 7.1% versus 2.8% in this trial and 2.3% in the EuroFRED registry.[9] Complete aneurysm occlusion at 1 year was 85.5% in the pooled Pipeline analysis, 57.6% in the current study, and 91.3% in EuroFRED, although EuroFRED occlusion results were not adjudicated by a core laboratory. It should be recognized that the pooled Pipeline analysis represents an earlier experience with flow diverters, and an aneurysm population that may be significantly different from more recent trials where aneurysm sizes tend to be smaller. These differences may account in some part for the more favorable results reported in the recent PREMIER trial.[17]

Study limitations

The chief limitation of the current study is the lack of a control group. Comparison with other trials is difficult because of significant differences in key features, such as allowed anatomical sites of included aneurysms, aneurysm characteristics such as size, and treatment-related issues such as the number of devices used.

CONCLUSIONS

As compared with historically derived performance benchmarks, the USA FRED pivotal trial successfully achieved favorable outcomes for the primary endpoints of both safety and efficacy in the treatment of intracranial aneurysms.

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Correction notice Since this article was first published online, the following authors have been added to the author group Louis J Kim, Steven W Hetts, Daniel L Cooke and Christopher F Dowd.

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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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Effectiveness / Safety Analysis

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As well as any of the following criteria:

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

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

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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);

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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%;

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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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