Evaluating the safety and technical effectiveness of a newly developed intravascular 'flow isolator' stent for the treatment of intracranial aneurysms: study protocol for a first-in-human single-arm multiple-site clinical trial in Japan

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ABSTRACT

Introduction Wide-neck or large intracranial aneurysms are difficult to cure by conventional surgical or endovascular procedures. A flow diverter (FD) is an implantable, stent-like, fine-mesh medical device for the treatment of intracranial aneurysms. Although endovascular treatment with FDs is becoming a routine first-line option, a systematic review noted the heterogeneity and publication biases of the clinical studies for FDs. We have developed a new honeycomb microporous covered stent (NCVC-CS1) as a ‘flow isolator’ for the endovascular treatment of intracranial aneurysms.

Methods and analysis We planned the NCVC-CS1_UAN as a first-in-human study to evaluate the safety and technical effectiveness of NCVC-CS1, a newly developed honeycomb microporous covered stent, for the treatment of intracranial aneurysms that are difficult to cure by conventional surgical or endovascular procedures. The study is a multicentre, open-label, uncontrolled, exploratory, medical device, investigator-initiated clinical study. The primary safety endpoint of this study is any stroke or death related to the procedure within 180 days, while for efficacy, the endpoint is complete obliteration of the target aneurysm and patency of the target vessel (less than 50% stenosis) confirmed by angiography at 180 days after the procedure.

Ethics and dissemination Full ethics approval of institutional review boards was obtained at all participating sites. A clinical trial notification as a new medical device for the treatment of intracranial aneurysms (figure 1A–C). Endovascular treatment with FDs is becoming a routine first-line option. Although some clinical studies have reported favourable results,2 3 a systematic review noted the heterogeneity and publication biases of the clinical studies of FDs.4 Recently, a randomised trial, which was halted due to safety concerns, failed to show improvement in the expected composite primary efficacy outcome of FDs (complete or near-complete occlusion of the aneurysm combined with an independent functional outcome) compared with standard treatment, such as coil embolisation or parent artery occlusion.5 A meta-analysis of treatment outcomes of posterior circulation

Strengths and limitations of this study

► NCVC-CS1_UAN is a first-in-human study to evaluate the safety and technical effectiveness of NCVC-CS1, a newly developed honeycomb microporous covered stent, for the treatment of intracranial aneurysms that are difficult to cure by conventional surgical or endovascular procedures.

► A major strength of this study is that it evaluates a novel ‘flow isolator’ based on completely new technologies.

► The main limitations of this study are its open study design and the lack of control arms.

INTRODUCTION

Wide-neck or large intracranial aneurysms are difficult to cure by conventional surgical or endovascular procedures.1 A flow diverter (FD) is an implantable, stent-like, fine-mesh medical device for the treatment of intracranial aneurysms (figure 1A–C). Endovascular treatment with FDs is becoming a routine first-line option. Although some clinical studies have reported favourable results,2 3 a systematic review noted the heterogeneity and publication biases of the clinical studies of FDs.4 Recently, a randomised trial, which was halted due to safety concerns, failed to show improvement in the expected composite primary efficacy outcome of FDs (complete or near-complete occlusion of the aneurysm combined with an independent functional outcome) compared with standard treatment, such as coil embolisation or parent artery occlusion.5 A meta-analysis of treatment outcomes of posterior circulation...
non-saccular aneurysms by FDs reported a long-term occlusion rate of 52% and an overall mortality of 21%. Thus, a safer and more effective implantable medical device is needed.

We have developed a covered stent (NCVC-CS1) with innumerable precise micropores (pore size 80–90 µm, opening ratio 30%–40%) for the endovascular treatment of intracranial aneurysms (figure 1D–F). The NCVC-CS1, a balloon-expandable cobalt chromium stent, has some structural benefits: the stents have flat luminal surfaces with a cover film, and their struts are completely impregnated in the cover film, which is extremely thin, less than 20 µm thick. These advantages give high flexibility and robust properties to the NCVC-CS1.

