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# Periprocedural to 1-year safety and efficacy outcomes with the Pipeline Embolization Device with Shield technology for intracranial aneurysms: a prospective, post-market, multi-center study

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## ABSTRACT

**Background** The first and second generations of the Pipeline Embolization Device (PED) have been widely adopted for the treatment of intracranial aneurysms (IAs) due to their high associated occlusion rates and low morbidity and mortality. The objective of this study was to evaluate the safety and effectiveness of the third-generation Pipeline Shield device (PED-Shield) for the treatment of IAs.

**Methods** The SHIELD study was a prospective, single-arm, multicenter, post-market, observational study evaluating the PED-Shield device for the treatment of IAs. The primary efficacy endpoint was complete aneurysm occlusion without significant parent artery stenosis or retreatment at 1-year post-procedure and the primary safety endpoint was major stroke in the territory supplied by the treated artery or neurological death.

**Results** Of 205 subjects who consented across 21 sites, 204 subjects with 204 target aneurysms were ultimately treated (mean age 54.8±12.81 years, 81.4% [166/204] female). Technical success (ie, deployment of the PED-Shield) was achieved in 98.0% (200/204) of subjects with a mean number of 1.1±0.34 devices per subject and a single device used in 86.8% (177/204) of subjects. The primary effectiveness endpoint was met in 71.7% (143/200) of subjects while the primary safety endpoint occurred in six (2.9%) subjects, two (1.0%) of which led to neurological death.

**Conclusions** The findings of the SHIELD study support the safety and effectiveness of the PED-Shield for IA treatment, evidenced by high occlusion rates and low rates of neurological complications in the study population.

**Clinical trial registration-URL** http://www.clinicaltrials.gov. Unique identifier: NCT02719522.



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## INTRODUCTION

Intracranial aneurysms (IAs) are common cerebrovascular abnormalities estimated to occur in 3%–5% of the general population.[1–3] Despite advances in conventional IA treatment, including surgical clipping and endovascular coiling or stent-assisted coiling, IAs are still associated with a high rate of adverse events (AEs) such as thrombosis, aneurysm rupture, recurrence, and retreatment.[4–7] Flow diversion addresses several of these limitations and is now broadly accepted as a suitable alternative to conventional IA treatment, especially for complex (eg, wide-neck) aneurysms.[6 8–10] The Pipeline Embolization Device (PED) (Medtronic Neurovascular, Irvine, CA) represents a paradigm shift and has expanded the therapeutic options for IA treatment.[4 6 11] Several clinical trials and retrospective studies have provided evidence for the safety and effectiveness of the first-generation PED in various aneurysm contexts.[12–15]

A major concern with the use of flow diversion devices is the possibility of ischemic complications, including thromboembolic complications and stenosis.[16 17] In 2015, a redesigned 'third-generation PED' called the Pipeline Flex Embolization Device with Shield Technology (Pipeline Shield device, [PED-Shield]) was introduced to minimize the likelihood of ischemic complications during IA treatment. The PED-Shield features similar implant and delivery systems to its predecessor, the Pipeline Flex Embolization Device (PED-Flex). Shield Technology refers a surface modification in which a synthetic phosphorylcholine polymer is covalently bonded to the Pipeline braid: this coating has been shown to decrease thrombogenicity in vitro, ex-vivo, and in vivo.[16–19]

The Pipeline Flex with SHield Technology Embolization – An International MulticEnter ObservationaL Post-Market StuDy (SHIELD) was conducted to assess the short-term and long-term safety and effectiveness of the PED-Shield in subjects undergoing treatment for IAs in a real-world, post-market setting.

## METHODS

### Study design and participants

SHIELD was a prospective, single-arm, multi-center, post-market, observational study of the PED-Shield in subjects undergoing treatment for IAs across 21 sites (online supplementary file 2) in the European Union, Israel, and Australia. Each participating site was required to train physicians delegated for implant procedures in the use of the PED device. Physicians were required to complete at least 20 flow diversion cases, including a minimum of 15

with PEDs, and using the PED-Flex or the PED-Shield in at least five cases. The study population consisted of subjects with IAs who consented to the study procedures at participating centers. Eligible aneurysms included those acutely ruptured (with a Hunt and Hess grade of ≤3) provided that the PED-Shield was used in strict accordance with its Instructions for Use and intended use during the treatment regimen. When required by local regulations, the study protocol and informed consent or data release form were approved by a local ethics committee. Written consent was obtained from all subjects. Subject inclusion and exclusion criteria are presented in online supplementary Table I.

