Original research

Coating (Coating to Optimize Aneurysm Treatment in the New Flow Diverter Generation) study: The first randomized controlled trial evaluating a coated flow diverter (p64 MW HPC): study design

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ABSTRACT

Background Due to its high efficacy, flow diversion is increasingly used in the management of unruptured and recanalized aneurysms. Because of the need for perioperative dual antiplatelet treatment (DAPT), flow diversion is not indicated for the treatment of ruptured aneurysms. To overcome this major limitation, surface modification—'coating'—of flow diverters has been developed to reduce platelet aggregation on the implanted device, reduce thromboembolic complications, and facilitate the use of coated flow diverter treatment in patients with single antiplatelet treatment (SAPT). COATING (Coating to Optimize Aneurysm Treatment in the New Flow Diverter Generation) is a prospective, randomized, multicenter trial that aims to determine whether the use of the coated flow diverter p64 MW HPC under SAPT is non-inferior (or even superior) to the use of the bare flow diverter p64 MW under DAPT in relation to thromboembolic and hemorrhagic complications.

Methods Patients with unruptured or recanalized aneurysms for which endovascular treatment with a flow diverter is indicated will be enrolled and randomly assigned on a 1:1 ratio to one of two treatment groups: p64 MW HPC with SAPT or p64 MW with DAPT.

Results The primary endpoint is the number of diffusion-weighted imaging lesions visualized via MRI assessed within 48 hours (±24 hours) of the index procedure. Secondary primary endpoints are comparing safety and efficacy in both arms.

Conclusions This randomized controlled trial is the first to directly compare safety and efficacy of coated flow diverters under SAPT with bare flow diverters under DAPT.

Trial registration number http://clinicaltrials.gov/ - NCT04870047.

CLINICAL RATIONALE

Flow diversion was introduced for endovascular treatment (EVT) of intracranial aneurysms more than 10 years ago.1 Initial indications were limited to unruptured, large, and giant aneurysms located at the level of the internal carotid artery (ICA) as well as recanalized aneurysms in the same location.1–4

Initial evaluation of flow diversion showed a relatively high rate of complications compared with standard coiling. For instance, in the Pipeline for Uncoilable or Failed Aneurysms Study (PUFS), 5.6% of patients treated with a Pipeline (Medtronic, Minneapolis, Minnesota, USA) presented with major ipsilateral stroke or neurological death.5 In the cumulative population of three Pipeline studies (PUFS, Aneurysm Study of Pipeline in an Observational Registry (ASPIRe), and International Retrospective Study of the Pipeline Embolization Device (IntrePED)), the rates of neurological morbidity and mortality were 5.7% and 3.3%, respectively.6 The progressive development of new-generation flow diverters and the improvement of physician skills have been associated with continual safety improvement. In the SAFE (Safety and Efficacy Analysis of FRED Embolic Device in Aneurysm Treatment) study evaluating FRED and FRED Jr flow diverters, 6-month morbidity and mortality were 2.0% and 1.0%, respectively.6 In Diversion-p64 evaluating the p64 flow diverter (phenox, Bochum, Germany), safety was also improved in comparison with first-generation devices with a low morbidity/mortality rate (2.42%) at 6-month follow-up.

Flow diversion is associated with great efficacy for complete aneurysm occlusion in the short-, mid-, and long-term follow-up. In PUFS, SAFE, and Diversion-p64, the rates of complete aneurysm occlusion at 1 year were 86.8%, 73.3%, and 83.7%, respectively.3–6–8 Due to this promising efficacy, treatment indications have expanded to include small aneurysms, distal aneurysms, and bifurcation aneurysms.6–8

Given the risk of thromboembolic complications (intra-stent thrombosis, distal emboli, etc), treatment with a flow diverter must include dual antiplatelet treatment (DAPT) before and after the procedure. Consequently, flow diversion treatment is typically not indicated in ruptured aneurysms as a first-line option. To overcome this limitation, surface-modified flow diverters that reduce platelet...
aggregation on the device, and thus thromboembolic complications, were invented to enable treatment with reduced antiplatelet treatment. The first device with this new surface modification, Pipeline with Shield technology (Medtronic, Dublin, Ireland), was introduced a few years ago. Shield technology is a surface modification in which a synthetic phosphorylcholine polymer is covalently bonded to the device. Unfortunately, the efficacy of this coating for reducing antiplatelet medication was not properly evaluated. Additionally, in a single-arm study (Pipeline Flex with Shield Technology Embolization – An International MultiCenter Observational Post-Market Study (SHIELD)), the majority of patients were treated with DAPT pre- and postprocedure, thus making it impossible to know whether the coating permits reduction of preoperative and postoperative antiplatelet treatment (APT).