The NCVC-CS1 showed excellent performance in our preclinical testing for the treatment of cerebral aneurysms with three important advantages. The first was rapid isolation of blood flow inside the aneurysms. A large portion of the aneurysm cavities disappeared immediately after stenting due to shielding of the aneurysm neck by the stents’ cover film. In addition, at the 1-month follow-up, all aneurysms had almost completely disappeared. The aneurysm cavities were packed with hard thrombus, and the luminal surface of the stents was covered with a thin tissue layer including endothelial cells.

The second advantage was rapid neointimal formation with complete endothelialisation at all stented segments, which was due to the microporous polyurethane functioning as a scaffold for vascular cell migration.

The last advantage was perfect patency of the perforating arteries after stenting. In a perforating artery rabbit model, all lumbar arteries remained patent for over 1 year, even after placement of a second, overlapping NCVC-CS1. At 2 months after stenting, the luminal surface was covered with complete thin neointimal formation. In addition, even in the prototype model of the NCVC-CS1, all branches were patent in a rabbit subclavian artery model. Therefore, it is highly likely that the NCVC-CS1 could be appropriate for the treatment of vertebral targets incorporating the posterior inferior cerebellar artery and the basilar artery.

FDs cannot fully demonstrate the three above-mentioned advantages. Therefore, the NCVC-CS1 is expected to have a stronger therapeutic effect than conventional devices. Because the NCVC-CS1 is considered a new technology going beyond FDs, it should be called a ‘flow isolator’, which may be a different genre of intravascular stent than FDs.

NCVC-CS1_UAN is designed as a first-in-human study to evaluate the safety and technical effectiveness of the NCVC-CS1 for the treatment of intracranial aneurysms that are difficult to cure by conventional surgical or endovascular procedures.

METHODS AND ANALYSIS

Study design
NCVC-CS1_UAN is a multicentre, open-label, uncontrolled, exploratory, medical device, investigator-initiated clinical study.

Study period
The planned study period has obtained ethics approval and has been approved by the Pharmaceuticals and Medical Devices Agency (PMDA), the Japanese regulatory agency, in December 2018. Since the PMDA requires long-term follow-up, the study participants will be followed up for 5 years after stent deployment according to a separate protocol.

Sample size
The planned subject number in this study is 12. The sample size was calculated based on the primary efficacy endpoint. A sample size of 10 would provide a two-sided 95% exact (Clopper-Pearson type) CI with a width equal to 44.2% (55.5% to 99.7%), assuming 90% complete obliteration of the target aneurysm and patency of the target vessel (PASS V.11; NCSS, Kaysville, UT, USA). A total of 12 patients will be recruited into the study, accounting for withdrawals from the study.
Endpoints

The primary endpoints of this study are (1) safety endpoint, any stroke or death related to the procedure within 180 days; and (2) efficacy endpoint, complete obliteration of the target aneurysm and patency of the target vessel (less than 50% stenosis) confirmed by angiography at 180 days after the procedure.

The secondary endpoints of this study are (1) technical success (stent placement in the target lesion covering the aneurysmal neck without occlusion of the target vessel), (2) any death within 180 days after the procedure, (3) any death due to neurological causes within 180 days after the procedure, (4) any adverse event or adverse device effect and (5) any neurological deficits.

Patient enrolment and study schedule

Complete inclusion and exclusion criteria are shown in box 1. Candidate patients who meet the inclusion and exclusion criteria for provisional registration are provisionally registered after they give informed consent. Registered patients receive dual antiplatelet therapy from at least 4 days before the study treatment. Within
60 days from provisional registration, patients undergo study device implantation after diagnostic cerebral angiography confirms that they meet the criteria for final registration. Because this is a first-in-human study, for the first three patients, enrolment is held after a patient is registered until the independent safety board confirms the 30-day safety for the patient. A summary of the study design is shown in figure 2. The schedule of evaluation is presented in table 1.

