Is adding Cilostazol to nimodipine improving neurological outcome of patients with Aneurysmal Subarachnoid Hemorrhage? A randomized, double blind, placebo-controlled trial

CASH

BIOMEDICAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

Version N°2.1 of 04/04/2025
Project Code : D24-P009/EU Clinical Trials number : 2024-516468-27-00

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SIGNATURE page for a biomedical research PROTOCOL

Research Research Code: D24-P009
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Title: Is adding Cilostazol to nimodipine improving neurological outcome of patients with Aneurysmal Subarachnoid Hemorrhage? A randomized, double blind, placebo-controlled trial

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The clinical trial will be conducted in compliance with the protocol, with the EU Clinical Trials Regulation No. 536/2014 and with the principles of good clinical practice.

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CONTENTS

1 SUMMARY

Full title	Is adding Cilostazol to nimodipine improving neurological outcome of patients with Aneurysmal Subarachnoid Hemorrhage? A randomized, double blind, placebo-controlled trial
Acronym	CASH
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Sponsor	Le GHU Paris Psychiatrie et Neurosciences
Scientific justification	Delayed neuronal damage following aneurysmal subarachnoid hemorrhage (SAH) is a major cause of mortality and handicap; it implies multiple factors involving delayed ischemia and vasospasm. To date, nimodipine is the only preventive drug known to improve neurological outcome of these patients and is the only pharmacological preventive treatment that is recommended by the European stroke organization. Many other drugs have been tested, with contradictory results; among them, cilostazol, a selective inhibitor of phosphodiesterase 3 (PDE 3), seems to get the more promising results on long-term handicap prevention. Its action includes an antiplatelet effect by increasing the availability of cyclic adenosine monophosphate (cAMP) via its inhibition of PDE 3 which degrades cAMP, thus increasing activity of protein kinase A (PKA) which leads to a downstream effect. In addition, an increase in NO production was observed in human aortic endothelial cells by a PKA-mediated activation of endothelial NO synthase (eNOS), leading to vasodilatation. The antithrombotic effect of cilostazol coupled with this vasodilatory action makes it a widely used treatment for arteriosclerosis obliterans, intermittent claudication, and prevention of a second ischemic stroke. Its action might go beyond this effect for preventing delayed cerebral ischemia following SAH; experimental studies show that cilostazol also attenuates cortical spreading and hydrocephalus, protects vascular endothelial cells and inhibits the proliferation of vascular smooth muscle cells. These numerous neuroprotective effects might explain its effectiveness, with a significative decrease (up to 50%) of unfavorable outcome rate, as described in several meta-analysis while other drugs or interventions focusing on vasospasm seem to fail in improving long-term functional outcome despite improving short-term radiographic results. Unfortunately, all cilostazol studies were conducted in Japan, with patients treated using fasudil, a potent Rho-kinase inhibitor, rather than nimodipine, as recommended by local guideline. Our hypothesis is that adding cilostazol to nimodipine in the acute phase of aneurysmal SAH improves long-term neurological outcome.
Primary objective and assessment criterion	Our hypothesis is that adding cilostazol to nimodipine for 14 days following aneurysmal subarachnoid hemorrhage improves neurological outcome 6-months after SAH, assessed by the modified Rankin scale.
Secondary objectives and assessment criteria	Functional status evaluated at 6 months: - MOCA score - Return to work - Activities of Daily Living

	- Instrumental Activities of Daily Living In-hospital morbi-mortality: - Length of Intensive Care Unit stay - Length of hospital stay - 28-day mortality Strong clinical and radiological predictive events of functional status: - Delayed cerebral ischemia, defined as the occurrence of focal neurological impairment or a decrease of at least 2 points on the Glasgow Coma Scale, which is not apparent immediately after aneurysm occlusion and not attributable to other causes. - Short term evolution of Angiographically defined vasospasm, defined as a reduction of calibre of proximal cerebral vessels seen on either CT-, MR- or catheter angiography - Cerebral infarcts, defined by a diagnosis of cerebral infarction performed by a CT or MR scan within 6 weeks, or on the latest CT or MRI scan made before death within 6 weeks, or at autopsy, not present on the CT or MRI scan between 24 and 48 h after early aneurysm occlusion and not
Experimental design	Multicentre, double-blinded, randomised, placebo-controlled, parallel-group superiority trial using an adaptive group-sequential design
Population involved	Adult patients admitted to an intensive care unit with subarachnoid hemorrhage caused by a ruptured cerebral aneurysm
Inclusion criteria	- Ruptured cerebral aneurysm occurring in the last 96 hours - Aneurysm successfully secured by surgical clipping or endovascular coiling - Consent of the patient or, if not possible, of a family member (emergency clause) - Registration in a national health care system
Non-inclusion criteria	- Precritical modified Rankin Scale (mRS) > 2 - Non-aneurysmal SAH - Delayed > 96h admission after first symptoms of SAH - Coma defined by GCS of 3-5 with untreatable aneurysm will be excluded” - - Known allergy to cilostazol - Pregnancy - Pre-existing major hepatic, renal, pulmonary or cardiac disease - Concomitant use of one other anti-platelet and/or anticoagulant agent - Tutelage or guardianship
Treatment being tested	Cilostazol - Phase III - Oral or enteral by gastric tube administration - Starting in the first 96 hours of occurrence of SAH - 100mg twice daily - For 14 days
Benchmark treatment	
Other procedures added by the research	Standard of care of SAH patients is not modified by the study, may vary across centres but must include: - Enteral or IV nimodipine administration - Vasospasm / DCI monitoring and treatment

	- Radiological assessment of brain damage by cerebral TDM or MRI at day 10-21 Face to face interview at 6 months by a clinical research assistant from the investigating centre or coordinating investigating centre.
Risks added by the research	**1.1 Level C**
Summary of the known and foreseeable benefits and risks for the research participants	The incidence rate of SAH is high, 10 per 100.000 among which 85% are caused by a ruptured aneurysm: neurological deterioration is frequent during the ICU stay and is mainly due to delayed cerebral ischemia. The most recent meta-analysis showed that cilostazol significantly reduced poor outcome patients with SAH, with an Odds ratio of 0.52 [0.37 – 0.74] for unfavourable outcome (16). Our trial aims to confirm that a 14 days administration of 100 mg twice a day of cilostazol will reduce by 30% long-term disability and cognitive impairment of aneurysmal SAH. If so, our trial might dramatically change the therapeutic management of aneurysmal SAH, as nimodipine did long time ago. Collective benefit is also expected, including the reduction of the length of hospital stay and need for rehabilitation. The study protocol will not interfere with other preventive or curative treatment of DCI and vasospasm, which will be kept to the discretion of the physician in charge. Major secondary effects of cilostazol are arrhythmia, abnormal bleeding, and allergy (frequency not reported). Most frequent adverse reactions are headache (up to 34%), palpitation (up to 10%), and diarrhoea (up to 19%). These side effects are however reported in patients taking cilostazol as a long-term therapy. In previous trial on DCI prevention in SAH, 14 days administration of cilostazol appeared safe since no difference in major adverse events rate was observed between cilostazol and control groups.
Practical procedure	Patients will be included within the first 96 hours after admission and randomly assigned to one of the following groups: the cilostazol group, who will receive cilostazol 100mg orally or by enteral tube two times a day for 14 days, or the control group, who will receive a placebo. This treatment should be started within the first 96 hours after hemorrhage.
Number of subjects chosen	630 patients
Research period	Inclusion: 42 months Participation: 6 months Total: 49 months
Number of inclusions expected per centre and per month	1.9 patients per centre and per month
Statistical analysis	2 interim analysis planned
Funding source	PHRC
Data Safety Monitoring Board anticipated	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

2.1 Hypothesis for the research

Delayed vasospasm of major cerebral arteries is considered the main cause of delayed cerebral ischemia (DCI) in patients with subarachnoid hemorrhage (SAH)[1]. However, reduction of angiographic vasospasm using intra-arterial vasodilatation or drugs such as clazosentan has not been shown to reduce DCI or long-term disability[2,3]. These findings have broader the conceptual view of DCI, by including to vasospasm other factors, such as microthrombosis, microvascular constriction, spreading depolarization and spreading ischemia.

Cilostazol is a selective inhibitor of phosphodiesterase 3 (PDE 3) and antiplatelet agent. Its physiological properties combine multiple mechanisms, including inhibition of both cyclic adenosine monophosphate (cAMP) and upregulation of endothelial NO synthesis.
In previous clinical studies, it has been shown to reduce DCI by increasing the release of nitric oxide levels from endothelial cells; by inhibiting the vascular smooth muscle proliferation; by suppressing the adhesion molecule expression on vascular membrane; and by inhibiting the platelet-derived growth factor production[4-6].

Our hypothesis is that the preventive administration of cilostazol improves long-term neurological outcome of patients presenting with SAH, by reducing DCI rate through these aforementionned multiple mechanisms.

2.2 Description of knowledge relating to the pathology in question

The incidence rate of subarachnoid hemorrhage (SAH) is approximately 10 per 100,000, among which 85% are caused by a ruptured aneurysm. It accounts for about 5% of all strokes. The mortality rate is 30-50% and delayed cerebral ischemia (DCI) affects about 30% of SAH survivors; the risk of DCI is correlated with the Fisher radiologic score and the World Federation of Neurosurgeons score and contributes to poor outcome, long-term disability and cognitive impairment[7] The DCI mainly occurs between the 4th and the 10th day after SAH[8,9] .

To date, only administration of nimodipine, as a preventive strategy of DCI, has been shown to improve long-term neurological outcome[10,11] . It is therefore widely used, although its efficacy is limited. Its mechanisms of action, as a calcium antagonist, include vasodilatation and antifibronolytic effect.

Data on curative treatment of vasospasm and DCI shows weak evidence and contradictory results, whether pharmacological or intra-arterial interventions. Therefore, management of these complications differs among intensive care units. However, it always includes close monitoring of clinical deterioration; when it occurs, hypertension therapy, intra-arterial dilatation and sometimes adjuvant therapy such as milrinone are used. If sedation is needed making clinical examination not reliable, monitoring of vasospasm with using transcranial Dopplers, electroencephalographic recordings and perfusion CTscans are performed, although the clinical consequences of a radiological vasospasm, when found, is often a matter of debate.

Despite advances in treatment and care protocols, the mortality and morbidity rate of SAH remains high: up to 40% patients of these adults are unable to return to work and even fewer are able to return to their previous occupations because of neurological impairment[1] Therefore, prevention of DCI remains a major priority.

2.3 Summary of relevant pre-clinical experiments and clinical trials

To date, four randomized controlled trials have assessed cilostazol in improving long-term outcome of adult patients with SAH.

In 2011, Suzuki and al. published the first prospective placebo-controlled study evaluating cilostazol in SAH patients[12] . A hundred patients were enrolled: although cilostazol did not significantly decrease the incidence of symptomatic vasospasm (37.3% in the control vs. 22.4% in the cilostazol group, p = 0.18) and cerebral infarction (27.5% in control vs. 10.2% in the cilostazol, p = 0.09). However, the modified Rankin scale at discharge was significantly improved: 2.6 in controls vs. 1.5 in the cilostazol group, p = 0.041.

Senbokuya and al. published a second randomized controlled trial in 2013[13] . In this study, data from 109 patients were analysed. Symptomatic vasospasm, angiographic vasospasm and incidence of new cerebral infarctions were significantly lower in the cilostazol group, respectively 13 vs. 40% p=0.0021, 50 vs. 77% p=0.006, and 11 vs. 29% p=0.03. Nevertheless, no statistically significant difference was found regarding mRS at 1, 3 and 6 months but the cilostazol group tended to have better outcomes defined as an mRS 0-2; at 6 months, 88.9% patients and 74.5% had a good outcome in the cilostazol and placebo groups, respectively p=0.08. The number of adverse events in both groups was similar.

Matsuda et al. in 2016 included 148 patients in a randomized placebo-controlled study[14] . Occurrence of symptomatic vasospasm was significantly less frequent in the cilostazol group: 10.8 vs. 24.3%, p = 0.031, as well as the proportion of patients with poor outcome: 5.4 vs. 17.6%, p = 0.011. Multiple logistic analyses showed that cilostazol administration was an independently associated with reduced poor outcome: OR 0.221, 95% CI 0.054–0.903, p = 0.035.