The p64 flow diverter has been evaluated in the largest clinical study dedicated to this kind of EVT (Diversion-p64). Diversion-p64 included 420 patients, showed a very low morbidity/mortality rate at the 6-month follow-up (2.42%), and a high rate of complete aneurysm occlusion at 12 months (83.7%). Recently, a new version of the p64 (p64 MW HPC) was introduced into clinical practice that has a surface modification (hydrophilic polymer coating (HPC)) made from a glycalyx-like glycan-based polymer covalently bonded to the surface of the p64flow diverter. In vitro experiments and animal studies have shown that HPC reduces platelet aggregation on the p64 flow diverter. The p64 MW HPC has also been evaluated in retrospective studies under DAPT and shows low procedural complication rates. The HPC surface modification aims to reduce platelet aggregation on the flow diverter, reduce thromboembolic complications, and minimize APT pre- and postprocedure. To properly evaluate the efficacy of HPC coating placed on the p64 flow diverter, COATING (Coating to Optimize Aneurysm Treatment in the New Flow Diverter Generation), a randomized controlled trial (RCT), was designed to compare the rate of thromboembolic complications in patients treated with bare p64 MW under DAPT and patients treated with coated p64 MW HPC under single antiplatelet treatment (SAPT). As this study is the first comparative evaluation of the HPC coating, the decision was made to use prasugrel or ticagrelor in the SAPT arm rather than aspirin, which is a less potent APT. Additionally, a preliminary short report has shown that implantation of an HPC-coated flow diverter (p48 MW HPC) under aspirin as SAPT can be associated with intra-stent thrombosis. Finally, clopidogrel was not accepted as SAPT in COATING because this medication is associated with a high rate of resistance.

As demonstrated by numerous studies, most thromboembolic complications occurring during EVT of intracranial aneurysms are asymptomatic. A definitive evaluation of thromboembolic events can be obtained by performing an MRI with diffusion weighted imaging (DWI) postoperatively, which is an MRI sequence with high sensitivity for detecting cerebral ischemic lesions. A meta-analysis showed that the overall incidence of DWI positive for thromboembolic events following EVT of intracranial aneurysms was 49%. Treatment with a flow diverter resulted in a higher rate of DWI positive for lesions (67%) than coiling alone (45%). To avoid heterogeneous reporting of thromboembolic events from one center to another, the COATING primary endpoint is based on the number of DWI lesions identified in participants in both arms of the RCT, which will be uniformly assessed by an independent core laboratory.

Investigational device: p64 MW HPC

The p64 MW (HPC) stands for both device versions: p64 MW (bare) and p64 MW HPC (coated). The p64 MW (HPC) flow modulation devices are low-porosity, self-expanding stents, which were developed as endovascular implants for the reconstruction of extra- and intracranial vessels by means of selective blood flow modulation. Typical indications for the use of the p64 MW (HPC) are saccular and fusiform aneurysms and other cranio-cervical vascular diseases. The p64 MW (HPC) devices are delivered in the cranio-cervical vasculature through a microcatheter with an inner diameter of 0.021 inches. The devices self-expand after leaving the microcatheter. Up to a certain point, prior to release in the target vessel, the device can be either completely moved back into the microcatheter to correct positioning or removed. The point of maximum implant deployment, which still allows retraction, is indicated by a platinum marker at the distal end of the transport tube. To avoid entry of the delivery wire tip in distal small sensitive vessels and to give more support during flow diverter deployment, the delivery wire can be moved (moveable wire=MW) proximally and distally, independently of the device itself.

Owing to the 64 platinum-filled nitinol wires used within p64 MW (HPC), the entire implant is visible under X-ray as opposed to only individual markers. When applied on the p64 MW HPC device surface, HPC reduces the thrombogenicity of the bare p64 MW version as confirmed by in vitro tests and animal studies.

Objectives and hypotheses

This study aims to assess the safety and efficacy of the coated p64 MW HPC flow modulation device under SAPT compared with the p64 MW flow modulation device under DAPT.

Objectives

The primary objective is to evaluate the safety of the p64 MW HPC flow modulation device under SAPT 48 hours after the index procedure.

Secondary objectives include evaluating the safety and the efficacy of the p64 MW HPC flow modulation device under SAPT for 365 days postprocedure.