Data analysis was performed on the intent-to-treat (ITT) population, which included all consented subjects in whom deployment of the PED-Shield was attempted. The full analysis set (FAS) population is a subset of the ITT population that included only those in whom the PED-Shield was implanted.

### Procedure and follow-up

Endovascular PED deployment was performed per the manufacturer's Instructions for Use. Antiplatelet therapy was administered pre- and post-device placement as per the standard of care for patients with IAs undergoing flow diversion therapy. Follow-up evaluations were performed per the standard of care via hospital visit or telephone at approximately 1 (±14 days), 3 (±30 days), 6 (±6 weeks), and 12 (±8 weeks) months' post-procedure. Subjects were asked to confirm their current antiplatelet regimen and report any relevant AEs.

### Study endpoints

The primary efficacy endpoint was complete aneurysm occlusion defined as Raymond–Roy grade 1 without significant parent artery stenosis (≤50%) or retreatment of the target aneurysm at 6 months, 1 year, or final follow-up. Occlusion and parent artery stenosis were assessed based on the last image available starting at the 6-month imaging window with preference for digital subtraction angiography (DSA), followed by CT angiography (CTA) and subsequently magnetic resonance angiography (MRA) imaging. The primary safety endpoint was any major stroke in the territory supplied by the treated artery or neurologic death at 1-year post-procedure. Stroke was defined as a focal neurological deficit of presumed vascular origin persisting for >24 hours from symptom onset with a neuroimaging study or other quantitative study excluding the possibility of a different etiology. Stroke severity was adjudicated by a designated Clinical Events Committee (CEC) and deemed 'major' if the subject had an increase in National Institutes of Health Stroke Scale (NIHSS) score of ≥4 persisting for 7 days or more, or 'minor' if the event resolved completely within 7 days or if the subject had an increase in NIHSS score ≤3.

Secondary safety endpoints included: major stroke in the territory supplied by the treated artery or neurological death at 30 days' post-procedure due to procedural complications; delayed intracerebral hemorrhage >30 days' post-procedure; and device deployment success rate at the target site. Investigators were required to report all AEs and serious adverse events (SAEs) with an underlying neurologic cause, bleeding events, and events deemed related to the study device or procedure. Neurological events of interest considered by the CEC included neurological death, stroke, intracranial hemorrhage, transient ischemic attack, cerebral infarction, focal neurological deficit, target aneurysm retreatment, ipsilateral cranial nerve palsy/neurological deficit, ipsilateral visual loss, and ipsilateral localized headache. An additional pre-specified safety analysis examined the occurrence of device-related neurological AEs at 1-year post-procedure. Event relatedness to study treatment and a single proximate cause were determined by the CEC for each individual event.

### Study committees

To minimize bias, all secondary safety endpoints and reportable AEs were adjudicated by an independent CEC (online supplementary file 2) comprised of three physicians knowledgeable in relevant disciplines and medical specialties. An Imaging Core Laboratory adjudicated safety events and qualitatively assessed aneurysm occlusion, wall apposition, and neck coverage by the PED-Shield (3 mm coverage of the PED-Shield device proximally and distally to the aneurysm neck) as well as branch coverage, aneurysm occlusion, parent artery stenosis, and device migration.

### Statistical analysis

Discrete variables are presented using frequency distributions and cross tabulations. Continuous variables are presented as the number of observations (N), mean, SD, median, minimum, and maximum values.

Missing data for subjects who failed to complete study follow-up without evidence of major stroke in the territory supplied by the treated artery or neurological death were imputed into the primary safety analysis using the multiple imputation procedure (*Proc MI*) available in Statistical Analysis System (SAS) for Windows (version 9.2 or higher, SAS Institute Inc. Cary, NC). Subjects who withdrew from the study prior to completion and had experienced a major stroke in the territory supplied by the treated artery or neurological death at any time were counted as having experienced the event of interest, and subjects who withdrew prior to study completion without evidence of a major stroke in the territory supplied by the treated artery or neurological death were counted as not having experienced the event of interest.

