Symposium: Redefining Flow Diversion using Pipeline™ Flex with Shield Technology™ – Release of New Clinical Data

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Received; 22nd November 2019, Accepted; 25th November 2019

Meeting summary

The symposium was sponsored by Medtronic and took place on Wednesday 4 September 2019 as part of the 12th Congress of the European Society of Minimally Invasive Neurological Therapy (ESMINT), Nice, France. Preliminary results within the INSPIRE registry highlight the real-world experience revealing complete occlusion in 70% of cases (N = 114); those aneurysms were not only in the carotid syphon but also in the posterior circulation. There was no significant parent artery stenosis in the majority of patients. Preliminary results were also presented for the Pipeline™ Flex Embolisation Device with Shield Technology™ which support the safety and efficacy of the device. The primary effectiveness endpoint was met in 71.7% of patients with complete aneurysm occlusion and no significant intimal hyperplasia or incident stenosis of >50%, and no retreatment.

KEYWORDS: ACUTE ISCHAEMIC STROKE, HAEMORRHAGIC STROKE, INSPIRE REGISTRY, INTRACRANIAL ANEURYSM, NEUROVASCULAR, PIPELINE FLEX™ EMBOLISATION DEVICE WITH SHIELD TECHNOLOGY™.

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Disclosures: Prof Laurent Spelle is a consultant for Medtronic plc

Support: The symposium was funded by Medtronic plc

Acknowledgements: Medical writing and editing support was provided by Dr Allison Kirsop, Scientific Writers Ltd, UK and Oruen Ltd, UK.

Introduction

The third generation Pipeline™ Flex Embolisation Device with Shield Technology™ (Pipeline Shield) is a modified version of the Pipeline Embolisation Device (PED), a routine first-line treatment option for intracranial aneurysms (IAs).[1] Pipeline Shield was developed to improve biocompatibility and reduce the risk of thrombogenicity, and with these improvements the aim is to reduce patient and medication risk factors.[2] New medical device inventions have increased the selection of therapeutic choice and provided more opportunities for effective treatment of different diseases.

With new technologies, new treatment options arrive, and thus new pathologies become treatable. Importantly, they also provide a new market for the industry. Nonetheless, new technologies also provide a challenge for physicians to select the most appropriate technique for individuals. However, new devices continue to become commercially available before clear scientific evidence for efficacy or safety has been established, generating uncertainty among physicians who question whether a device is recommended because of good scientific evidence, or merely due to commercial interest.

Product Surveillance and a new approach to neurovascular device encapsulation – the INSPIRE registry

Prof Istvan Szikora explained how the INSPIRE neurovascular product surveillance registry (NCT02988128)[3] is a unique surveillance platform, set up to collect clinical data on safety and efficacy to generate therapy evidence for haemorrhagic and acute ischaemic stroke therapies. This large scale, prospective, multi-device, multi-centre, observational study will provide continuous monitoring of safety and performance of any new devices introduced to the neurovascular field by the sponsor, Medtronic Neurovascular. INSPIRE is an innovative model for new product surveillance and can follow a new device introduced to the market, making it easier for physicians to make informed choices. The design of the registry includes a large number of worldwide sites (N = 40) and all eligible patients treated by new technologies can be enrolled in the study. The registry is designed to collect data from routine clinical practice applied at each site and ensures that these data are representative of real-world experience. The sites are consistently monitored, safety is assessed by the Clinical Event Committee (CEC), and efficacy is determined by a core lab.

The benefits of the registry include provision of a high volume of reliably collected data to aid physicians in optimising treatment strategies. It is also intended to help the industry understand patterns of product use and improve product safety and performance; for example, hospital managers and health care payers can choose the best options for their practice from a financial point of view, and decision makers can set reimbursement rules on a state or insurance company level. These advantages of the registry are in line with recent trends in Europe which affect medical device regulations and such legislation will make this approach more common in the future (Directive 2017/745 of the European Parliament and Council).[4]

Other imminent projects include INSPIRE ANEURYSM – a one-year analysis of 600 patients treated with Pipeline Shield on completion of follow-up, and a further analysis of 180 patients treated with Pipeline Flex across 12 sites in France for continuing reimbursement purposes – enrollment closure is expected to be December 2019. INSPIRE STROKE will follow to investigate new stroke devices including React™ aspiration catheters and Solitaire™ X to be introduced by Medtronic in the near future; enrollment for these studies will start by the end of 2019.