Hypotheses

The primary hypothesis will test whether the p64 MW HPC flow modulation device under SAPT is non-inferior to the p64 MW flow modulation device under DAPT when treating aneurysms with regard to the number of DWI lesions, visualized 48 hours after the index procedures. If non-inferiority is established, a test for superiority (secondary hypothesis) of the test arm to the control arm will be performed (adaptive design).

Clinical investigation design

COATING is a prospective, multicenter RCT with two arms consisting of the p64 MW HPC flow diverter under SAPT (test arm) compared with the p64 MW under DAPT (control arm).

Endpoints

- **Primary endpoint:** The primary endpoint will be the number of DWI lesions within 48 hours (±24 hours) of the index procedure as visualized on 3T-MRI.
- **Secondary safety endpoints:** The secondary safety endpoints are of equal clinical importance and are as follows:
  - Morbidity/mortality rate at 30 days.
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- Rate of neurological death or major stroke (ischemic or hemorrhagic, defined as an increase of 4 or more points according to the National Institutes of Health Stroke Scale score) in the territory supplied by the treated artery (180 days and 365 days postprocedure).
- Rate of subjects who experience a decline in the modified Rankin Scale (mRS) score of 3 points or more (mRS score ≥3), or an increase of 2 points from baseline mRS score (180 days and 365 days postprocedure).
- Rate of subjects with more than six DWI lesions or territorial stroke (48 hours postprocedure).\(^{18}\)
- Rate of an intracranial hemorrhage from delayed aneurysm rupture (from the day after the index procedure) (180 days and 365 days postprocedure).
- Rate of delayed intracranial hemorrhage unrelated to aneurysm rupture (180 days and 365 days postprocedure).

**Secondary efficacy endpoints:** The secondary efficacy endpoints are of equal clinical importance and are as follows:

- Rate of device deployment at the target site without technical complications (day 0).
- Rate of complete aneurysm occlusion using the 3-grade scale (180 days and 365 days postprocedure).
- Rate of target aneurysm recurrence (180 days and 365 days postprocedure).
- Rate of target aneurysm re-treatment (180 days and 365 days postprocedure).
- Rate of intra-stent stenosis and/or thrombosis at the target site (180 days and 365 days postprocedure).
- Mean length of hospital stay (from hospital admission and up to hospital discharge).

**Methods**

Data will be recorded in an electronic case report form. Subjects’ image material will be pseudonymized and uploaded by the study sites via a secure, web-based system. An independent and blinded core laboratory (online supplemental annex 1) will evaluate the image material for relevant study endpoints.

All serious adverse events and adverse events of special interest will be assessed and reported by the study center and will be adjudicated by the Clinical Event Committee (online supplemental annex 1). An adverse event of special interest (serious or non-serious) is a noteworthy scientific concern for which a rapid communication by the investigator to the sponsor is required. In COATING, special attention will be paid to the following events: transient ischemic attack; stroke; thromboembolic events; side branch occlusion; hemorrhagic events; intra-stent stenosis; and peripheral events (including groin hematoma requiring surgical treatment or EVT and/or APT modification, bleeding from the gastrointestinal tract, or other peripheral bleeding requiring APT modification).

**Subjects**

**Inclusion criteria:**

- Subject is at least 18 years of age.
- Subject has a saccular, unruptured, or recanalized intracranial aneurysm. The subject may also have a previous ruptured aneurysm, provided rupture of this aneurysm occurred more than 30 days from the index procedure.
- Subject will be treated for only one target aneurysm during the index procedure except for segmental disease (multiple aneurysms located on the same arterial segment, which will be treated with one investigational device or investigational telescopic devices).
- Subject has already been selected for flow diversion therapy as the appropriate treatment.
- Subject has a mRS score ≤2 preprocedure, as determined by a certified assessor independently of the index procedure.
- Subject provides written informed consent verifying the use of his/her data (according to data protection laws).