Outcomes' variables were recorded on a dichotomous scale and summarized using a two-sided 95% Clopper–Pearson exact binomial CI. The upper and lower bounds of the CI were compared with those derived from previous Medtronic-sponsored clinical studies using Pipeline devices.[13 14] The incidence of a major stroke in the territory supplied by the treated artery or neurological death at 1-year post-procedure was examined relative to a threshold of 15%, while the incidence of aneurysm occlusion without significant parent artery stenosis was examined relative to a threshold of 50%. All data analyses were performed using SAS for Windows (version 9.2 or higher, SAS Institute Inc. Cary, NC).

## RESULTS

### Demographics and aneurysm characteristics

Of 205 subjects who consented across 21 sites, 204 subjects with 204 aneurysms were treated after exclusion of one patient with a stenotic artery. The mean age of subjects was 54.8±12.81 years and 81.4% (166/204) were female. Patient baseline characteristics including comorbidities are presented in table 1.

The baseline morphology of target IAs was saccular in 94.1% of subjects (192/204) and 75% (152/204) were located in the intracranial segments (C2–C7) of the internal carotid artery (ICA). Mean aneurysm size (maximal diameter) was 8.5±5.61 mm, neck length was 4.6±2.39 mm, and dome/neck ratio was 1.6±0.90. Fifty percent of target aneurysms (102/204) were small (<7 mm), 33.8% (69/204) were medium (7–13 mm), 13.7% (28/204) were large (13-<25 mm), and 2.5% (5/204) were giant (≥25 mm). Most target aneurysms (81.4%, 166/204)

**Table 1** Patient baseline characteristics

| Characteristic | Summary (n=204) |
|---|---|
| Age (years) | 54.8±12.81 |
| Female | 166 (81.3%) |
| Cigarette smoking | 98 (48.0%) |
| Currently | 45 (46.0%) |
| Previous | 53 (54.1%) |
| Comorbidities | |
| Family history of stroke/TIA | 26 (12.7%) |
| Hypertension | 89 (43.6%) |
| Controlled | 85 (95.5%) |
| Uncontrolled | 4 (4.5%) |
| Diabetes | 15 (7.3%) |
| Type 1 | 1 (6.7%) |
| Type 2 | 14 (93.3%) |
| Hyperlipidemia | 44 (21.6%) |
| Atrial fibrillation | 9 (4.4%) |
| Cardiovascular disease | 7 (3.4%) |
| Coronary heart disease | 8 (3.9%) |
| Subarachnoid hemorrhage (excluding rupture of target aneurysm) | 19 (9.3%) |
| Multiple aneurysms present* | 51 (25.0%) |
| Additional aneurysm present in parent artery* | 25 (12.3%) |

Data are n (%) or mean±SD.
*Core laboratory reported.

were unruptured at the time of study enrollment, and 23.0% (47/204) were treated previously. The complete characteristics of target aneurysms are summarized in table 2.

## Antiplatelet therapy

A total of 195 (95.6%) subjects received antiplatelet therapy prior to study treatment (online supplementary table II). Dual antiplatelet therapy (DAPT) was administered pre-procedure (≥7 days) in 29.2% (57/195) of subjects, on days 1–6 pre-procedure in 53.3% (104/195), on the day of the procedure in 93.3% (182/195), and immediately prior to the procedure in 82.6% (161/195). Almost all subjects (99.0% [193/195]) received DAPT post-procedure, and of these, 20% (39/195) interrupted DAPT within 3 months and continued with SAPT (either aspirin [19.5%] or clopidogrel [0.5%]). Twelve percent (12.3% [24/195]) of subjects never interrupted DAPT during follow-up.

SAPT was administered pre-procedure (≥7 days) in 2.1% (4/195) of subjects, on days 1–6 pre-procedure in 4.6% (9/195), on the day of the procedure in 4.1% (8/195), and immediately pre-procedure in 6.7% (13/195). Only 1.0% (2/195) of subjects received SAPT post-procedure.

## Procedure characteristics

A total of 252 PED-Shield devices were implanted, with an average of 1.1±0.5 devices implanted per subject (online supplementary table III). The majority of subjects (86.8% [177/204]) were implanted with a single PED-Shield device. In the remaining subjects, multiple devices were implanted to cover additional length by overlapping (39.1%, 9/23) or to achieve multiple layers for increased mesh density (21.7%, 5/23). Device implantation was unsuccessful in four patients.