Sugimoto et al. in 2018 included 50 cases that were randomly assigned to cilostazol (n=23) and placebo (n=27) groups[15] . Among the 48 analysed patients, those from the cilostazol group tended to have a better clinical outcome than those from the control group, according to the eGOS at 6 months after SAH (74% versus 56%). This difference was however not statistically significant (odds ratio 1.437, 95% CI 0.376 to 5.483, P=0.596).

These four studies were selected in recent meta-analysis[16] , which concluded that cilostazol might be beneficial in SAH patients with an OR of 0.52 [0.37 – 0.74] for unfavourable outcome.

It must be noted that that all these studies have been conducted in Japan, have included relatively small cohorts and have administered the fasudil, a potent Rho-kinase inhibitor, instead of the nimodipine.

Our study will be therefore the first to evaluate whether cilostazol, in addition to nimodipine, decreases the rate of long-term disability in a large cohort of patients with aneurysmal SAH.

2.4 Description of the population to be studied and justification for the choice of participants

Adult patients admitted to an intensive care unit (ICU) for an aneurysmal SAH occurred within the last 96 hours.

We decided to include only aneurismal SAH because of the low incidence rate of DCI and bad outcome in non-aneurismal SAH. Moreover, we decided to include all stages and grades of SAH. Indeed, previous studies suggested that it might be beneficial for all patients regardless of their severity.

Since we hypothesised that cilostazol will improve the outcome by preventing treatment DCI, it should be started at the early phase of SAH before the risk period for DCI, which begins at day 4.

2.5 Identification and description of the experimental medication or medications

Cilostazol is a selective inhibitor of phosphodiesterase 3 (PDE 3) and antiplatelet agent. It is available in a tablet form and can be administered orally or through a gastric tube after being crushed.

2.6 Description and justification of the dosage, administration method, administration design and treatment period.

Patients will be included within the first 96 hours after SAH onset and randomly assigned to either cilostazol or placebo group. The dose of cilostazol will be 100mg twice a day for 14 days,.
The dosage of cilostazol is similar to the one tested in the four previous trial that documented benefit[12-15].

Pharmacokinetics justification

We reviewed ten human studies that have directly quantified cilostazol's pharmacokinetics under varied dosing and design protocols. In healthy volunteers—primarily Korean subjects—one study reported an AUC of 12,100 ± 4,880 ng·h/ml , while Cmax values ranged from 283.7 to 1,623.9 mg/ml over doses from 25 to 300 mg . Elimination half-life consistently approximated 11 hours , and Tmax varied between 2.4 and 4 hours ; one report estimated apparent clearance (CL/F) at 12.8 l/h.[17–26]

Genetic analyses indicate that CYP3A5 and CYP2C19 variants significantly affect clearance and half-life, whereas ABCB1 appears to have no effect, overall the variance explained by polymorphism was 7% underlining a relevant but limited effect of genetics on cilostazol pharmacokinetics. A study in subjects aged 50 and older found no significant influence of age or gender . Investigations of drug interactions reveal no notable pharmacokinetic change when cilostazol is co-administered with probucol, but co-administration with simvastatin increases simvastatin AUC by 64% and its active metabolite by 31%. The drug will be delivered in oral form if patient is able to swallow the tablet. If not, tablets will be crushed by the nurse in charge of the patient, and given by oral or enteral route through feeding tube if required. Administration of crushed tablet will be standardized at specific timing in each center. In case a patient can eat a meal, the delay between administration and meal will be of 30 minutes minimum

Based on the available data in healthy human studies, the most common cilostazol dose across studies was 100 mg, administered either as a single dose or twice daily. Several studies used this dosing regimen:

- Single 100 mg doses were used in studies by Choi and Kim[17,18]
- Multiple 100 mg twice-daily doses were used in studies[19,20]
- Some studies also investigated 50 mg doses[21,22] or a range of doses. One dose-escalation study examined doses from 25 mg to 300 mg[23] .

The most common route of administration was oral, and for multiple-dose studies, the typical regimen was twice daily (BID) dosing[19,24].

Dosage in SAH

More specifically on subarachnoid hemorrhage, the dose of **100 mg twice daily for 14 days** was chosen based on **previous clinical trials** evaluating cilostazol in subarachnoid hemorrhage (SAH) patients. Specifically:

- Previous randomized controlled trials (RCTs) in Japan, such as those by **Suzuki et al. (2011), Senbokuya et al. (2013), Matsuda et al. (2016), and Sugimoto et al.**

(2018), have used this dosage with **documented efficacy in reducing delayed cerebral ischemia (DCI)** and **improving neurological outcomes**.

- Pharmacokinetically, cilostazol is a **phosphodiesterase 3 inhibitor** that **increases cyclic AMP (cAMP), leading to vasodilation and antiplatelet effects**. These mechanisms contribute to its potential protective role in preventing secondary ischemia after SAH.
- Preclinical studies have shown that cilostazol inhibits **vascular smooth muscle proliferation**, **enhances nitric oxide (NO) synthesis**, and **reduces microthrombosis**, mechanisms that are relevant in SAH pathophysiology.

Thus, the 100 mg BID dose was selected to match the dosage in prior successful studies while ensuring a **favorable safety profile, for which adverse events are depicted in the section 10**.

2.7 Summary of the known and foreseeable benefits and risks for the research participants

The incidence rate of SAH is high, 10 per 100.000 among which 85% are caused by a ruptured aneurysm: neurological deterioration is frequent during the ICU stay and is mainly due to delayed cerebral ischemia. The most recent meta-analysis showed that cilostazol significantly reduced poor outcome patients with SAH, with an Odds ratio of 0.52 [0.37 – 0.74] for unfavourable outcome[16]. Our trial aims to confirm that a 14 days administration of 100 mg twice a day of cilostazol will reduce by 30% long-term disability and cognitive impairment of aneurysmal SAH. If so, our trial might dramatically change the therapeutic management of aneurysmal SAH, as nimodipine did long time ago. Collective benefit is also expected, including the reduction of the length of hospital stay and need for rehabilitation.

The study protocol will not interfere with other preventive or curative treatment of DCI and vasospasm, which will be kept to the discretion of the physician in charge.

Major secondary effects of cilostazol are arrhythmia, abnormal bleeding, and allergy (frequency not reported). Most frequent adverse reactions are headache (up to 34%), palpitation (up to 10%), and diarrhoea (up to 19%). These side effects are however reported in patients taking cilostazol as a long-term therapy. In previous trial on DCI prevention in SAH, 14 days administration of cilostazol appeared safe since no difference in major adverse events rate was observed between cilostazol and control groups.

3 OBJECTIVES

3.1 Primary objective

Our main objective is to show that 100mg twice a day of cilostazol over 14 days improves the modified Rankin scale at 6-months in aneurysmal SAH treated with nimodipine, against placebo (Appendix 1)

3.2 Secondary objectives

<u>Secondary objectives are the functional status assessed at 6 months:</u>

-SubArachnoid Hemorrhage Outcome Tool (SAHOT) Score (Appendix 2)
-MOCA score (Appendix 3)
-Return to work
-Activities of Daily Living (Appendix 4)
-Instrumental Activities of Daily Living (Appendix 5)

And In-hospital morbi-mortality:

-Length of ICU stay
-Length of hospital stay
-28-day mortality

We will also assess the effects of cilostazol on the occurrence of:

-Delayed cerebral ischemia, defined as the occurrence of focal neurological impairment or a decrease of at least 2 points on the Glasgow Coma Scale, which does not occur immediately after aneurysm occlusion and which is not ascribable to other causes.

-Cerebral artery vasospasm, defined as a reduction of the diameter of the proximal cerebral vessels seen on either CT-, MR- or catheter angiography

-Cerebral infarcts, detected on the CT scan or MRI performed with 6 weeks, (or on the latest CT scan or MRI performed before death within 6 weeks, or at autopsy), but not present on the earlier CT or MRI scan performed between 24 and 48 h after early aneurysm occlusion and not ascribable to other causes

4 WE WILL ALSO MONITOR THE OCCURRENCE OF CILOSTAZOL-RELATED ADVERSE AND SERIOUS ADVERSE EVENT.PLAN FOR THE RESEARCH

4.1 Concise description of the primary and secondary assessment criteria

4.1.1 Primary assessment criterion

Modified Rankin Scale (mRS) assessed at 6 months in a structured face-to-face interview. Favorable outcome is defined by an mRS score 0 to 2, and unfavorable outcome by a mRS from 3 to 6. (Appendix 1)

The Modified Rankin scale allows to score the functional state. It is the most widely used outcome in patients with SAH[17]. It can be passed in a face-to-face interview by physicians, physical therapists, a research assistant or research nurses. Its overall agreement is 81% (κ=0.74, κw=0.91) when structured interview is used and displays an excellent repeatability.

4.1.2 Secondary assessment criteria

The main pitfall of the modified Rankin Scale is the overrating of patients that develop cognitive impairment. We thus chose to assess separately cognitive impairment with using specific scales, including the MOCA, ADL and IADL. The SAHOT (SAH-outcome tool) will be finally assessed, as it has been recently developed and validated but not yet commonly used as the mRS[18] .

1. SAHOT score (Appendix 2)
2. MOCA score at 6 months (Appendix 3)
3. Return to work at 6 months
4. Activities of Daily Living (ADL) at 6 months (Appendix 4)
5. Instrumental Activities of Daily Living (IADL) at 6 months (Appendix 5)

Other generic morbidity criterion will be used.

6. Length of Intensive Care Unit (ICU) stay
7. Length of hospital stay
8. 28-day mortality

We will also assess the occurrence of cerebral vasospasm, delayed cerebral ischemia and new cerebral infarction as they represent potential confounding factors. Of note cerebral vasospasm diagnosis will be left to the discretion of physician as the strategy to undergo arterial MR/CT scan or DSA differs widely across centres but interpretation of these exams will be requested to be standardized in all participating centres. As aforementioned, New cerebral infarcts will be considered when detected on the CT scan or MRI performed with 6 weeks, (or on the latest CT scan or MRI performed before death within 6 weeks, or at autopsy), but not present on the earlier CT or MRI scan performed between 24 and 48 h after early aneurysm occlusion and not ascribable to other causes

9. Occurrence of DCI during the ICU stay

<u>DCI will be defined as the occurrence of</u>

- Focal neurological deficit (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or
- Decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its components [eye, motor on either side, verbal]).

- for at least 1 hour,
- not apparent immediately after aneurysm occlusion, and
- cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies

10. Occurrence of cerebral vasospasm on a brain imaging on digitally substracted angiography (DSA) or Magnetic resonance/computed tomography angiogram (MR/CTA) performed upon clinical signs of delayed cerebral ischemia or severe impairment of cerebral blood velocity in transcranial doppler

<u>Cerebral Vasospasm diagnosis will be defined upon DSA or MR/CTA.</u>

On angiograms in DSA or MR/CTA, the severity of vasospasm will be considered none or mild if there is a less 33% decrease in arterial diameter on angiography, moderate if there is a 34% to 66% decrease, or severe if there is at least a 67% decrease.

DSA or MR/CTA will be performed when:

- There are signs of delayed cerebral ischemia as described above.
- There is a severe impairment of cerebral blood flow velocity assessed with help of transcranial doppler (tCD), as defined below. tCD will be performed at the discretion of the physicians in charge. tCD is a non-invasive radiation free exam that can be used at bedside. Its repetition allows a better detection of vasospasm and is routinely performed. Cerebral vasospasm severity will be evaluated according to this scale:

Degree of cerebral blood velocity alteration	Mean flow velocity (cm/s)	Lindegaard ratio
Mild	120-149	3-6
Moderate	150-199	3-6
Severe	>200	>6

11. Occurrence of new cerebral infarcts

New cerebral infarct is considered when detected on the CT scan or MRI performed with 6 weeks, (or on the latest CT scan or MRI performed before death within 6 weeks, or at autopsy), but not present on the earlier CT or MRI scan performed between 24 and 48 h after early aneurysm occlusion and not ascribable to other causes such as surgical clipping or endovascular treatment. Hypodensities on CT imaging resulting from ventricular catheter or intraparenchymal hematoma should not be considered cerebral infarctions secondary to DCI.

12. Occurrence of cilostazol-related major adverse events, including: arrythmia, abnormal bleeding and allergy.

13. Occurrence of cilostazol-related minor adverse events include: tachycardia, fever, fainting, nausea, vomiting and stomach pain.

4.2 Description of research methodology

4.2.1 Experimental plan

CASH is a multicentre, double-blinded, randomised, placebo-controlled, parallel-group superiority trial in adult, using an adaptive group-sequential design, to demonstrate that cilostazol plus nimodipine is safe and superior to placebo plus nimodipine for improving modified Ranking Score (mRS) at six months.
Two interim analyses for futility and efficacy are planned.