**Exclusion criteria:**

- Subject who is currently prescribed any long-term antiplatelet and/or anticoagulation medication.
- Subject has undergone a surgery including endovascular procedures in the past 30 days prior to the study procedure.
- Subject has had an intracranial hemorrhage in the past 30 days prior to the study procedure.
- Subject with target aneurysm previously treated with a stent or flow diverter.
- Subject is expected to be treated for another aneurysm during the 30 days following the index procedure.
- Subject with a confirmed stenosis in parent artery.
- Subject with a blister-like aneurysm, fusiform aneurysm, dissecting aneurysm, or aneurysm associated with a brain arteriovenous malformation.
- Subject has a preprocedure mRS score >2.
- Any known contraindication to treatment with the p64 MW flow modulation device and the p64 MW HPC flow modulation device, in accordance with device instructions for use.
- Subject who has undergone ipsilateral carotid artery stenting within 3 months of the index procedure.
- Known serious sensitivity to radiographic contrast agents.
- Known sensitivity to nickel, titanium metals, or their alloys.
- Subject is already enrolled in other clinical trials (including the COATING study) that would interfere with study endpoints.
- Known renal impairment as defined by a serum creatinine >2.5 mg/dL (or 220 μmol/L) or glomerular filtration rate <30.
- Subject has a contraindication to MRI or angiography for any reason.
- Subject with a comorbid disease or condition that would confound the neurological and functional evaluations or compromise survival or ability to complete follow-up assessments.
- Subject with any known allergy to heparin, aspirin, or other antiplatelet medications.
- Pregnant woman or breast-feeding.
- Adults who lack the capacity to provide informed consent, and all those people deprived of their liberty in prisons or other places of detention.

**Randomization**

Once informed consent has been signed and confirmation received that the subject meets all eligibility criteria, the treatment team will obtain a randomization assignment using a web-based randomization system. Randomization (1:1 ratio) is stratified by anatomical location. The strata variables are proximal and distal for aneurysm location.

The following locations are considered proximal:

- Internal carotid artery (ICA) extradural.
- Internal carotid artery intradural (including ICA tip).
- Vertebrabasilar artery (including basilar artery tip).

Distal locations are:

- Subject will be treated for only one target aneurysm during the index procedure except for segmental disease (multiple aneurysms located on the same arterial segment, which will be treated with one investigational device or investigational telescopic devices).
- Subject has already been selected for flow diversion therapy as the appropriate treatment.
- Subject has a mRS score ≤2 preprocedure, as determined by a certified assessor independently of the index procedure.
- Subject provides written informed consent verifying the use of his/her data (according to data protection laws).

**Exclusion criteria:**

- Subject who is currently prescribed any long-term antiplatelet and/or anticoagulation medication.
- Subject has undergone a surgery including endovascular procedures in the past 30 days prior to the study procedure.
- Subject has had an intracranial hemorrhage in the past 30 days prior to the study procedure.
- Subject with target aneurysm previously treated with a stent or flow diverter.
- Subject is expected to be treated for another aneurysm during the 30 days following the index procedure.
- Subject with a confirmed stenosis in parent artery.
- Subject with a blister-like aneurysm, fusiform aneurysm, dissecting aneurysm, or aneurysm associated with a brain arteriovenous malformation.
- Subject has a preprocedure mRS score >2.
- Any known contraindication to treatment with the p64 MW flow modulation device and the p64 MW HPC flow modulation device, in accordance with device instructions for use.
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- Subject with any known allergy to heparin, aspirin, or other antiplatelet medications.
- Pregnant woman or breast-feeding.
- Adults who lack the capacity to provide informed consent, and all those people deprived of their liberty in prisons or other places of detention.
Anterior communicating artery/anterior cerebral artery.
- Pericallosal artery.
- Middle cerebral artery.
- Posterior inferior cerebellar artery.
- Posterior cerebral artery.

Medications: antiplatelet regimen
Each enrolled subject must follow either a prasugrel or ticagrelor regimen. As clopidogrel is associated with a high rate of resistance, it is probably not the ideal drug and is not part of the protocol. The choice of medication is based on standard of care at each study site. Antiplatelet responder tests are mandatory prior to the procedure.

In the SAPT arm (p64 MW HPC device), the patient will receive prasugrel or ticagrelor one to several days preprocedure, on the day of the procedure, and for 6 months postprocedure. The dose for ticagrelor is 2 × 90 mg/day. The dose for prasugrel is at least 1 × 5 mg/day if APT starts several days preprocedure. Alternatively, a loading dose of a maximum of 60 mg can be used preoperatively if necessary. After 6 months, ticagrelor or prasugrel will be stopped and replaced by aspirin for at least 6 months, with a minimum dose of 100 mg/day.

In the DAPT group, aspirin (minimum 1 × 100 mg/day) is added to prasugrel or ticagrelor a few days preprocedure, on the day of the procedure, and for 6 months postprocedure. After 6 months of DAPT, prasugrel or ticagrelor will be discontinued.

Procedure
The study procedure is performed under general anesthesia according to standard local practices. Access to the cerebral circulation is obtained via standard access techniques (including radial access).

The use of coils, stents, or intrasaccular flow disrupters is permitted as adjunctive devices. Other flow diverters are not permitted.