**Table 2** Target aneurysm characteristics

| Characteristic | Summary (n=204) |
|---|---|
| Aneurysm side | |
| Right | 95 (46.6%) |
| Left | 100 (49.0%) |
| Midline | 9 (4.4%) |
| Parent artery location | |
| ACA | 8 (3.9%) |
| A1 (origin to anterior communicating) | 3 (1.5%) |
| A2 (distal to anterior communicating) | 5 (2.5%) |
| Anterior communicating artery | 12 (5.9%) |
| MCA | 16 (7.8%) |
| M1 (origin to bifurcation) | 2 (1.0%) |
| M2 (distal to bifurcation) | 1 (0.5%) |
| MCA bifurcation | 13 (6.4%) |
| ICA | 155 (76.0%) |
| C1 (cervical segment) | 2 (1.0%) |
| C2 (petrous segment) | 1 (0.5%) |
| C3 (lacerum segment) | 3 (1.5%) |
| C4 (cavernous segment) | 8 (3.9%) |
| C5 (clinoid segment) | 18 (8.8%) |
| C6 (ophthalmic segment) | 84 (41.2%) |
| C7 (communicating segment)* | 39 (19.1%) |
| Vertebral | 13 (6.4%) |
| V4 (intradural) | 13 (6.4%) |
| Aneurysm morphology | |
| Saccular | 192 (94.1%) |
| Fusiform | 10 (4.9%) |
| Pseudo-aneurysm | 2 (1.0%) |
| Rupture status | |
| Unruptured | 166 (81.4%) |
| Ruptured | 38 (18.1%) |
| Previously treated | 47 (23.0%) |
| Coil embolization | 44 (93.6%) |
| Surgical clipping | 2 (4.3%) |
| Other | 1 (2.1%) |
| Aneurysm measurement | |
| Aneurysm maximal diameter (mm) | 8.5±5.61 |
| Small (<7 mm) | 102 (50.0%) |
| Medium (7 -<13 mm) | 69 (33.8%) |
| Large (13 -<25 mm) | 28 (13.7%) |
| Giant (≥25 mm) | 5 (2.5%) |
| Dome width (mm) | 7.3±5.01 |
| Dome height (mm) | 7.4±5.07 |
| Aneurysm neck length (mm) | 4.6±2.39 |
| Dome/neck ratio | 1.6±0.90 |
| Parent artery diameter proximal to target aneurysm (mm) | 3.7±0.74 |
| Parent artery diameter distal to target aneurysm (mm) | 3.2±0.62 |

Data are n (%) or mean±SD. Results are based on pre-procedure imaging assessed by the independent imaging core laboratory
*C7 includes the carotid terminus.

Index procedure time, defined as the mean time from skin incision to skin closure, was 100.5±92.02 min and the mean cumulative fluoroscopy time was 36.1±27.98 min. Adjunctive devices were used in 29.8% of subjects (18.6% adjunctive

**Table 3** Primary effectiveness endpoint through 1 year post-procedure by aneurysm location (FAS population with observed data)

| Primary effectiveness endpoint† | Rate* | 95% CI |
|---|---|---|
| All aneurysms | 143/200 (71.7%) | (65.0% to 77.7%) |
| Intracranial ICA (C2-C7 including terminus) | 109/144 (75.7%) | (67.9% to 82.4%) |
| Non-intracranial ICA | 28/45 (62.2%) | (46.5% to 76.2%) |
| C1 | 1/2 (50.0%) | (1.3% to 98.7%) |
| Vertebral | 8/13 (61.5%) | (31.6% to 86.1%) |
| MCA | 7/13 (53.8%) | (25.1% to 80.8%) |
| ACA | 6/8 (75.0%) | (34.9% to 96.8%) |
| AComm | 6/9 (66.7%) | (29.9% to 92.5%) |

Data are % (n/N). FAS population is n=200; representing the number of patients with follow-up information.
*Numerator represents subjects who had complete aneurysm occlusion without significant parent artery stenosis (>=50%) at 1-year post-procedure or without re-treatment of the target aneurysm. Occlusion and stenosis are based on core laboratory data, and retreatment is based on site reported data.
†The primary effectiveness endpoint was assessed using the last adjudicated image at any time starting from day 141, unless the last image is a CTA and there is a DSA within 90 days prior to the CTA, in which case the DSA was used, or the last image is an MRA and there was a DSA or CTA within 90 days prior to the MRA, in which case the DSA or CTA was used. If both existed, DSA was preferred over CTA.
ACA, anterior cerebral artery; AComm, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery.

coiling and 10.8% adjunctive balloon). Resheathing was performed for 19.4% (49/252) of devices. The most common reasons for resheathing were repositioning (49.0%, 24/49), distal braid opening (24.5%, 12/49), and delivery technique (14.3%, 7/49).