4.2.2 Investigational centers

Several selected centers will participate in the study. The list of Investigators will be managed separately from the study protocol and Competent Authorities will be kept informed of the update of the list.
Patients will be recruited during hospitalization.

4.2.3 Identification of the subjects

During or at the end of the research, the data transmitted to the sponsor by the investigators (or any other specialized contributors) will be rendered non-identified. Under no circumstances should the names or addresses of the participants be made clear. The sponsor will ensure that each person who is subject to the research has given his or her consent for access to individual data concerning him or her that are strictly necessary for the research.

For this research, the subjects will be identified as follows:

Centre No. (3 numerical positions) - Selection order No. of the person in the centre (4 numerical positions) - surname initial - first name initial

This reference is unique and will be retained for the entire research period.

4.2.4 Randomisation

After screening for inclusion and non-inclusion criteria, and obtaining consent, patients will be randomized (1:1 ratio) to cilostazol or placebo groups by logging onto a randomization website using a pre-prepared randomization list, balanced by randomly variable block size. Randomization will be stratified by centre, age (<50 years; >=50 and <=75Years; >75 years); and severity (Fisher grade from I to III; Fisher grade IV)

Randomisation will occur in an online data entry platform, guaranteeing the concealment of the experimental arm assigned to the doctor performing the inclusion and randomisation of the patient.

The randomisation code will be disclosed once recruitment is completed.

4.2.5 Blinding methods and provisions put in place to maintain blindness

The physician investigator in each participating ICU will, after the patient fulfils the inclusion criteria and gives consent to participate in the CASH trial, use the online platform for data entry to randomize the patient, which in turn will allocate the participant to one of the two groups, from a pre-prepared randomization list.

The randomization will be held in an online platform for data entry, and as such, ensures allocation concealment by not releasing the randomization code until the recruitment is completed.

At the moment of randomisation in the e-CRF, visible to the investigator will only appear that *"the patient was successfully randomised"*; no other code will appear in the e-CRF. At the moment of randomisation, an email will inform the hospital pharmacy that a patient has been included and randomised; only the pharmacist will have access to the randomisation arm.

Both trial participants, care providers, and outcome assessors will be blinded after the patients' assignment to one of the trial groups. The double blinding will be provided by the hospital pharmacy of promotor establishment using placebo pills similar to commercial pills. Nurses in charge will be blind to the study as well as the physician and research technician in charge of outcome assessment.

In case of accidental loss of treatment, a form has to be completed with informations regarding the reason of the loss, the number of the patient and the number of days of treatment. The promotor will process the accident and will authorize or not the pursuit of the treatment. If the authorization is granted, the investigator site has to complete a form in the e-CRF for exceptional dispensing and will receive the code allowing the good dispensation according to the randomisation arm.

4.2.6 Procedures for breaking the blind, if applicable

Unblinding may be requested at any time and for any reason considered indispensable by the investigating physician, if a serious adverse event occur attributable to cilostazol, by calling the Délégation à la Recherche Clinique et à l'Innovation (Delegation for Clinical Research and Innovation) or the Pharmacy of Centre Hospitalier Sainte-Anne at the numbers given to each centre in the study protocol.

In exceptional cases in which curative anticoagulation or antiaggregation is deemed necessary by the caring physicians, unblinding will be realized and a 10-hour wash out period will be advised in case of belonging to the cilostazol arm.

5 PROCEDURE FOR THE RESEARCH

Consent will be obtained by an investigator from the patient, or from a relative if the patient is unable to consent, or using the emergency clause according to French Law if no relative could be contacted within 24 hours. If the patient is unable to consent, a pursuit consent will be sought as soon as the patient will be able to express its wills.

Visits will be conducted daily throughout the stay in intensive care until D28. If the patient has been discharged from the ICU, a visit will be made at D28 to collect primary and secondary outcome data. An electronic case report file will be available to the research team

of each institution, on an online platform (Research Electronic Data Capture, REDCap, Vanderbilt University, Study data will be collected and managed using REDCap electronic data capture tools hosted at Centre Hospitalier Sainte-Anne. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; 4) procedures for data integration and interoperability with external sources.

5.1 Inclusion visit

Inclusion visit will be conducted by the investigator of the participating centres. The inclusion visit will allow to check the inclusion and non-inclusion criteria.

Inclusion criteria will be:

- Age >18 yo
- Admission to an ICU
- Aneurysmal SAH diagnosis made upon radiologic findings in CT scan or MRI
- Clinical onset of SAH within the last 96 hours -
- Aneurysm successfully secured by surgical clipping or endovascular coiling
- Consent of the patient or, if not possible, from a proxy (emergency clause)
- Registration in a national health care system

Non-inclusion will be

- Precritical modified Rankin Scale (mRS) > 2
- Non-aneurysmal SAH
- Delayed>96h admission after first symptoms of Aneurysmal SAH
- Coma defined by GCS of 3-5 with untreatable aneurysm will be excluded
- Known allergy to cilostazol
- Pregnancy
- Pre-existing major hepatic, renal, pulmonary or cardiac disease
- Concomitant use of one other anti-platelet and/or anticoagulant agent
- SAH diagnosed on LP with no evidence of blood on CT.
- Tutelage or guardianship

During the inclusion visit, the following characteristics will be collected:

Demographic data:

- Age
- Sex
- Medical history (High blood pressure, tobacco use, drugs use, cocaine use, n° Unit of alcohol/d consumed, diabetes and other comorbidities according to the Charlson score (see Appendix 6)

SAH history

- Date of onset
- Initial loss of consciousness
- Onset seizure
- Meningeal syndrome
- Sudden headache

Severity at hospital admission

- WFNS score
- GCS
- Motor deficit
- Pupillary status

Radiologic findings on first CT:

- Localisation of aneurism having bled (anterior, posterior circulation)
- Multiple aneurism
- Largest aneurism size (mm)
- Hijdra score,
- Fisher score
- Intraventricular haemorrhage
- Intraparenchymal hematoma
- Acute hydrocephalus
- Area of previous ischemia
- Area of recent ischemia
- Fisher scale (Appendix 9)

Specific complications up to inclusion:

- High intracranial pressure (ICP) when measured (normal ICP will be considered if not monitored) > 20mmHg
- **Radiological findings at inclusion or >6hours after aneurism treatment**
  - Area of recent ischemia
  - Recurrent bleeding
  - Acute hydrocephalus

Treatment up to inclusion:

- Time from symptoms to treatment (hours)
- Endovascular therapy
- Surgical clipping
- Hemicraniectomy
- Hematoma resection
- Lobectomy
- Mechanical ventilation
- Catecholamine administration
- Continuous sedation
- Extraventricular drainage
- Therapy intensity level (Annexe 5)

Clinical examination at the time of inclusion:

- SAH severity according to WFNS,
- GCS score,
- Neurological focal sign at admission
- Anisocoria

5.2 Follow-up Visits

Follow up visits will be performed daily from day 1 to day 28. One Brain imaging will be realized 24/48 hours after the aneurism treatment and one between day 28 and 45 after randomization. Transcranial doppler, MR CTA or DSA results will be collected when realized.

Day 1 to day 28
Vital status
Compliance to treatment
Experimental Treatment administration will be collected daily

Safety follow up

- Any major Cilostazol-related adverse event will be assessed:
  - Arrythmia from auricular origin
  - Arrythmia from ventricular origin
  - Abnormal bleeding
  - Allergy
- Other minor Cilostazol-related adverse events:
  - Tachycardia,
  - Fever
  - Fainting
  - Nausea
  - Vomiting
  - Stomach pain

Cerebral vasospasm

- Blood flow velocity increase on TCD
- Cerebral vasospasm diagnosed upon MR/CTA or DSA and its severity (mild/moderate/severe)

Delayed cerebral ischemia

- New focal deficit
- Glasgow point decrease
- No other cause

Treatment in the last 24 hours

- Continuous sedation
- Mechanical ventilation
- Extraventricular drain
- Therapy Intensity Level (TIP) for Raised ICP treatment (See Appendix 7)
- Hypertension therapy
- Vasopressors (epinephrine/norepinephrine/dobutamine)
- Milrinone administration
- Endovascular treatment (Balloon therapy or vasodilatator administration)
- Other treatment
- At ICU discharge, the modified Rankin scale will be evaluated by a blinded research technician in case of lost to follow up.

5.3 End of research visit at 6 months

The end of research visit will be made at 6 months or when the patient terminates the study.

Primary outcome

The physician, physical therapist, research assistant or research nurse will collect blindly the mRS if the patient is alive. A face-to-face structured interview will be held during which the modified Rankin scale will be assessed (Appendix 1, 17).

Functional and cognitive status will be collected during the patient's consultation at 6 months, with using:

-SAHOT Score
-MOCA score
-Return to work
-Activities of Daily Living
-Instrumental Activities of Daily Living

The in-hospital morbity indicators will be collected, including:

-Length of Intensive Care Unit stay
-Length of hospital stay

The occurrence of cerebral vasospasm and DCI during ICU stay will be assessed, with collecting

-Delayed cerebral ischemia, defined as the occurrence of focal neurological deficit or a decrease of at least 2 points on the Glasgow Coma Scale, which does not occur immediately after aneurysm occlusion and which is not ascribable to other causes.

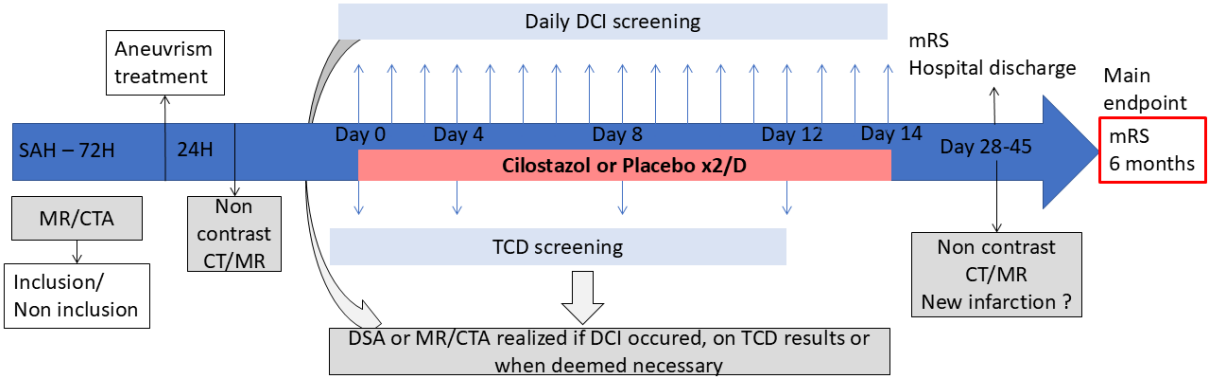
-Cerebral artery vasospasm, defined as a reduction of the diameter of the proximal cerebral artery on either CT-, MR- or catheter angiography

-Cerebral infarcts, considered when detected on the CT scan or MRI performed with 6 weeks, (or on the latest CT scan or MRI performed before death within 6 weeks, or at autopsy), but not present on the earlier CT or MRI scan performed between 24 and 48 h after early aneurysm occlusion and not ascribable to other causes

5.4 Expected length of participation and description of the chronology and duration of the research.

Inclusion period	42 months
The included subjects' length of participation, of which:	
• Treatment period:	2 weeks
• Follow-up period:	6 months
Total research period:	49 months

5.5 Table or diagram summarising the chronology of the research



Actions	***Inclusion visit***	*Day 0-28*	*End of research 6 months*
Informed consent	*x*		
History	*x*		
*Clinical exam**	*X*	*X*	*X*
*Para-clinical exam**	*X*	*X*	*X*
Medical procedures (ECG, etc.)			
Dispensation of treatments		*X*	
Compliance	*X*	*X*	*X*
Adverse events		*X*	*X*

***A complete description of Clinical exam, paraclinical exam and tests are described specifically in each visit in section 5.1 to 5.3**

5.6 End of the trial

The end of the reseach is defined as the date when the last visit of the last patient included in the study occurs.