Imaging
The primary safety endpoint is evaluated with 3T-MRI performed 48 hours (±24 hours) postprocedure. At least four sequences should be acquired:
- DWI sequence with ≤5 mm slice thickness.
- Fluid-attenuated inversion recovery sequence (in axial plane), in addition to any other sequences according to local preference, with a slice thickness of ≤5 mm and ≥256 × 256 matrix.
- T2* (gradient echo) sequence with ≤5 mm slice thickness and ≥256 × 256 matrix.

SAMPLE SIZE: NUMBER OF SUBJECTS AND SITES
The study’s primary endpoint will be the number of DWI lesions within 48 hours (±24 hours) of the index procedure as visualized on 3T-MRI. Assuming a normal distribution, the intra-subject lesion numbers will be compared between the two randomized treatment arms (randomization allocation ratio is 1:1) using a one-sided Mann-Whitney test.

There is limited peer-reviewed information available for mean number and SD of ischemic lesions expected in both treatment arms; therefore, selection of non-inferiority margins is based on a combination of statistical reasoning as a proportion of the expected SD and clinical judgment of what is considered an unimportant difference. The prespecified non-inferiority margin is three lesions based on the expected SD of approximately six lesions; the non-inferiority margin represents ~50 of a SD. With a type 1 error rate of 5% and a type 2 error rate of 10%, an observed difference of 0 and a SD of 6.0 lesions, 74 subjects per arm would be required to reject the null hypothesis in favor of the alternative and demonstrate non-inferiority. If the difference in the average number of lesions remained 0 (test minus control), with a type 1 error rate of 5% and a type 2 error rate of 15%, and the SD was actually 7.0 lesions, 83 subjects per arm would be required to reject the null hypothesis in favor of the alternative and demonstrate non-inferiority.

Given the short time frame of primary outcome assessment (48 hours ±24 hours) no dropout rate is included in this sample size estimation, but consideration for MRI scans not being performed or non-interpretable has been taken into account. Based on clinical expertise, we expect that we will not be able to assess the primary endpoint for two subjects per arm. To account for missing/non-interpretable MRI scans, the sample size will be increased to 83 subjects per arm for a total of 170 subjects.

An interim assessment will be performed after 50% of the target population has been enrolled with the purpose of ensuring that if the results are promising, the study will not be underpowered. The interim assessment will be performed by an independent Data Monitoring Committee to examine the incidence of DWI lesions between the test and the control group. This interim assessment could mean that the target enrollment is increased to a maximum of 200 subjects.

Please refer to online supplemental annex 2 for the site list.

ETHICS
The COATING study will be submitted to ethics committees (national or local depending on each country regulations) in each participating country.

CONCLUSIONS
Flow diversion is the most efficacious endovascular technique for the treatment of intracranial aneurysms with a high rate of complete aneurysm occlusion at mid- and long-term, and a very low rate of aneurysm recanalization. However, owing to the need for pre- and postoperative DAPT, its use is restricted to unruptured and recanalized aneurysms. The development of flow diverters with a coating that reduces platelet aggregation on the device and potentially reduces thromboembolic events may allow clinicians to reduce the APT to SAPT.

p64 MW HPC is not the first coated flow diverter; however, it will be the first to be properly evaluated in a comparative study (COATING). In the coated flow diverter arm, APT is reduced to SAPT to compare this association with current clinical practice (bare flow diverter + DAPT). If COATING is positive (non-inferiority or better superiority), it will support the use of p64 MW HPC with SAPT and potentially enlarge indications for flow diversion.

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Contributors All authors have: provided a substantial contribution to the conception and design of the studies and/or the acquisition and/or the analysis of the data and/or the interpretation of the data; drafted the work or revised it for significant intellectual content; approved the final version of the manuscript; and agreed to be accountable for all aspects of the work, including its accuracy and integrity. LP is the guarantor of this work.

Funding phenox GmbH funded the COATING trial.

Competing interests LP consults for Balt, MicroVention, Perflow, phenox, Vesalio. XB receives payment from MicroVention and Stryker for presentations and educational events. VC consults for MicroVention and Balt and receives educational grants from Medtronic and Stryker. HH is co-founder and previous shareholder of phenox GmbH and femtos GmbH. PK consults for Medtronic, MicroVention, phenox, Stryker. JK consults for MicroVention/Sequent. LS consults for Stryker, MicroVention, Medtronic, and Balt. Other authors report no conflict of interest.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by French ethics committee (Comité de protection des personnes) Sud-Est 3. Reference number: 2021-025. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The COATING CIP is available on request to the corresponding author. NA.

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REFERENCES