### Post-procedure aneurysm status

Complete wall apposition of the PED-Shield device as adjudicated by the Imaging Core Laboratory analysis was achieved in 93.1% (190/204) of subjects. Coverage of the entire aneurysm neck was documented in 97.5% (199/204) of subjects. None of the five subjects without complete neck coverage underwent retreatment. Complete stasis was achieved in 10.8% (22/204) of subjects, significant stasis in 52.5% (107/204), and no disruption of inflow jet in 36.8% (75/204). Complete occlusion of the target aneurysm was achieved in 1.0% (2/204) and residual aneurysm was observed in 99.0% (202/204) of subjects.

### Effectiveness endpoint

The primary effectiveness endpoint was evaluated in the FAS population (n=200) (table 3). In this population, one (0.05%) subject required retreatment and 188 (94.0%) had evaluable images. Data for 11 subjects required multiple imputation. The primary effectiveness endpoint success criterion was met in 71.7% of subjects (95% CI: 64.95% to 77.74%). Evaluable imaging was available for 188 subjects through 1 year, and an additional one subject had retreatment, thus a total of 189 subjects had evaluable effectiveness endpoint data. A total of 27.5% (52/189) of subjects failed to meet the primary effectiveness endpoint due to the presence of residual aneurysm (20.2%, 38/188), residual neck (4.8%, 9/188), stenosis >50% (1.1%, 2/188), and target aneurysm re-treatment (2.1%, 4/189). The lower bound of the 95% CI was 65.0%, which was above the prespecified threshold of 50%. Thus, the primary effectiveness threshold was met.

**Table 4** Post-procedure target aneurysm occlusion at 1 year and last follow-up post-procedure (ITT population with observed data)

| | 6 Month* | 12 Month* | Last follow up† |
|---|---|---|---|
| Complete occlusion | 92/130 (70.8%) | 61/79 (77.2%) | 141/188 (75.0%) |
| Residual neck | 7/130 (5.4%) | 4/79 (5.1%) | 9/188 (4.8%) |
| Residual aneurysm | 31/130 (23.8%) | 14/79 (17.7%) | 38/188 (20.2%) |

Data are % (n/N). ITT population is n=204, representing the number of patients with follow-up information.
*6months (±6 weeks), 1 year (±8 weeks).
†The last adjudicated image at any time starting from day 141, unless the last image is a CTA and there was a DSA within 90 days prior to the CTA, in which case the DSA was used, or the last image was a MRA and there was a DSA or CTA within 90 days prior to the MRA, in which case the DSA or CTA was used. If both existed, DSA was preferred over CTA.

The primary effectiveness endpoint was also analyzed by aneurysm location. Complete occlusion without significant parent artery stenosis or retreatment at 1-year post-procedure was achieved in 75.7% (109/144) of subjects with intracranial ICA aneurysms and 62.2% (28/45) of subjects with non-ICA aneurysms.

In the ITT population, complete aneurysm occlusion was achieved in 70.8% (92/130) of subjects at 6 months and 77.2% (61/79) at 1 year, or 75.0% (141/188) at last available follow-up. Two subjects died prior to 1-year follow-up. A summary of post-procedure aneurysm occlusion data is presented in table 4. The secondary effectiveness endpoint (deployment success at the target site) was observed in 98.0% (200/204) subjects.

### Safety endpoints

A summary of AEs through 1-year post-procedure is presented in online supplementary table IV. During 1-year follow-up, 139 AEs were reported in 90/204 (44.1%) subjects. Of these, 41 were serious in 36/204 (17.6%) subjects and 98 were non-serious in 71/204 (34.8%) subjects. A total of 21 device-related neurological AEs were reported in 20/204 (9.8%) subjects during this period. Per CEC adjudication, there was a 48% (98/204) incidence of AEs with a total of 155 AEs observed over the 1-year follow-up period. Of these, 58 AEs in 21.6% (44/204) of subjects were considered serious and 97 AEs in 36.3% (74/204) of subjects were considered non-serious.