5.7 Distinction between care and research

TABLE: Distinction between procedures associated with "care" and procedures added because of the "research "

Procedures and treatments carried out as part of the research	**Procedures and treatments associated with <u>care</u>**	**Procedures and treatments added because of <u>the research</u>**
Treatments	DCI and vasospasm preventive and curative treatments (must include nimodipine administration)	Cilostazol or placebo administration during 14 days
Consultations	Routine visits from the physician in charge	Face to face interview at 6 months

Blood samples	Left to the discretion of the physician	None
Imaging, etc.	Imaging (CT scan, MRI, TCD) left to the discretion of the physician	All the imaging techniques evaluating secondary objectives are routinely realized

5.8 Termination rules

5.8.1 Criteria and methods for prematurely terminating the research treatment

5.8.1.1 Different situations

- Temporary termination of treatment, the investigator must document the reason for stopping and restarting the treatment in the subject's source file and the case report form (CRF)
- Premature termination of treatment, but the subject is still included in the research, until the end of the subject's participation, the investigator must document the reason (if during the administration period, the patient get out of the ICU, the treatment will stop).
- Premature termination of treatment and end of participation in the research.

The investigator must:

- Document the reason(s)
- Collect the assessment criteria when participation in the research ends, if the subject agrees
- In case of severe adverse event, subject will be closely monitored and followed.

5.8.1.2 Criteria and methods for the premature termination of the research

- Any subject can withdraw from participating in the research at any time and for any reason.
- The investigator can temporarily or permanently end a subject's participation in the research for any reason that affects the subject's safety or which would be in the subject's best interests.
- In case of loss of follow-up, the investigator must try to contact the subject by any means possible in order to know at least if the patient is still alive, and report it in the patient's file.

If a subject leaves the research prematurely, data relating to the subject can be used unless an objection was recorded when the subject signed the consent form.

If consent is withdrawn, no data about the subject may be used unless the subject states in writing that he/she does not object. In practice, the subject is excluded from the research.

The case report form must list the various reasons for ending participation in the research:

- ☐ Ineffective
- ☐ Adverse reaction
- ☐ Other medical problem
- ☐ Subject's personal reasons
- ☐ Explicit withdrawal of consent

5.8.2 Follow-up of the subjects after the premature termination of treatment

Ending a subject's participation does not affect the normal management of the subject's illness in any way.
If there are serious adverse events, the investigator must notify the sponsor and monitor the subject for a month following the premature termination of treatment. If treatment is stopped prematurely due to a serious adverse event, a serious adverse event notification form will be sent by fax (01 44 84 17 99) to the sponsor. The serious adverse event will be monitored until it is resolved.
If a data and safety monitoring board (DSMB) has been created, this committee can specify and/or validate the monitoring methods.

5.8.3 Methods for replacing subjects, if applicable

A 10 % dropout rate of patients has been estimated and considered for the calculation of the number of subjects to be included.

5.8.4 Terminating part or all of the research

Le GHU Paris Psychiatrie et Neurosciences as sponsor or the Competent Authority (ANSM) can prematurely terminate all or part of the research, temporarily or permanently, upon the recommendation of a data and safety monitoring board in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are seen in an arm being treated or if there is a discrepancy in the serious adverse reactions between the 2 arms being treated, and which require a reassessment of the benefit-risk ratio for the research [to be adapted].
- in the case of interim analysis: stopping treatment to demonstrate the efficacy of one of the arms being treated or on the other hand stopping due to futility
- likewise, unexpected facts, new information about the product, in light of which the objectives of the research or of the clinical programme are unlikely to be achieved, can lead Le GHU Paris Psychiatrie et Neurosciences as sponsor or the Competent Authority (ANSM) to prematurely halt the research
- Le GHU Paris Psychiatrie et Neurosciences as sponsor reserves the right to permanently suspend inclusions at any time if it appears that the inclusion objectives are not met.

If the research is terminated prematurely, the decision and justification will be given by the sponsor, Le GHU Paris Psychiatrie et Neurosciences, to the Competent Authority (ANSM) and to the CPP within 15 days, along with recommendations from the Data and Safety Monitoring Board (if applicable).

5.8.5 Screen failure

A subject who signed a consent form, but did not meet the inclusion/exclusion criteria is classified as a screen failure. Subject number, demographics and reason for screen failure will be recorded.

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Adult patients admitted to an ICU with SAH related to a ruptured cerebral aneurysm occurring within the last 96 hours.

- Aneurysm successfully secured by surgical clipping or endovascular coiling

- Consent of the patient or, if not possible, from a proxy (emergency clause).
- Registration in a national health care system

6.2 Non-inclusion criteria

- Precritical modified Rankin Scale (mRS) > 2
- Nonaneurysmal SAH
- Delayed >96h admission after first symptoms of SAH
-
- Coma defined by GCS of 3-5 with untreatable aneurysm will be excluded”
- Known allergy to cilostazol
- Pregnancy
- Pre-existing major hepatic, renal, pulmonary or cardiac disease
- Concomitant use of one other anti-platelet and/or anticoagulant agent
- SAH diagnosed on Lumbar puncture with no evidence of blood on CT.
- Tutelage or guardianship

6.3 Recruitment methods

Patient’s screening for recruitment will take place in all the participating ICUs.
An information form will be given to the patient or, if not possible, to a family member.

	Number of subjects
Total number of subjects chosen	*630*
Number of centres	9
Inclusion period (months)	*42*
Number of subjects/centres	*79*
Number of subjects/centre/months	***1.9***

7 TREATMENT ADMINISTERED TO RESEARCH PARTICIPANTS

7.1 Description of the experimental medication or medications

7.1.1 Experimental medication 1

Cilostazol 100mg tablets
Packaging type : blisters
Two times a day (every 12 hours) for 14 days, 28 tablets in total
Storage: room temperature
Shelf life: 3 years

Oral form if patient is able to swallow the tablet. If not, tablets will be crushed by the nurse in charge of the patient, and given by oral or enteral route through feeding tube if required. OF note administration of crushed tablet will be standardized at specific timing in each center. In case a patient can eat a meal, the delai between administration and meal will be of 30 minutes minimum

Of note a market authorization (Autorisation de Mise sur le Marché) is available in France for cilostazol in chronic arteritis but no marketed anymore since 2010 in France. The GHU Paris Psychiatry and Neurosciences pharmacy will import cilostazol which is also marketed in Europe. The blinding as well as the creation of a placebo will be subcontracted to a competent GMP establishment. The logistic will be centralized by the pharmacy of the GHU Paris and the pharmaceutical circuit will be co-constructed between GHU Paris and pharmacies of the different investigator centres (storage and delivery).

7.2 Description of the non-experimental treatment or treatments (medications required for carrying out the research)

7.2.1 Non-experimental medication 1

As recommended by French and European guidelines, a preventive medication of DCI by nimodipine has to be administered during the ICU stay. The posology, route (IV or enteral) and length of treatment is left to the discretion of the caring physician.

7.3 Description of the traceability elements that accompany the experimental medication or medications

Designated pharmacists responsible for the receipt, handling and dispensing of study drugs (active and placebo) will maintain study drug records during the study: details of how all phases of dispensing and withdrawal of unadministered drugs will be monitored and controlled, and the patient code/kit code correspondence will be described in the Pharmacy Manual to be established prior to the start of the study.

The investigator must maintain an accurate record of the shipment, storage, and dispensing of the study drug in a drug accountability log. An accurate record including the date and amount of study drug dispensed to each subject must be available for inspection at any time. A study CRA assigned to monitor the investigational site will review these documents once study drug has been received by the investigational site. Study drug will be accounted for on an ongoing basis during the study.
Further guidance and information for the final disposition of unused study intervention are provided in the Investigator Manual.

7.4 Authorised and prohibited treatments (medicinal, non medicinal, surgical), including rescue medications

Authorised treatments include every other preventive or curative treatments (medical or radiologic) for vasospasm and DCI, notably the use of milrinone, vasopressors for hypertension therapy (norepinephrine, dobutamine or epinephrine).
Unauthorised treatments include other antiplatelet agent or curative anticoagulation treatment. In case of an anticoagulation or antiaggregant is deemed necessary by the caring physicians, unblinding of the randomization will be realized and a 10 hours washout period will be advised before anticoagulation start if possible if the patient was randomized to the cilostazol arm.
Cilostazol dosage is modfied by CYP3A4 inhibitors (clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal and grapefruit**) or**

CYP2C19 inhibitors (e.g., Chloramphenicol, Clomipramine, Delavirdine, Fluoxetine, Fluvoxamine, Gemfibrozil, Imipramine, Isoniazide, Lansoprazole, Miconazole**)**, thus these drugs will be prohibited during the administration of cilostazol. In case of a proton pump inhibitor will be prescribed, pantoprazole will be preferred as it has a limited to no effect on **CYP2C19 inhibitors**[19] If any of the other drug is prescribed, cilostazol dosing will be reduced to 50 mg BID to mitigate interaction risks.

7.5 Methods for monitoring compliance with the treatment

pharmacy visits will be planned, reporting:

- Number of tablets administered
- Number of tablets returned to the pharmacy

8 ASSESSMENT OF EFFICACY

8.1 Description of parameters for assessing efficacy

Primary outcome

It is the Modified Rankin score (mRS):

It will be assessed at 6 months by physicians, physical therapists or research assistant or research nurses who would have been specifically trained to pass this score and who will be unaware of the trial-group assignments, during a face-to-face interview with patient. This structured interview will strengthen the interrater agreement (17)

Methods for secondary assessment criterion collection

At the 6 months interview and after collection of the mRS, one will proceed to the assessment of

- The SAHOT score (Appendix 2). For facilitating its collection and reduce time of the consultation, the SAHOT questionnaire will be sent to the patients before the 6 months face-to-face interview.
- MOCA score at 6 months (Appendix 3), which will be passed during the 6 months face-to-face interview by the trained investigator.
- Return to work at 6 months
- Activities of Daily Living (ADL) at 6 months (Appendix 4) and Instrumental Activities of Daily Living (IADL) at 6 months (Appendix 5), which will be passed during the 6 months face-to-face interview by the trained investigator.

Radiological endpoints will be collected daily during the ICU stay. Delayed cerebral ischemia is defined in the section 4.1.2 Highest velocity in the mean cerebral artery evaluated in tCD will be collected when available. MR/CTA DSA vasospasm will be scored as mild, moderate or severe according to the narrowing of the cerebral arteries.

8.2 Anticipated methods and timetable for measuring, collecting and analysing the parameters for assessing efficacy

Efficacy will be assessed with help of the mRS at 6 months, during a structured face-to-face interview of the patients which will involve one of the physicians, physical therapists, research assistants or research nurses of any participating centre. The organisation of the structured

face-to-face interview will be as similar as possible between centres. During this M6 visit, the secondary outcomes- related scores will also be collected:

- SAHOT
- MOCA score
- Activities of Daily Living
- Instrumental Activities of Daily Living
- Return to work

During hospital stay, other parameters evaluating efficacy will be prospectively collected and reported on the e-CRF:

- Length of stay in the ICU
- Length of hospital stay
- 28-day mortality

9 SPECIFIC RESEARCH COMMITTEES:

Dénomination anglo-saxonne	Dénomination française	Caractéristiques
Independent Data Monitoring Committee (IDMC) or Data Safety Monitoring Board	Comité de surveillance indépendant (CSI)	Membres indépendants de l'investigateur
Steering Committee	Comité de Pilotage Comité Scientifique	Investigateurs, promoteur…
Endpoint Adjudication Committee	Comité de validation des évènements critiques	Travail en aveugle

Note: the Data Safety Monitoring Board (DSMB) is described in section 10.

9.1 Scientific committee

- Members of the committee: Schimpf Caroline, Mazeraud Aurélien, Tarek Sharshar, Cinotti Raphael
- Missions: define the objective, write the protocol, propose modifications to the protocol during the research
- Operating methods: Distant meetings with prespecified agenda upon Coordinator Investigator request

9.2 Steering committee

- Members of the committee: Caroline Schimpf, Isabelle Dufaure-Gare, Aurélien Mazeraud, Guillaume Turc, Khaoussou Sylla, Sylvain Leroy

- Missions: To propose guidelines during the course of the research, taking note of the recommendations of the independent monitoring committee, if any. The DRCI sponsor remains the decision maker.
- Operating methods: *Distant meetings with prespecified agenda upon promotor request*

9.3 Endpoint Adjudication Committee

✓ The adjudication committee's role is to analyze patient data in detail and conclude whether the event (endpoint) is present or not.The committee will therefore be made up of specialists in the pathology or endpoint of the trial. It is not necessarily independent of the trial, but the main thing is that it acts blindly. There is therefore a lot of preparatory work to provide the committee with anonymized and undated data.