In his concluding remarks, Prof Szikora emphasised that this new approach should result in a stronger cooperation between industry and the neurovascular medical community with greater potential to improve patient safety, treatment efficacy, and importantly, the physician's trust of the device and manufacturer.

INSPIRE 6-month results of initial patient cohort treated with Pipeline™ Flex with Shield Technology™ (Pipeline Shield)

Prof Laurent Spelle presented the preliminary results for the Pipeline Shield device. A total of 600 patients have been enrolled on the study and the first 6-month follow-up results are available for 114 patients in the INSPIRE registry study treated with Pipeline Shield. The endpoint was an assessment of the composite criteria of complete aneurysm occlusion without significant parent artery stenosis. Secondary endpoints were device- and procedure-related adverse events (AEs), the existence of the parent artery stenosis, and the existence of aneurysm retreatment. Also collected in this study were data for anti-platelet drug regimen.

A cohort of 114 patients were enrolled to treat 138 aneurysms. Individuals were predominantly female (78%, 89/114) and the average age was 55 years. Past medical history revealed a large number of smokers among the study group. Generally, in this cohort, Pipeline Shield devices used were in the carotid syphon (68%), middle cerebral artery (MCA, 5%), and in the posterior circulation. Findings revealed that most aneurysms were saccular with very few fusiform. The dimensions of aneurysms were interesting;

73% of cases were small at <10 mm, a propensity of the use of the flow diverter which is a different scenario to that of a decade ago. As expected, most aneurysms were non-ruptured, and these were reported in 75% of cases.

The Pipeline Shield device was successfully implanted in 98% of patients with a relatively short procedure time and an average total procedural time of approximately one hour. Adjunctive coiling was used in 17 procedures of the 114 patients treated, and most patients (92%, 105/114) received dual antiplatelet therapy (DAPT). However, there is some emphasis of the point that 6% of patients received single antiplatelet therapy (7/114, 57.1% aspirin only) which may be a factor in future decisions of whether to continue DAPT with this technology.

The primary endpoint at 6 months is a composite endpoint of complete occlusion without significant parent artery stenosis and this was achieved in approximately 70% of cases. These preliminary data are site-reported, and it is noted that no patients were lost to follow-up, and there were no deaths. Secondary endpoints at 6 months were aneurysm occlusion and the existence of any parent artery stenosis; complete occlusion (progressive thrombosis) was reached in 70% of patients and there was no significant stenosis in 90% of cases. Additionally, preliminary modified Rankin Scale (mRS) scores reflect cumulative morbidity at two time points: 0 (76.8%) and 1 (15.9%) at baseline, and 0 (74.7%) and 1 (19.5%) at 6 months after the procedure.

Regarding safety, clarification through the CEC is necessary due to the range of AEs reported (Table 1). As an example, cardiac tamponade is clearly linked to the procedure but not to the device itself, while headache is a mild event and drowsiness is not well understood. Therefore, the CEC is

Table 1. Site Reported Device- or Procedure-Related Serious Adverse Events (SAEs) From the Preliminary 6-Month Results of 114 Patients Treated With Pipeline Flex™ With Shield Technology™.

SAFETY EVENTS

0 deaths at discharge and 6 month follow-up

SITE REPORTED DEVICE OR PROCEDURE RELATED SERIOUS ADVERSE EVENTS		
AE TERM	**SYSTEM ORGAN CLASS**	**PREFERRED TERM**
Left Middle Cerebral Artery Territory Ischaemia	Nervous System Disorders	Cerebral Ischaemia
Limb Ataxia on the Right Side and Unsteadiness in Walking: Small Cerebellar Infarction	Nervous System Disorders	Cerebellar Infarction
Transitory Ischaemic Attack: Dizziness, Disartria and Blurry Vision	Nervous System Disorders	Transient Ischaemic Attack
Transient Ischaemic Non Stroke	Nervous System Disorders	Transient Ischaemic Attack
Haemorrhagic Stroke	Nervous System Disorders	Haemorrhagic Stroke
Target Aneurism Post-Treatment Rupture, Subarachnoidal-Ventricular Haemorrhage	Nervous System Disorders	Intraventricular Haemorrhage
Cardiac Tamponade	Cardiac Disorders	Cardiac Tamponade
Right Internal Carotid Artery Dissection (Extracranial)	Nervous System Disorders	Carotid Artery Dissection
Headache	Nervous System Disorders	Headache
Drowsiness	Nervous System Disorders	Somnolence
Aneurysm Recanalisation	Surgical and Medical Procedures	Aneurysm Repair
Weak Arterial Pulse in Right Foot	Investigations	Pedal Pulse Abnormal
Skin Rash due to Iodinated Contrast Allergy	Immune System Disorders	Contrast Media Allergy
Aneurysm Non-Occlusion (Raymond-Roy Class 3)	Nervous System Disorders	Intracranial Aneurysm
Headache	Nervous System Disorders	Headache

required to perform an extensive amount of work which will be presented in 2020. The next step will be to provide the full analysis once the results are available for the 12-month follow-up. Additionally, there will be an independent analysis of clinical complications by the CEC and imaging will be performed by an independent core lab.