CEC-adjudicated neurological events of interest in the ITT population are presented in online supplementary table V. Three subjects with missing data required imputation. The primary safety endpoint occurred in 3.2% of subjects during the study. The upper bound of the 95% CI was 6.7%, which was below the prespecified threshold of 15.0%: therefore, the primary safety endpoint of the study was met.

Six subjects (2.9%) experienced a major stroke in the territory supplied by the treated artery, two (1.0%) of which led to neurological death. Three strokes were ischemic (thromboembolic) in etiology; two of these subjects received pre- and post-procedure DAPT (clopidogrel and aspirin); and one subject only received SAPT with abciximab on the day of the procedure. One subject who experienced hemorrhagic conversion of ischemic infarct received pre-procedure DAPT with clopidogrel and aspirin (plus ticagrelor for 2 days' pre-procedure) and post-procedure DAPT with ticagrelor and aspirin. For the remaining two cases of stroke, one subject received pre- and post-procedure SAPT (prasugrel) and the other received pre-procedure SAPT (clopidogrel), day-of platelet pool and aspirin, and post-procedure DAPT (clopidogrel and aspirin). Five of the major stroke events occurred in subjects with target saccular aneurysms in the ICA (C2 to C7) and one

subject had a target aneurysm in the bifurcation segment of the middle cerebral artery.

Stroke (major and minor) was the most common event in the periprocedural (Day 0, 2.0% [4/204]) and acute periods (Days 1–30, 4.4% [9/204]), while target aneurysm retreatment was the most common event in the delayed period (Days 31–365, 1.5% [3/204]). No multiple imputation was performed for the secondary safety endpoints. No subjects experienced an intracerebral hemorrhage >30 days' post-procedure.

Details of CEC-adjudicated device-related SAEs are presented in online supplementary table VI. A total of 19 device-related SAEs occurred in 17/204 (8.3%) subjects during 1-year follow-up. Of these, seven SAEs in 7/204 (3.4%) subjects were observed during the peri-procedural period (Day 0), nine SAEs in 8/204 (3.8%) subjects during the acute period (Days 1–30), and three SAEs in 3/204 (1.5%) subjects during the delayed period (Days 31–365).

A total of 40 SAEs in 33/204 (16.2%) subjects were adjudicated as procedure-related by the CEC. Of these, 13 SAEs in 12/204 (5.9%) subjects occurred during the peri-procedural period (Day 0), 25 SAEs in 22/204 (10.8%) subjects during the acute period (Days 1–30), and two SAEs in 2/204 (1.0%) subjects during the delayed period (Days 31–365). Details of CEC adjudicated procedure-related SAEs are presented in online supplementary table VII.

## DISCUSSION

The SHIELD study examined the safety and effectiveness of the PED-Shield with 1 year of follow-up data in a large patient cohort and in a real-world, post-market setting. Treatment of IAs with the PED-Shield resulted in high rates of complete occlusion of the target aneurysm with low morbidity, mortality, target aneurysm rupture, and target aneurysm retreatment. Furthermore, both of the *a priori*-specified two-sided 95% CI thresholds for the primary safety and efficacy endpoints were met, suggesting that the PED-Shield is a safe and effective device for IA treatment.

This study resulted in a high rate of successful deployment and low mean number of devices deployed per aneurysm, in agreement with the PFLEX study,[20] and studies using the second-generation PED device.[21 22] The use of fewer devices has been associated with a lower rate of complications with PED,[21] highlighting the importance of optimized deployments systems and training by the neurointerventionalist.

High rates of complete occlusion (70.8% and 77.2% at 6 months and 1 year, respectively) and low rate of retreatment (0.05%) among subjects treated with the PED-Shield in the present study are comparable to two previous studies of the PED-Shield: the PFLEX study, which reported complete aneurysm occlusion in 82% of subjects at 1 year and no target aneurysm recurrence or retreatment after complete occlusion,[23] and an observational study that noted complete aneurysm occlusion in 79.7% and 85.3% of cases at 6 months and 1 year, respectively.[24] Our findings are also consistent with reports evaluating previous generations of the PED, which indicated complete occlusion rates ranging from 73.6% to 78.6% at 6 months and from 78.9% to 86.8% at 1 year.[25] Additionally, studies of similar aneurysm sizes including the PREMIER[14] and IntrePED studies[15] reported target aneurysm retreatment rates at 1 year of 2.9% and 1.9%, respectively. Slightly lower complete occlusion rates in the SHIELD study compared with previous studies might be attributed to the real-world, post-market nature of the data, as well as differences in inclusion criteria, number of patients with risk factors, aneurysm characteristics, and operator or center-specific factors.