**Centres and investigators**

To join the trial, centres were required to apply for open recruitment by the Japanese Medical Association (JMA).

**Independent safety evaluation board**

The independent safety evaluation board is composed of three individuals not involved in study conduct who have expertise in multiple disciplines, including a neurosurgeon, a neurointerventionist and a neurologist. All serious adverse events are reported to and discussed by the independent safety board, and the 30-day safety of the first three patients is evaluated.

**Independent radiological image evaluation**

All cerebral angiography images are evaluated by an independent experienced neurointerventionist.

**Data management, monitoring and auditing**

The system for electronic data capture and data management is validated to meet the regulatory requirements. On-site monitoring, including source document verification and audit, is planned.

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**Table 1**  Schedule of evaluation of the NCVC-CS1 feasibility study

| Entry          | Treatment | 3 days | 30 days | 90 days | 180 days |
|---------------|-----------|--------|---------|---------|----------|
| Inclusion/exclusion criteria | X         |        |         |         |          |
| Signed consent form          | X         |        |         |         |          |
| Provisional enrolment        | X         |        |         |         |          |
| Medical/treatment history*   | X         |        |         |         |          |
| Neurological assessment      | X         | X      | X       | X       | X        |
| mRS score                   | X         |        | X       | X       | X        |
| Laboratory tests†           | X         |        |         |         |          |
| CTA/MRA‡                    | X         |        |         |         |          |
| Medication§                 | X         | X      | X       | X       | X        |
| Cerebral angiography¶       | X         |        |         |         | X        |
| Final enrolment             | X         |        |         |         |          |
| Endovascular procedure**    | X         |        |         |         |          |
| Adverse events              | X         | X      | X       | X       | X        |

*History of cerebrovascular diseases, neurosurgical treatments, cerebral endovascular treatments, hypertension, dyslipidemia, diabetes mellitus and so on.
†Haematology, biochemistry and coagulation.
‡Location, size, form, maximum diameter, neck diameter and parent artery diameter of the target aneurysm.
§Antiplatelets, anticoagulants and medications for complications.
¶Location, size, form, maximum diameter, neck width and parent artery diameter of the target aneurysm.
**Site of puncture, anaesthesia and medical devices used in the procedure.
CTA, CT angiography; MRA, magnetic resonance angiography; mRS, modified Rankin scale.
Statistical analysis
Analyses will be done in all patients recruited into the study as a primary analysis population. Patient demographic data and safety and efficacy endpoints will be analysed descriptively, with continuous data expressed as means with SD or medians with range (minimum and maximum), and categorical data will be expressed as numbers and percentages.

The primary safety and efficacy endpoints will be summarised as numbers and percentages with their two-sided 95% exact CI, using the Clopper-Pearson method. In addition, the Kaplan-Meier method will be used to estimate the event-free survivals of the safety and efficacy endpoints. For other endpoints, data will be summarised using appropriate statistics. All analyses will be performed according to a prespecified statistical analysis plan using SAS V.9.3 or later. The statistical analysis plan will be prepared separately and finalised before database locking.

Patient and public involvement
Patients or public were not involved in the design or conduct of the study, and no attempt was made to assess the burden of the intervention by patients themselves.

ETHICS AND DISSEMINATION
A clinical trial notification as a new medical device, much like a US Investigational Device Exemption application, was accepted by PMDA before it started. The study was registered in Clinicaltrials.gov and started in May 2016. After the first patient was enrolled on 12 October 2016, the new stents were implanted in eight patients by the end of November 2017. The study should be followed up by a pivotal study to obtain satisfactory data for an application for marketing approval. The long-term safety information will be obtained in a separate protocol, which is an observational one. The main results of this study and the long-term safety observational study will also be submitted for publication in a peer-reviewed journal.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Full ethics approval of the institutional review boards (IRBs) was obtained at all participating sites (National Cerebral and Cardiovascular Center IRB, Kyoto University Hospital IRB, Juntendo University Hospital IRB and Kobe City Medical Center General Hospital IRB).

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