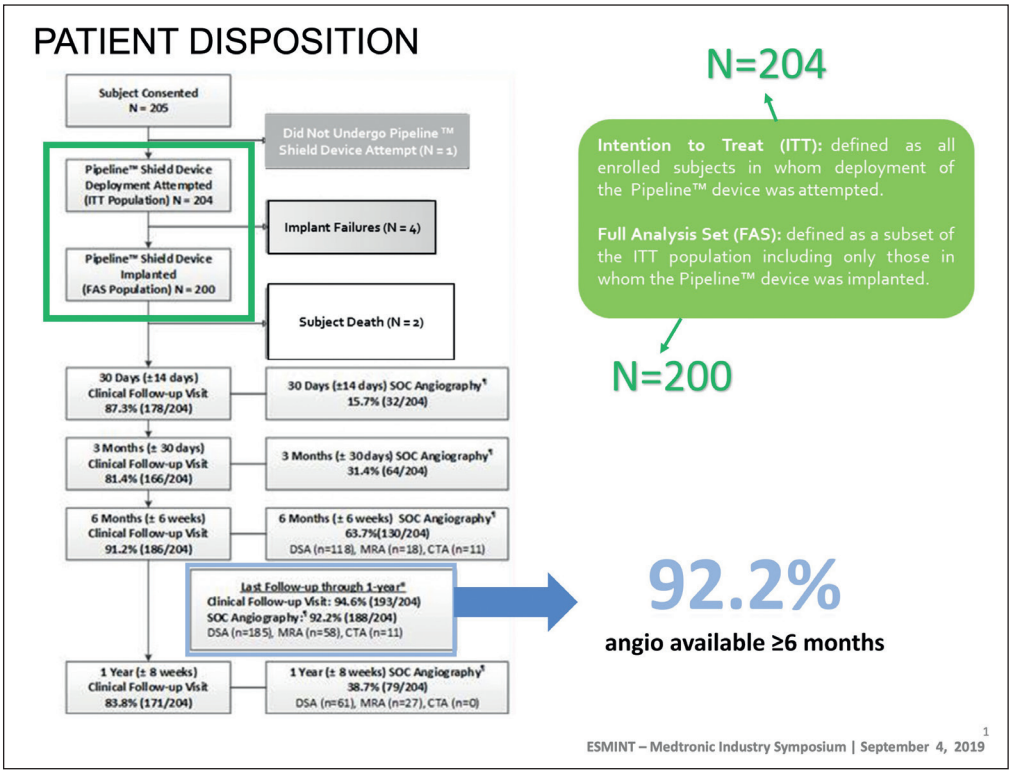
Pipeline™ Flex With Shield Technology™ Embolisation: An International Multicentre Observational Post-Market Study of Treated Intra-Cranial Aneurysms

The study protocol was a prospective, single-arm, multi-centre, post-market observational trial which looked at the real-world experience with the Pipeline™ Flex Device with Shield Technology™, and preliminary results were presented by Prof Hal Rice. A total of 205 subjects were enrolled in 21 centres throughout Europe, Israel and Australia. Exclusion criteria were relatively standard and included major surgery within the last 30 days, target aneurism in the basilar artery (there were 13 vertebrobasilar cases in the cohort) and any previous stent within the parent artery. Subjects were selected and included if it was decided that endovascular treatment with a flow diverting stent was the most appropriate treatment; the parent artery vessel had to be between 1.5 mm and 5.0 mm. Of the 205 patients who consented, one patient opted out of having the procedure performed. Of the remaining Intention to Treat (ITT) cohort (N = 204), there were four implant failures bringing a final Full Analysis Set (FAS) population of 200 patients (Figure 2). There were two deaths in the cohort (1%). A robust follow-up reflected the real-world experience – there was no prescriptive follow-up but, more precisely, there was an analysis of what is being done in many centres around the world. The analysis revealed that 92.2% of patients had angiography performed after 6-12 months post-implantation of the device.