- Members of the committee: Ghazi Hmeydia, Mazeraud Aurélien, Caroline Schimpf, Camille Legouy
- Missions: Secondary endpoints adjudication
- Operating methods: Meetings when 25, 50, 75 and 100% of the patients are monitored.

✓ Outcomes concerned :

Secondary endpoints adjudication

✓ Primacy of the opinion of the adjudication committee:

The adjudicated outcome takes precedence over that of the investogator

10 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE RESEARCH

10.1 Description of parameters for assessing safety

SmPC will describe more detailed information on the known and anticipated risks and reasonably expected adverse events (AEs) of cilostazol.

10.2 Anticipated methods and timetable for measuring, collecting and analysing the parameters for assessing safety

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs as detailed in this Section of the protocol.

10.3 Procedures in place for recording and reporting adverse events

Adverse events will be collected by physicians in charge on a daily basis, and reported through an e-CRF by investigators. They will be classified as mild, moderate or serious adverse events.

10.3.1 Definitions (Regulation (EU) N° 536/2014 (REC)

Adverse event Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

- **Adverse drug reaction**
  Any response to a medicinal product which is noxious and unintended.

- **Serious adverse event**
  Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

- **Unexpected adverse reaction**
  An adverse reaction, the nature, severity or outcome of which is not consistent with the applicable product information: the summary of product characteristics (SmPC) for an authorised product or the investigator's brochure for an unauthorised investigational product.

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<u>According to the notice to sponsors of clinical trials for medications (ANSM)</u>:

- **New safety issue**

Any new information regarding safety:
- that could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the trial
- or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the trial

Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction occurring
b) suspected unexpected serious adverse reactions (SUSAR) occurring in patients who have finished the trial and about whom the sponsor is notified by the investigator, who also provides any follow-up reports
c) any new fact relating to the conduct of the clinical trial or the development of the experimental medication, if the new fact is likely to affect participant safety
Examples:

- a serious adverse event likely to be related to the investigations and to the trial's diagnostic procedures and which could modify the conduct of this trial
- a significant risk for the trial participants such as ineffectiveness of the experimental medication used in the trial in treating a life-threatening illness
- significant safety results from a recently completed research carried out on animals (such as a carcinogenicity research)
- the premature termination, or temporary interruption, of a trial conducted with the same experimental medication in another country, for safety reasons

- an unexpected serious adverse reaction associated with a non-experimental medication required for carrying out the trial, (e.g., challenge agents, rescue treatment)

d) recommendations from the data safety monitoring board (DSMB), if applicable, if they are relevant to the safety of the participants

e) any unexpected serious adverse reaction reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication

10.3.2 The investigator's roles

10.3.2.1 Regulatory obligations of the investigator

The investigator must notify the sponsor, **immediately on the day when the investigator becomes aware**, of all the serious adverse events, except those that are listed in the protocol (see. section 10.3.3.1) or in the investigator's brochure as not requiring immediate notification.

These serious adverse events are recorded in the "adverse event" section of the case report form and the investigator must immediately notify the sponsor's Vigilance division (see 10.3.4).

10.3.2.2 The investigator's other roles

The investigator must document the serious adverse event as thoroughly as possible and provide the medical diagnosis, if possible.

The investigator assesses the severity of the adverse events by using an adverse events rating scale, attached to the protocol, by using general terms:

- *Mild: tolerated by the patient, does not interfere with daily activities*
- *Moderate: sufficiently uncomfortable to affect daily activities*
- *Serious: preventing daily activities*

The investigator assesses the causal relationship between the serious adverse events and the experimental medication(s) added by the research.

10.3.3 Specific features of the protocol

All serious and non-serious adverse events must be reported in the CRF.

10.3.3.1 Serious adverse events that do not require the investigator to immediately notify the sponsor

These serious adverse events are only recorded in the "adverse event" section of the case report form.

- **Normal and natural evolution of the pathology:**

Normal and natural evolution of aneurismal SAH is quite variable:

- Even without initial neurological deficit, patients are closely monitored after securisation of the aneurism because of the risk of DCI, vasospasm, hydrocephalus, rebleeding, or any other unspecific complication. Patients in worse neurological condition can be initially intubated; the duration of mechanical ventilation dependst on the subsequent neurological improvement and intercurrent ICU complications.
- Securisation of the aneurism can be performed with endovascular coiling or surgical clipping and lead to ischemic stroke

- Death occurs in approximately 30% of all cases.
- DCI can occur from day 4 until the 21th day after SAH. This risk peaks about the 10th day. DCI can require hypertension therapy and infusion of vasopressor, adjunctive pharmacological treatment, notably milrinone, and endovascular treatment of vasospasm can be requested, but in a centre-dependant way
- Other organ failure might occur as patients might require prolonged ventilatory support and developed ICU related complications, such as nosocomial infection.
- Initial hydrocephalus can worsen the neurological status; it can occur from the first to 15th day. It can require an external ventricular drain. The drain can often be weaned during hospitalisation but if not, internal ventricular drainage can be implanted. It is associated with a risk of nosocomial menigitis.
- When the risk of DCI or other neurological complication is considered low enough, the patient is transferred to the ward until the patient is discharged from the hospital to either the patient's home or a rehabilitation centre.

- **<u>Adverse events likely to be associated with the treatments prescribed as part of the patient's care during the monitoring of the research</u>**

10.3.3.2 Serious adverse events that require the investigator to immediately notify the sponsor

The investigator must report all adverse events that meet one of the seriousness criteria below, except for events listed in section 10.3.3.1 as not requiring notification: 1- Death 2- Life threatening situation 3- Requiring hospitalisation or prolonging hospitalisation 4- Persistent or significant disability or incapacity 5- Congenital abnormality or birth defect 6- Or any other adverse event considered "medically significant"

❖ For serious adverse events related to the experimental medication(s) and which are expected:

- the -SmPC for the **« cilostazol »** speciality, found in (Appendix 5), should be consulted.

❖ The serious adverse events associated with specific research procedures or exams, and which are expected, are:

- Poorly tolerated auricular or ventricular arrythmia
- Abnormal bleeding (requiring blood transfusion or not)
- Allergy

10.3.3.3 Other events that require the investigator to immediately notify the sponsor

- **<u>Adverse events that are "not serious" but which are significant for the safety of participants</u>**
- The following adverse event will be assessed:
  - Well tolerated arrythmia from auricular origin
  - Well tolerated arrythmia from ventricular origin
  - Tachycardia,
  - Fever
  - Fainting

  - Nausea
  - Vomiting
  - Stomach pain
- The investigator must notify the sponsor about these "nonserious" adverse events, in accordance with the same procedures and deadlines as serious adverse events (see section 10.3.4). These events can be considered "medically significant".

- ***In utero* exposure**

The sponsor must be notified immediately about any pregnancy during which the foetus (from the pre-embryonic stage up to birth) could have been exposed at a given time to an experimental medication, even if the pregnancy is not associated with an adverse event.

Notification is required if the exposure involves:
- the mother,
- the father if the experimental medication is genotoxic.

10.3.4 Procedures and deadlines for notifying the sponsor

Notification of an SAE must initially be provided in a written report using the special form for reporting SAE. The report must be signed by the investigator.

Each item in the form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

This initial notification must be followed by one or more detailed follow-up report(s), in writing and signed, within a maximum of 8 days in the case of a fatal or life-threatening event and within 15 days for all other cases.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results of additional exams, etc.). These documents must be made anonymous. In addition, the documents must include the following: research acronym, number and initials of the subject, nature and date of the serious adverse event.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has left the trial.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor via fax only to the Vigilance Division of the DRCI, fax No. **01 45 65 76 09**.

For studies using e-CRF:
- the investigator completes the SAE notification form in the e-CRF, validates, prints and signs the form before sending it *via* fax.
- if it is not possible to connect to the e-CRF, the investigator will complete, sign and send the SAE notification form found in the Investigator Worksheet**.** As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must comply with all requests from the sponsor for additional information.

For all questions relating to the notification of an adverse event, the DRCI can be contacted via email: drci@ghu-paris.fr

The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy, using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAE.
If the exposure involves the father, the investigator must obtain the mother's permission before collecting information about the pregnancy.

The initial pregnancy notification, the SAE follow-up reports and all other documents must be sent to the sponsor via fax only to the DRCI, fax No. **01 45 65 76 09**.

10.3.5 Period for notifying the sponsor

The investigator must report all SAE that occur in research subjects:
- after the date on which treatment with an experimental medication began
- throughout the period during which the participant is monitored, as determined by the research
- for up to 4 or more weeks after the participant stops treatment using the experimental medication
- with no time limit, if the SAE is likely to be due to the experimental medication or to the research procedures (for example, serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities).

10.3.6 The sponsor's roles

The sponsor, represented by its DRCI, continuously assesses the safety of each experimental medication throughout the research.

10.3.6.1 Analysis and declaration of serious adverse events

The sponsor assesses:
- the seriousness of all adverse events reported
- the causal relationship of these events with each experimental medication and/or specific medical procedures/exams added by the research and with other possible treatments
- the expected or unexpected nature of these adverse reactions

All serious adverse events which the investigator and/or the sponsor believe could reasonably have a causal relationship with the experimental medication are considered as suspected adverse reactions.

All suspected unexpected serious adverse reactions (SUSAR) are declared by the sponsor, within the legal time frame, to the Agence Française de Sécurité Sanitaire des Produits de Santé (ANSM, French Health Products Safety Agency) and to the relevant Comité de Protection des Personnes (CPP, ethical committee).

- The initial declaration must be made with no delay after the date on which the serious adverse event occurs in the case of death or of a life-threatening diagnosis.

- The initial declaration must be made with no delay after the date on which the serious adverse event occurs in the case of other serious situations.

- The follow-up declaration must be made with no delay.

Any suspected unexpected serious adverse reaction must also be declared electronically in the Eudravigilance European database for adverse events due to medications, established by the European Medicines Agency (EMA).

The sponsor must notify all relevant investigators about any data that could adversely affect the safety of the research subjects.

Specific cases of serious adverse events of special interest:
At the request of ANSM, the sponsor may be asked to declare serious adverse events of special interest, in accordance with the same procedures and deadlines as SUSARs.

Specific case of double-blind trials
As a general rule, the sponsor declares a suspected unexpected serious adverse reaction to the competent authorities and to the CPP after having broken the blind on the experimental medication.
In exceptional situations, and if the ANSM grants permission when requested by the sponsor in the sponsor's clinical trial authorisation application, the methods for unblinding and for declaring suspected unexpected serious adverse reactions can be modified. These methods will then be defined in detail in the research protocol (see section 4.2.6).

10.3.6.2 Analysis and declaration of other safety data

This relates to any safety data or new fact that could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the research, or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the research.

New facts must be declared to the competent authorities within 15 calendar days of the sponsor becoming aware. Additional relevant information must be sent within an additional 8 days after the 15-day deadline.

10.3.6.3 Annual safety report

Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- an analysis of the safety of the research subjects
- a description of the patients included in the trial (demographic characteristics, etc.)
- a line listing of suspected serious adverse reactions that occurred during the period covered by the report
- a cumulative summary tabulation of serious adverse events that have occurred since the start of the research

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorised the trial.

10.3.7 Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) can be established by the sponsor. Its primary mission is to serve as a committee for monitoring safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The DSMB is mentioned in Article L. 1123-7 of the French Public Health Code.

The sponsor is responsible for justifying the creation or absence of a supervisory committee to the Competent Authority (ANSM) and to the CPP.

A DSMB will be convened for this biomedical research. The members of the DSMB will be named after the research starts. During the first meeting of the DSMB, a chairman will be appointed and the members will determine their operating methods and the meeting schedule. All missions as well as the precise operating methods of the DSMB will be described in the DSMB's charter for the research.

General information about the DSMB
The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research upon interim analysis. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of:
    - safety data: serious adverse reactions
    - efficacy data: proven futility or efficacy

The DSMB is appointed by the sponsor and is made up of at least 3 people with no connection to the research, including at least one clinician specialising in the pathology being studied and one specialist in the medication being studied (or a pharmacologist/pharmacovigilance specialist), and possibly a methodologist/biostatistician, particularly in the case of interim analysis.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research.

The DSMB must hold its preliminary meeting before the first inclusions of the first subject and ideally before the protocol is submitted to the competent authority and the CPP. The committee's agenda will be as follows:

Definition of the DSMB's missions:

- Validation of the research methodology:

The proposed methodology for the clinical trial will be validated by the DSMB so that it does not jeopardise the safety of subjects, in particular relating to the inclusion and randomization methods.