The occurrence of major stroke (ischemic or hemorrhagic), neurologic morbidity, and neurologic death at 30 days and 1-year post-procedure in the SHIELD study are consistent with reports of no major stroke or neurologic death and a neurological complication rate of 6.6% at 1-year post-procedure in the PFLEX study.[20 23] Moreover, the safety endpoints in the present study are comparable with findings from previous studies using earlier versions of the PED device.[12 14 15] The PREMIER study reported a major stroke rate of 2.1% and neurologic death <1% at 1 year.[14] Major neurologic morbidity and mortality rates were 5.6%, 8.4%, and 6.8% in the PUFS trial,[13] International Retrospective Study of the Pipeline Embolization Device (IntrePED),[15] and Aneurysm Study of Pipeline in an Observational Registry (ASPIRe),[12] respectively. The overall CEC-adjudicated rate of SAEs in the SHIELD study was 21%: however, the rate of device-related SAEs was only 8.3%. These rates are lower than those reported in the PUFS trial (41% and 20%, respectively)[13] and may be in part related to the inclusion of patients with risk factors in order to provide a real-world context.

Since the metal structure of flow diverters has been thought to increase thrombogenicity,[26 27] low overall rates of neurologic morbidity and mortality reported in this study and previous studies implementing Shield Technology may be in part related to the non-thrombogenic phosphorylcholine device coating.[16–19] One recent study evaluated the safety and thrombogenicity of the PED-Shield in patients with aneurysmal subarachnoid hemorrhage receiving SAPT.[28] Although the cohort was small (14 patients), complete or near-complete occlusion was attained in 12 subjects and there were no ischemic or hemorrhagic complications in patients who received a post-operative heparin infusion.[28] In the PFLEX study, there were no procedural or periprocedural thromboembolic events, but one patient (2%) experienced a thromboembolic event at 1 year.[23] A more recent study in 41 patients with 44 unruptured cerebral aneurysms reported no thromboembolic or hemorrhagic events during procedures, one periprocedural thromboembolic event (2.4%) in a patient who also had atrial fibrillation, and no thromboembolic events during follow-up.[29] In the present study, there were three thromboembolic events during follow-up, resulting in an event rate of 1.5%, consistent with previous reports and much lower than thromboembolic event rates of up to 6.5% reported for previous-generation PEDs.[15 30] Taken together, these findings support low thrombogenicity and improved safety of the PED-Shield relative to its predecessors.

A main limitation of the SHIELD study was a single-arm design and lack of a direct comparator. A second important limitation was that the majority of aneurysms were located in the ICA. Other areas of the cerebral vasculature need to be evaluated separately since aneurysms of the ICA have a lower risk of complications compared with those located elsewhere in the anterior circulation.[20] Third, the majority of aneurysms had an average size of <13 mm and a mean dome to neck ratio of <2.0, such that the findings of the SHIELD study may not be generalizable to large and giant aneurysms or wide-necked aneurysms (dome to neck ratio >2.0). Finally, it is noteworthy that follow-up (and therefore adverse event reporting) was performed in accordance with standard clinical practice at each respective center: accordingly, there was no single follow-up structure or timetable. Although we attempted to mitigate this issue by reporting follow-up at 6 months, 12 months, and last follow-up, this may nonetheless have introduced some bias into the study findings. An important strength of the study lies in its prospective, multicenter design

and the inclusion of a larger cohort of subjects than previous studies using the PED-Shield.

## CONCLUSIONS

The findings of the SHIELD study indicate that the PED-Shield offers high occlusion rates, low neurologic morbidity and mortality, low device and procedure complication rates, and low target aneurysm recurrence and retreatment when implemented for the treatment of IAs, particularly small- and medium-sized aneurysms. Future studies are warranted to confirm these findings in large, giant, and wide-neck aneurysm contexts.

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