Of the ITT cohort (N = 204), cigarette smoking (48%) and hypertension (43.6%) were two of the key risk factors reported. Several patients had multiple aneurisms (1–7), the cohort was mostly female (166/204, 81.4%), and the mean age was 54.8 ± 12.8 years with a broad age range of between 19 – 94 years. The rupture status of patients in the cohort is reported as: Never Ruptured (166/204, 81%), Previously Ruptured (34/204, 16.7%), and Acutely Ruptured within 30 days of the procedure, (3/204, 1.5%, Hunt & Hess (H&H) score <4). Approximately half of the 80 (39.2%) symptomatic patients had a previous rupture or acutely ruptured aneurysm, and the remainder reported localised headache. Previously treated aneurysms were coil embolisation (44/47), previous surgical clipping (2/47), and other (1/47). For the acutely ruptured within 30 days of procedure category (N = 3), 2 patients had an H&H score of 1, and one patient had a score of 2.

Prof Rice went on to describe the distribution of the aneurysms; most were located in the artery circulation (13 patients in the V4 segment of the distal vertebral artery), with 76% in the carotid from

Figure 2. Study Design for Post-Market Surveillance of Treated Intracranial Aneurysms With Pipeline Flex™ With Shield Technology™.



* Screen failure is defined as subject signs the informed consent or data releases form (DRF) but fails to meet study inclusion/exclusion criteria, or an attempt to implant the PFLEX with Shield technology is not performed.

** Implant failure are enrolled subjects who underwent the study procedure and in whom an attempt to implant the device was made but was unsuccessful.

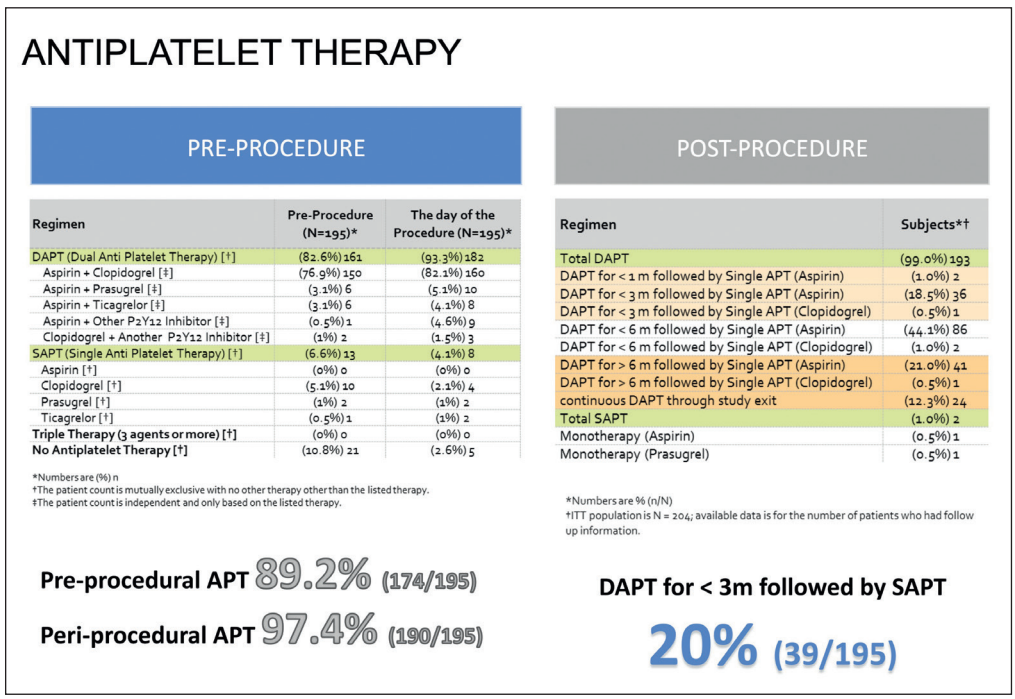
segments 1 – 7, the majority of which were in C5, C6 and C7 paraophthalmic, paraclinoid, and supraclinoid segments. Interestingly, there are 16 cases in the middle cerebral artery of which 13 had middle cerebral artery bifurcation; anterior cerebral artery (8/204) with anterior communicating aneurysms (A2 segment, 5/204; A1 segment, 3/204).

The size of target aneurysms was between 1.3 – 36.3 mm and for half of the cohort these were small at <7 mm. Medium sized aneurysms were between 7 and 13 mm and occurred in 34% of patients (69/204). There were large aneurysms in 14% (28/204) and a total of 5 giant aneurysms were reported in 2.5% of patients (5/204). Morphology showed the aneurysms were mainly saccular (94%) with 4–5% fusiform, and there were two cases of pseudo-aneurysms (1%). Multiple aneurysms were present in 25% of patients (51/204) and half of those had additional aneurysms in the adjacent parent artery (12.3%, 25/204).