- Validation of tolerance monitoring methods:
    - nature of the evaluated parameters
    - frequency of the evaluations, consultation schedule

- Validation of termination criteria:
    - criteria for terminating a subject's participation for tolerance reasons

- criteria for the temporary or permanent termination of the research (leading to the establishment of certain recommendations ("stopping rules"))

- Modification of the protocol and recommendations:

In light of the analysis of tolerance data for the research, the DSMB can, when applicable: propose substantial modifications in order to modify certain data, in particular relating to the protocol (inclusion and non-inclusion criteria, monitoring, additional exams, etc.). Likewise the DSMB can issue any recommendations it deems useful in order to best ensure the safety of the research subjects and to maintain a favourable benefit-risk balance throughout the research.

Definition of the DSMB's operating methods:
- meeting types (open session, then closed sessions) and schedule
- desired methods and format of SAE notification from the sponsor to the DSMB

The DSMB appoints its chairman at the first meeting.

The sponsor retains decision-making authority. When applicable, the sponsor delivers its decision, with justification, and DSMB reports to the Competent Authority (ANSM) and the CPP.

11 DATA MANAGEMENT

11.1 Data collection methods

Study data will be collected and managed using REDCap electronic data capture tools hosted at Centre Hospitalier Sainte-Anne. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; 4) procedures for data integration and interoperability with external sources.

11.2 Identification of data collected directly in the CRFs and that will be considered as source data

Patients will be identified through their initials, number center and randomization number.

11.3 Right to access source data and documents

11.3.1 Access to data

In accordance with GCPs:
- the sponsor is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research will be carried out, to the source data, to the source documents and the reports, with the goal of quality control and audit by the sponsor
- the investigators will make available to those in charge of monitoring, quality control and audit relating to the biomedical research the documents and personal data strictly necessary for these controls, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.3.2 Source documents

Source documents are defined as any original document or object that can prove the existence or accuracy of a piece of information or a fact recorded during the research. These documents will be kept for 15 years by the investigator or by the hospital in the case of a hospital medical file. Electronic Health record and Radiological reports will be kept by the investigators of each centre

11.3.3 Data confidentiality

Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information about the experimental medications, the research, the research subjects and in particular the identity of the subjects and the results obtained.
These individuals, as well as the investigators themselves, are subject to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code).
During or after the biomedical research, the data collected about the research subjects and sent to the sponsor by the investigators (or any other specialised parties) will be made non-identifying.
Under no circumstances should the names and addresses of the subjects involved be shown.
The sponsor will ensure that each research subject has given permission in writing for access to personal information about him or her which is strictly necessary for the quality control of the research.

11.3.4 Data security

11.3.4.1 ***Measures Implemented Upstream:***

- Presence of a full-time Data Protection Officer (DPO) and Chief Information Security Officer (CISO) internally;
- Raising awareness among employees about personal data protection (both in paper and digital formats), privacy, and cybersecurity;
- Confidentiality and IT tool usage charters in place and signed by all employees, partners, and service providers;
- Established Information Security Policy (PSSI);
- Regular IT system audits and remediation of any identified risks;
- Cybersecurity aspects :
    - Securing remote access via VPN + MFA,
    - TLS access for web applications,
    - Pseudonymization and encryption of data,
    - Segmentation (separating web sections from databases),
    - Logical access control through ID+Password authentication, with deactivation of unused accounts after 3 months,
    - Account blocking after multiple failed login attempts,
    - Securing IT communication channels (firewall, traffic monitoring probes),
    - Inventory (CMDB) and hardware redundancy,
    - Access granted per project,
    - Securing operations: daily backup policy for VMs and servers, PSSI;
    - Data archiving policy preventing any subsequent modification or extraction;
    - Strict compliance with the principle of data minimization;
    - Protection against malware (XDR solution, DMZ servers, and traffic control).

11.3.4.2 Measures to Be Implemented in Case of a Data Security Breach to Mitigate Possible Negative Effects:

- Restoration of lost data via daily backups in case of loss of availability or unintended modification;
- Set of measures preventing the reuse of data in case of theft, interception, etc. (encryption through VPN + MFA + TLS access for web applications);
- Personal data breach management policy (notification of the incident to the CNIL, general and personal communication to affected individuals, etc.).

11.4 Data processing and storage of documents and data

11.4.1 Identification of the manager and the location(s) for data processing

The data management will be realized in the DRCI of GHU Paris Psychiatrie et Neurosciences with Didier André and the statistical analysis will be done by Isabelle Dufaure-Gare.

11.4.2 Data entry

Data entry will be carried out on electronic media via a web browser connecting to the REDCAP server hosted at GHU Paris Psychiatrie et Neurosciences center

11.4.3 Data processing (CNIL, the French Data Protection Authority) in France

This research falls under the "Méthodologie de référence" (MR-001) according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978 relating to information technology, data files and privacy. This change was approved in a decision made on 5 January 2006. Le GHU Paris Psychiatrie et Neurosciences, the research sponsor, has signed a commitment to comply with this " Méthodologie de référence "

The processing of personal data for this research falls under the scope of the provisions of Articles 53 to 61 of the Law of 6 January 1978 relating to information technology, data files and privacy, modified by Law No. 0204-801 of 6 August 2004.

11.4.4 Archival

Specific documents for biomedical research relating to a medication for human use will be archived by the investigator and the sponsor for a period of 15 years after the end of the research.

This indexed archival includes, in particular:

- A sealed envelope containing the original copies of all information sheets and consent forms signed for all individuals at the centre that participated in the research for the investigator
- A copy of all the information notes and consent forms signed for all subjects at the centre that participated in the research for the sponsor
- "Research" binders for the Investigator and the sponsor, including:
  - the successive versions of the protocol (identified by the version no. and date), and the appendices
  - the ANSM authorisations and CPP favourable opinions

- letters of correspondence
- the inclusion list or register
- the appendices specific to the research
- the final research report

- The data collection documents

11.5 Ownership of the data

Le GHU Paris Psychiatrie et Neurosciences is the owner of the data, which cannot be used or disclosed to a third party without its prior approval.

12 STATISTICAL ASPECTS

12.1 Description of statistical methods to be used including the timetable for the planned interim analyses

CASH is a multicentre, double-blinded, randomised, placebo-controlled, parallel-group superiority trial in adult, using an adaptive group-sequential design, to demonstrate that cilostazol plus nimodipine is safe and superior to nimodipine alone will improve modified Ranking Score (mRS) at six months.

Two interim analyses for futility and efficacy are planned.

Populations

For the statistical analysis, the following populations are defined:

Population	Description
Intent-To-Treat (ITT) Population	The ITT population will include all randomised participants. ITT participants will be analysed according to the randomised treatment, regardless of the actual treatment received. All efficacy analyses will be performed on the ITT population.
Per Protocol (PP) Population	The PP population will include all participants in the ITT with at least 80% of doses received to define adherence to treatment. The PP population will be used for supportive analyses of efficacy measures.
Safety Population (SP)	The SP will include all randomised participants who received at least one treatment (active or placebo). The SP will be analysed according to the actual treatment received. This population will be used for safety analyses.

Description of the statistical methods, including the timing of planned interim analyses

The statistical analysis plan (SAP) will be developed and finalised before the database is locked.
Below is a description of the planned statistical analysis. Further details will be presented in the statistical analysis plan (SAP).
All statistical analyses will be performed with SPSS version 26 or RStudio. For analyses performed with RStudio, the script used will be provided.
The baseline is defined as the last evaluation performed before the start of the study treatment, day 1 (V1).
All data collected after the start of the study treatment are defined as post-baseline.

Baseline characteristics will be summarised by the treatment group. The mean and standard deviation (SD) or median and interquartile range (IQR) for skewed variables will be summarised for continuous measures.
The proportion in each category will describe categorical variables.
In addition, the 95% confidence interval (CI) will also be calculated as indicated.
All categorical variables will be summarised by treatment with numbers and percentages of participants.
All continuous variables, including changes from baseline, will be summarised by treatment with means, standard deviations or medians and interquartile range [IQR] for skewed variables.
The following formula will be used, depending on how the post-basal endpoint is defined, for each scheduled visit and for each time point at which both baseline and post-basal values are available:

- Change from baseline = post-baseline value - baseline value
- Percentage change from baseline = (post-baseline value - baselinevalue)/basal value*100%
- Ratio to baseline = post-baseline value / baseline value

Primary objective

The analysis of clinical effectiveness will be performed on the ITT population.
For the assessment of the primary objective, the percentage of patients who responded to treatment per experimental arm will be evaluated. Specifically, treatment will be considered effective when mRS at six months is ≤2.
Therefore, the treatment response variable will be dichotomised as follows
0 if the mRS is > 2 (non-responder patient)
1 if the the mRS value is ≤ 2 (responders).
A logistic regression model adjusted by centre, age (continuous), and severity at inclusion, considering the dichotomised value of the mRS (<=2, >2) as the response variable, and will be used. Consequently, the efficacy of the experimental treatment will be expressed as an adjusted Odds Ratio, and the 95% confidence interval and NNT index will be provided.
Sensibility analysis
The described analysis for the assessment of clinical efficacy will be repeated in the per-protocol population and after the replacement of missing data of mRS at six months, on the one hand, according to a "worst case scenario" logic and on the other hand, using multiple imputations.

Secondary efficacy analyses

Secondary analyses of clinical effectiveness will be performed on the ITT population. Analyses on per protocol population may be carried out.
A logistic regression model adjusted by centre, age (continuous) and severity at inclusion will be used considering the dichotomised mRS value at six months (≤1 versus >1).
The time-to-event variables will be analysed using the Cox proportional hazards model, including randomisation arm, age (as a continuous variable), severity at inclusion, and centre as model terms. The hazard ratio between the arms will be presented with the 95% CI and p-value of the model. Kaplan-Meier curves will be presented by the arm for each appropriate endpoint.
For the primary objective, both overall and by subgroups, the following statistics will be provided: effect size, confidence intervals, number needed to treat and absolute risk reduction as appropriate.
All tests will be two-sided with a unilateral significance level of 0.025% adjusted for the interim analysis.

Subgroup analyses

Subgroup analyses will be performed to assess the consistency of the treatment effect between subgroups without multiplicity adjustment. The following subgroups will be assessed for the primary endpoint:

- Fisher grade I to III versus IV
- Age: <50 years; >=50 and <=70 years; >70 years

The treatment effect for the total population and subgroups will be represented using forest plot graphs.
For HR and OR in subgroup analyses, the significance of the interaction will be tested using the method proposed by Altman & Bland 2003.

Treatment of missing data

For the analysis of the primary endpoint, in the event of study exit prior to evaluation of the primary endpoint (6 months), the last recorded mRS value will be used (LOCF method, mRS at ICU discharge) patients will be considered as non responders if no mRS are recorded.
For all other variables, in case of a significant proportion of missing data (>10% of subjects), a sensitivity analysis using multiple conditional imputation techniques by chained equations (MICE) will be performed, according to a conservative principle, using the mean severity at inclusion as the central position parameter and an estimate of the intra-patient variability in the placebo group as the dispersion parameter. Sensitivity analysis based on imputed data will be considered secondary.
Further details on the treatment of missing data will be provided in the SAP.

12.2 Definition of Estimands in the CASH Trial

We define two primary estimands corresponding to the intention-to-treat (ITT) and per-protocol (PP) analyses, as well as an additional estimand incorporating neurological mortality.

12.2.1 Primary Estimand – Intention-to-Treat (ITT) Analysis

This estimand aims to assess the effect of cilostazol added to nimodipine on the modified Rankin Scale (mRS) at 6 months, considering all randomized patients, regardless of intercurrent events.

- Target Population: All randomized patients.
- Variable of Interest: mRS at 6 months, dichotomized as favorable outcome (mRS 0-2) vs. unfavorable outcome (mRS 3-6).
- Handling of Intercurrent Events:
  - Early treatment discontinuation → "Treatment Policy" strategy: Patients remain in their randomized group, regardless of treatment adherence.
  - Death before 6 months → "Composite" strategy:
    - Neurological death → Counted as mRS=6.
    - Non-neurological death → Counted as mRS in ITT analysis and a secondary analysis excluding these patients.
  - Loss to follow-up → "Composite" strategy: Last observation carried forward (LOCF) with multiple imputation as a sensitivity analysis.
- Estimation Method: Logistic regression adjusted for age and initial severity (GCS grade) and centre.

🔷 Justification: This approach respects the ITT principle, ensures comparability between groups, and provides a realistic assessment of treatment effect.

12.2.2 Secondary Estimand – Per-Protocol (PP) Analysis

This estimand aims to measure the effect of cilostazol only in patients who completed the treatment without interruption.

- Target Population: Patients who received at least 80% of prescribed doses over the 14-day treatment period.
- Variable of Interest: mRS at 6 months (favorable vs. unfavorable) otherwise LOCF.
- Handling of Intercurrent Events:
  - Early treatment discontinuation → "Principal Stratum" strategy: Only patients who completed treatment are analyzed.
  - Death before 6 months → "Composite" strategy (mRS=6 if neurological, secondary analysis excluding non-neurological deaths).
- Estimation Method: Logistic regression model restricted to patients who completed treatment.

🔷 Justification: This analysis assesses the specific effect of cilostazol without treatment adherence interference.

12.2.3 Additional Estimand – Impact of Mortality on the Analysis

An additional estimand will be conducted to specifically evaluate the impact of neurological vs. non-neurological mortality:

- Target Population: All randomized patients.
- Variable of Interest: mRS at 6 months, considering:
  - mRS=6 for neurological deaths.
  - Exclusion of non-neurological deaths in a secondary analysis.

🔷 Justification: This analysis differentiates the specific effects of treatment on neurological mortality, which is crucial for interpreting the trial results.

12.3 Management of Intercurrent Events – Methodological Approach

In this trial, we do not anticipate the use of rescue therapy, nor the occurrence of an intercurrent event directly related to the drug. The selected strategies reflect this specificity.

Intercurrent Event	Strategy for ITT Estimand	Strategy for PP Estimand	Justification
Early treatment discontinuation	"Treatment Policy" – Analyze in randomized group	"Principal Stratum" – Exclude	Maintains comparability in ITT, assesses adherence in PP.
Neurological death	"Composite" – Counted as mRS=6	"Composite" – Counted as mRS=6	Maintains comparability between groups.
Non-neurological death	"Composite" – Sensitivity analysis	"Composite" – Sensitivity analysis	Excludes deaths unrelated to the study in a secondary analysis.
Loss to follow-up before 6 months	"Composite" – LOCF + Multiple Imputation	"Composite" – LOCF + Multiple Imputation	Reduces bias due to missing data.

12.4 Statistical Analysis and Sensitivity Tests

To ensure robust conclusions, we will apply multiple sensitivity analyses, in addition to ITT and PP analyses:

1. Complete Case Analysis (excluding patients with missing data).
2. Multiple Imputation of missing data to assess the impact of lost-to-follow-up cases.
3. Scenario analysis excluding non-neurological deaths.

Safety analysis

For each patient and each type of toxicity described according to the CTCAE (V.5.0), the worst-case category identified during treatment will be used for the descriptive analysis.

Safety Measures

Safety will be assessed using:

• Incidence of treatment-related adverse events (TEAEs)

• Incidence and severity of treatment-emergent adverse events (TEAEs)

• Incidence of serious adverse events (SAEs)

• Incidence of TEAEs and SAEs leading to discontinuation of study medication.

• Changes in blood chemistry, hematology and coagulation parameter results

• Changes in vital signs including temperature, pulse, respiratory rate, systolic and diastolic blood pressure

• Changes in physical examination results

• Changes in electrocardiogram (ECG) results

These data will be described using lists and tables.

12.5 Sample size estimation

To estimate the sample size, as no direct efficacy studies of cilostazol versus nimodipine or in combination with nimodipine versus placebo were available, a literature search was conducted to verify the possibility of performing a network meta-analysis that would allow an evaluation for indirect comparisons.
Reference is made to a network meta-analysis [Dayyany, 2022] on prophylactic therapies for cerebral vasospasm secondary to SAH.
The literature search of the referenced network meta-analysis stopped in February 2020; therefore, an update was performed on Medline according to the same strategies from February 2020 to December 2022.
Therefore, for the network meta-analysis, trials using nimodipine, cilostazol or fasudil (the usual comparator or in combination with cilostazol) as prophylaxis in at least one arm of the study were selected. Concerning the outcome as per the main objective of the CASH study (mRS assessed at six months, where the favourable outcome is defined as the mRS score of 0 to 2, and unfavourable outcome of 3 to 6) for the studies where the assessment was made using the GOSE, the results were converted as in Table 1. The meta-analysis was performed with MetaXL Version 5.3[1], a fixed-effects model was used, and the method for calculating the weighted average effect was the inverse of variance heterogeneity. The global heterogeneity of the model was assessed using the H inconsistency index [2].
The selected studies, the model description, and the results are reported in Appendix 8.

Table 1. GOSE vs mRS conversion table

Modified Rankin Scale (mRS)	Glasgow Outcome Scale (GOS)
0 - No symptoms. 1 - No significant disability. Able to carry out all usual activities, despite some symptoms. 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.	4 - Moderate disability 5 - Low disability
3 - Moderate disability. Requires some help, but able to walk unassisted. 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted. 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent. 6 - Dead.	1 - Death 2 - Persistent vegetative state 3 - Severe disability

A total of 9 studies with a cumulative number of 1732 patients were included in the network meta-analysis; the details are given in Table 2.

Table 2: Trials selected for network meta-analysis and events for each study arm favourable outcome at the longest follow-up

			Active			Control		
Active	**Control**	**Study name**	**Nb**	**Cases**	**Non-cases**	**Nb**	**Cases**	**Non-cases**
Nimodipina	Placebo	Petruk,1988	72	28	44	82	28	54
Nimodipina	Placebo	Pickard, 1989	278	223	55	276	185	91

Nimodipina	Placebo	Ohman, 1991	104	86	18	109	86	23
Fasudil	Placebo	Shibuya, 1992	136	98	38	136	95	41
Fasudil	Nimodipina	Zhao, 2006	33	27	6	34	28	6
Fasudil plus Nimodipine	Nimodipina	Zhao_2, 2011	55	49	6	60	48	12
Cilostazol plus Fasudil	Fasudil	Suzuki, 2011	49	39	10	51	24	27
Cilostazol plus Fasudil	Fasudil	Sembukuya, 2013	54	39	15	55	36	19
Cilostazol	Placebo	Matsuda, 2016	74	60	14	74	61	13
			855	**649**	**206**	**877**	**591**	**286**

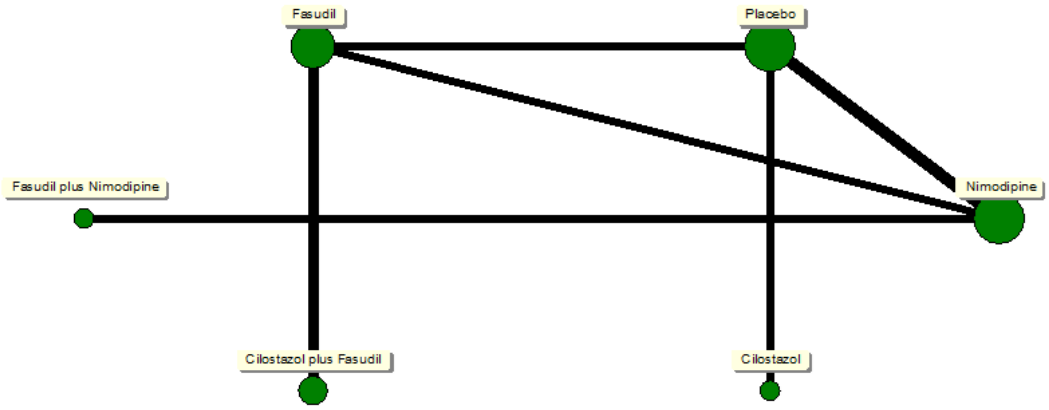

Figure 1. Network plot

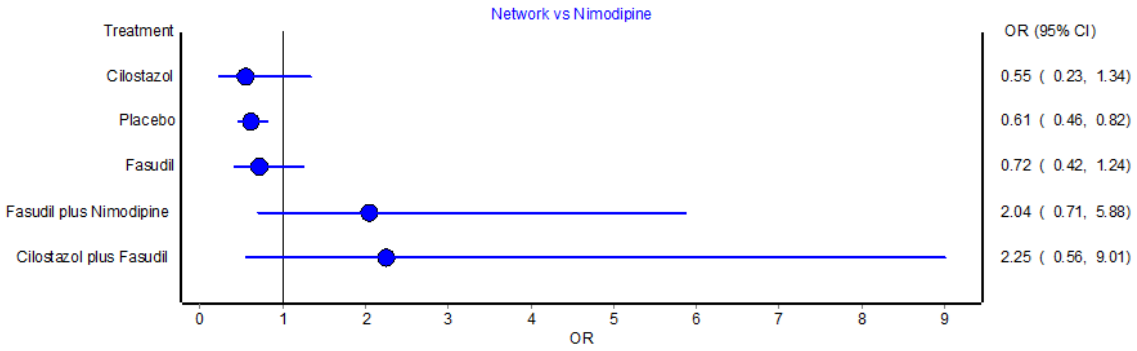

Figure 2. Forest plot

The network meta-analysis versus nimodipine, where the outcome is the patient's status at at the longest follow-up, shows a non-inferiority of fasudil versus nimodipine (OR=0.720; 95% CI unilateral lower bound =0.050).

The efficacy trend of the combination of fasudil plus cilostazol (OR= 2.25; 95% CI unilateral lower bound=0.705) and fasudil plus nimodipine (OR=2.04; 95% CI unilateral lower bound=0.840) compared to treatment with nimodipine alone appears to be sharper.

Considering that in both Japan and China, the standard prophylaxis after SAH is fasudil or fasudil plus cilostazol, considering only trials evaluating combination versus monotherapy with nimodipine or fasudil, the greater efficacy of combination therapy is apparent.
The results of the meta-analysis and the forest plot are reported below. A low heterogeneity was found (I2=0.45; p=0.16); therefore, the inverse variance heterogeneity model was applied (Doi, 2015)

Study	OR	LCI 95%	UCI 95%	Weight (%)
Zhao, 2011 (fasudil plus nimodipine vs nimodipine)	2.042	0.709	5.880	24.322
Suzuki, 2011 (fasudil plus cilostazol vs fasudil)	4.388	1.809	10.641	34.665
Sembukuya, 2013 (fasudil plus cilostazol vs fasudil)	1.372	0.608	3.099	41.013
Pooled	2.261	1.108	4.614	100.000
Statistics				
I-squared	44.9			
Cochran's Q	3.63			
Chi2, p	0.163			

In light of the results obtained for the sample size estimation, an OR between the two arms of 1.86 is assumed as a precaution. This assumption sets the proportion of patients who will obtain a favourable outcome in the control arm at 65% and the proportion of responders in the experimental arm at least 76%. These proportions may appear high, but it should be noted that the study does not include patients with early death and without surgery.
The experimental design includes two intermediate analyses; a sequential group test and the O'Brian-Fleming Analog spending function for alpha and beta errors were used.
Therefore set unilateral alpha at 0.025 and the power of the test (1-beta) at 0.80, 284 patients are needed per experimental arm; details are given in table 3 and figure 1.
A drop-out rate of no more than 10% is expected so that the sample size will be 630 patients (315 per experimental arm).
All estimates for the interim analyses are made without considering the inflation quota for drop-out patients. Therefore this evaluation will be made at the planned number of patients who completed the study. Only the final analysis will bear any inflationary share of the sample.