Regarding the number of devices used, 88% (177/204) had a single Pipeline Shield Device, two devices were used by 9% of patients (18/204) and 3% (5/204) used 3 or more. The average Index Procedure time was 100 minutes and cumulative fluoroscopy time was 36 minutes. Adjunctive devices were used in approximately 30% of cases: coils (20%), balloons (14%) and other devices (1%). Again, reflecting real-world experience at the centres, antiplatelet therapy was also evaluated. Pre-procedural antiplatelet therapy was received by 89% of the cohort (174/195), peri-procedural (97%, 190/195), and post-procedure the average time for most patients was 6 months of DAPT. Interestingly, 20% of the cohort had <3 months of this treatment (Figure 3).

The primary effectiveness endpoint was 100% complete aneurysm occlusion without significant parent artery stenosis (>50% to be called significant) or retreatment of the target aneurysm. A total of 71.7% of patients failed to achieve the primary effectiveness endpoint: residual neck in 9 patients, residual aneurysm in 38 patients, stenosis >50% was asymptomatic in 2 patients, and target aneurysm retreatment in 4 patients, giving a total of 27.5% or 52 patients. A closer look at the parent artery stenosis endpoint results revealed 98.9% of patients had no significant parent artery stenosis, and 2 patients at the 12-month follow-up had significant stenosis, albeit asymptomatic. Data for aneurysm occlusion show that with monitoring there is a fairly standard trend. At 6 months there is 71% complete occlusion increasing at 12 months to 77%, which is characteristic. Rates of residual aneurysm at 6 months (23.8%) decreased significantly to 17.7% after 12 months and this decrease is also seen in the data for residual neck, a fairly common trend over the last 10 years seen in multiple publications with the Pipeline device.

Figure 3. Post-Surveillance Study Preliminary Results of Pre- and Post-Procedure Anti-platelet Therapy Cohort (N = 195) Treated With Pipeline Flex™ With Shield Technology™.



Regarding the primary safety outcome, the multiple imputation method was used. The core concept of multiple imputation is that subjects with no imaging are assigned a modeled probability of meeting the endpoint based on baseline characteristics; they are neither ignored nor counted as failures but incorporated as a probabilistic outcome (even in the absence

of outcome data as yet). Major stroke in the territory supplied by the treated artery or neurological death through the 12-month post-procedure was 3.23%. A closer look reveals that 5/153 were in the internal carotid artery (ICA) with one in the C5 segment and the vast majority in the C6 segment. In the non-ICA territory, out of 16 patients having major stroke there was a single instance in the middle cerebral artery.

CEC adjudicated serious adverse events (SAEs) show that general site complications were fairly standard at 3 – 3.5% with groin or haemorrhage/haematoma and pseudoaneurysm. However, focusing on neurologic SAEs there were 2 deaths and stroke in 13 patients, of which half of those were major stoke. There were 9 reports of intracranial haemorrhage (ICH) and it is noted that all major neurologic events occurred within the first 30 days; no events occurred after 30 days post-treatment. Further examination of the 13 stroke patients in the cohort reveals that 6 were major stroke (2.9%), 7 were minor stroke (3.4%), and 10 were ischaemic events (4.9%). For ICH, 6/9 were intraparenchymal (2.9%), 3/9 were sub-arachnoid (1.5%), and there was target aneurysm rupture in 2 patients (1%).

Summary

Of 204 patients enrolled in the study, there were 4 device failures leaving 200 successful implantations of the Pipeline Shield device. A total of 76% of target aneurysms were located in the ICA and a reasonable number in the anterior communicating artery and middle cerebral artery bifurcation. Most aneurysms were small at <7 mm within a wide range of 1.3 – 36 mm. The primary effectiveness endpoint was met in 71.7% of patients with complete aneurysm occlusion and there was no significant intimal hyperplasia or incident stenosis of >50%, and no retreatment. Complete occlusion was reported in 75% of patients and no significant stenosis in 98.9%. The primary safety endpoint was 3.23% in 6 patients with major stroke in 2.9% and neurologic death in 2% of patients, respectively. Therefore, this study supports the safety and efficacy of the Pipeline Shield device and concurs that the device is effective in targeting aneurysm occlusion in a safe and efficacious manner with the safety endpoints, and primary effective endpoints described.

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