Table 3. Summary Report - ——————————————————————————————

Item	Value
Maximum Number of Stages (Design):	3
Current Stage:	0
Alternative Hypothesis:	P1 - P2 < 0 (one-sided)
Alpha Spending Function:	O'Brien-Fleming Analog
Beta Spending Function:	O'Brien-Fleming Analog
Futility Boundaries:	Binding
Target Alpha:	0.025
Alpha (from simulations):	0.025
P1:	0.65
P2:	0.76
N1 (if final stage reached):	284
N2 (if final stage reached):	284
Target Power:	0.8
Power (from simulations):	0.8016
Maximum Information:	692.8

Information Report
Maximum Information: 692.8519
Alternative Hypothesis: P1 - P2 < 0 (one-sided)
Alpha: 0.0250

Stage	Target information proportion	Target sample size N1	Target sample size N2	P1	P2
1	0.33	95	95	0.65	0.76
2	0.67	189	189	0.65	0.76
3	1.00	284	284	0.65	0.76

Alpha Spending
Target Final Stage Alpha: 0.0250
Spending Function: O'Brien-Fleming Analog

Stage	Information proportion	Alpha spent this stage	Cumulative alpha spent	Percentage alpha spent at this stage	Cumulative percentage
1	0.33	0.0001	0.0001	0.4	0.4
2	0.67	0.0059	0.0060	23.8	24.2
3	1.00	0.0190	0.0250	75.8	100.0

Beta Spending for Futility
Target Cumulative Beta at Final Stage: 0.2000
Spending Function for Futility: O'Brien-Fleming Analog

Stage	Information proportion	Beta spent this stage	Cumulative beta spent	Percentage beta spent at this stage	Cumulative percentage
1	0.33	0.0264	0.0264	13.2	13.2
2	0.67	0.0901	0.1165	45.7	58.3
3	1.00	0.0835	0.2000	41.7	100.0

Boundary Probabilities for δ = -0.11
Number of Simulations: 100000
Futility Boundaries: Binding
After Efficacy Boundary Crossing: Hold Out
After Binding Futility Boundary Crossing: Hold Out
Alternative Hypothesis: P1 - P2 < 0 (one-sided)
P1: 0.65
P2: 0.76
δ: -0.11

Stage	N1	N2	Efficacy		Futility	
			Boundary	Probability	Boundary	Probability
1	95	95	-3.7103	0.0253	0.2701	0.0277
2	189	189	-2.5111	0.4166	-1.1224	0.0885
3	284	284	-1.9308	0.3597	-1.9308	0.0821

Average N1: 226.
Average N2: 226

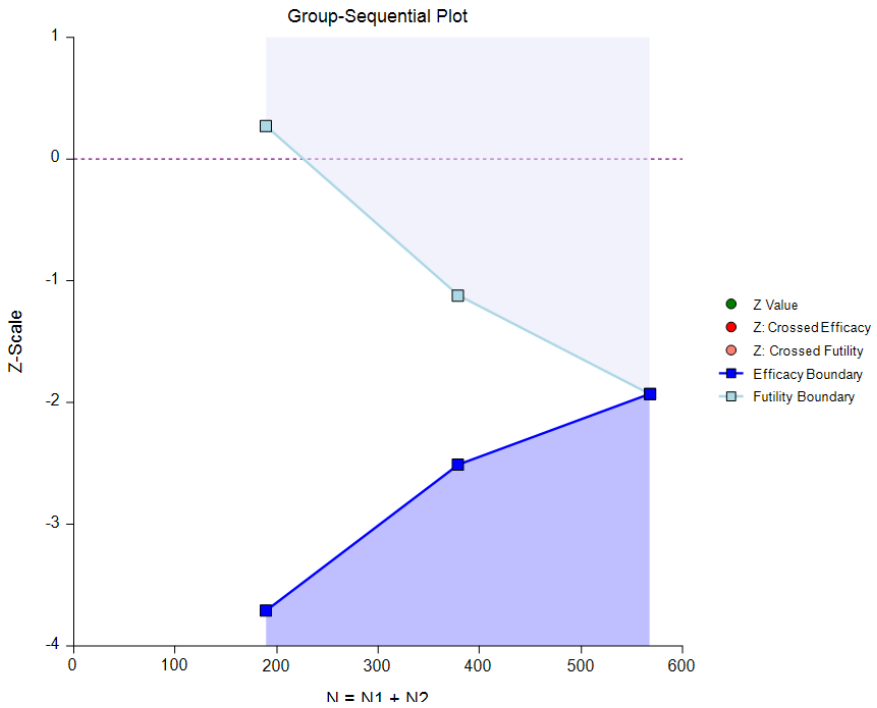

Figure 1.

12.6 Specify if subjects who leave the research prematurely will be replaced and in what proportion.

The primary outcome is assessed only one time 6 months after Day 0 (5 months and a half after last day of treatment) that could lead to patient's loss to follow up. Nevertheless, SAH is a serious condition that requires a long and close patient's monitoring. That will limit patient's loss to follow up. The patients who leave study prematurally (for loss to follow up or death) won't be replaced and will be considered as non responder patients in the main analysis of primary criterion.
Some sensitivity analyses will be performed with complete cases only.
Only, the particular circumstance of patient resignation will lead to exit patient of the primary analysis. A 10% rate of non evaluable patients is foreseen.

12.7 Interim analysis

The group-sequential study design provided two interim analyses when 190 and 378 patients completed the study. Figure 2 shows the stopping limits for the first interim analysis.

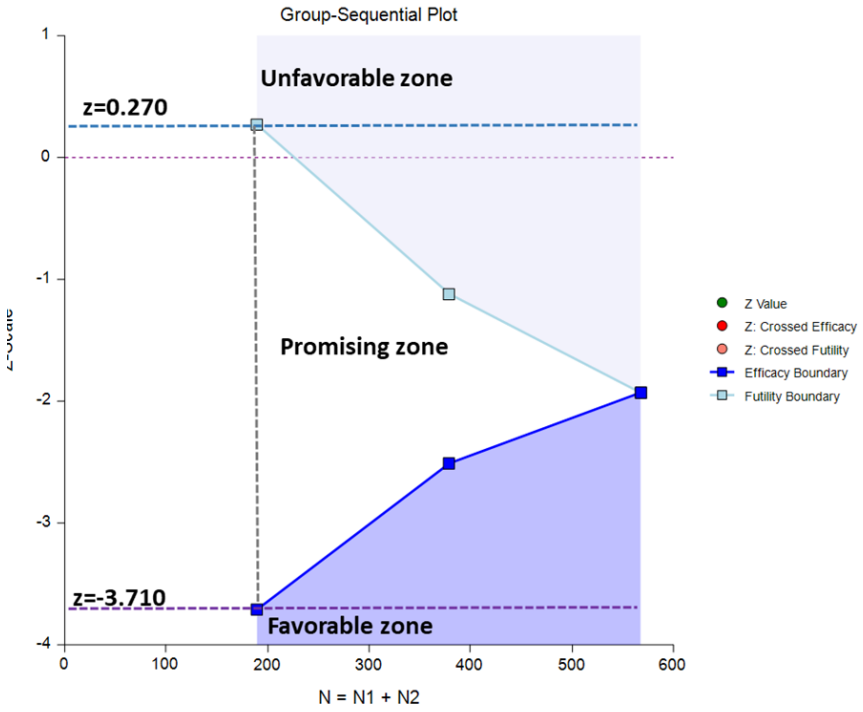

Figure 2.

Three conditions will be possible:

- Z-statistics in the favorable zone: stop for efficacy (z<=-3.710)
- Z-statistics in the unfavorable zone: stop for futility (z>=0.270)
- Z-statistics in the promising zone (z>-3.710 and <0.270)

For the first interim analysis, only the conditions of futility and efficiency will be verified. A blinded statistical analysis of the study objective will be carried out and provided to the BMDC, which will advise on the continuation of the study.

Figure 3 shows the stopping limits and the conditions for adaptive re-estimation of the sample size for the second interim analysis.

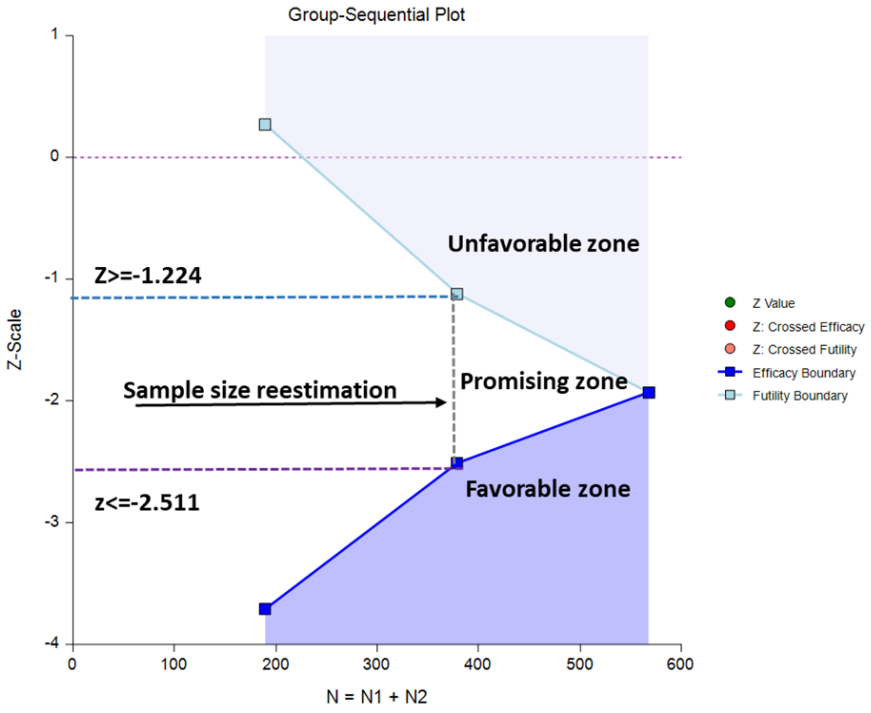

Figure 3.

Three conditions will be possible:

- Z-statistics in the favorable zone: stop for efficacy (z<=-2.511)
- Z-statistics in the unfavorable zone: stop for futility (z>=-1.224)
- Z-statistics in the promising zone (z>-2.511 and <-1.224)

A blinded statistical analysis of the study objective will be carried out and provided to the IMDC, which will advise on the continuation of the study.

Regarding the possibility of falling into the promising zone and considering clinically valid increase in patients with a favourable outcome compared to the control arm of at least 8 percentage points (NNT@12), two simulations with 100,000 samples were performed.

First, given the sample size (630 patients), the response rate in the control group was from 0.68 to 0.70, and the response rate in the experimental group was fixed at 0.76; the boundary equal to -1.9308 as the O'Brian-Fleming expenditure function for the third interim analysis; solving then for beta (Table 4 shows the simulation plan).

Table 4. Simulation Design for the last look

Scenario	Power	N1	N2	Alpha	Responders control	Responders treatment
1	0.580	315	315	0.025	0.68	0.76
2	0.477	315	315	0.025	0.69	0.76
2	0.379	315	315	0.025	0.70	0.76

The second simulation, with the same sample size and the same boundary, but in this case, varying the response rate in the experimental group (from 0.76 to 0.70) and response rate in the control group fixed at 0.65 (Table 3 shows the simulation plane)

Table 4. Simulation Design for the last look

Scenario	Power	N1	N2	Alpha	Responders control	Responders treatment
1	0.556	315	315	0.025	0.65	0.73
2	0.656	315	315	0.025	0.65	0.74
2	0.753	315	315	0.025	0.65	0.75

Should one of the scenarios occur, a new sample size estimate will be possible. A conditional power analysis for the emerging z-value will be performed and provided to the IDMC.

Independent Data Monitoring Committee (IDMC)

An independent Data Monitoring Committee (IDMC) will closely review the safety data and efficacy of the interim analysis and provide recommendations for the continuation of the study. The IDMC will be composed of at least three members, of which at least one will be a specialist in the domain of neurology and at least one in the domain of reanimation and a methodologist. The members of the IDMC will be appointed before the protocol is submitted to the ethics committee for final approbation.

13 QUALITY CONTROL AND ASSURANCE

Each biomedical research project managed by Le GHU Paris Psychiatrie et Neurosciences is ranked from A to D according to the projected risk incurred by research subjects using the classification of biomedical research sponsored by Le GHU Paris Psychiatrie et Neurosciences

13.1 General organisation

The sponsor must be responsible for the safety and respect of those subjects who have agreed to participate in the research. The sponsor must implement a quality assurance system to best monitor the conduct of the research in the investigation centres.

For this purpose, the sponsor shall delegate Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the research locations, after having carried out initial visits.

The objectives of monitoring the research, as defined in the French Good Clinical Practices (BPC section 5.18.1), are to verify that:

- the rights, safety and protection of the research subjects are met
- the data reported is exact, complete and consistent with the source documents
- the research is carried out in accordance with the protocol in force, with the French GCPs and with the legislative and regulatory provisions in force

13.1.1 Strategy for opening the centres

The strategy for opening the centres established for this research is determined using the appropriate monitoring plan. All centres will be opened simultaneously.

13.1.2 Level of centre monitoring

In the case of this research, which is considered an intermediate risk, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the research. Thus, the sponsor and the coordinating investigator have agreed on the logistic score and impact, resulting in a research monitoring level to be implemented: level C.
Mandatory elements concerning patients' consent will be fully monitored. As the main endpoint is of primarily importance, its level of monitoring will be 100%. Considering a C level of risk, which is considered intermediate, the level of monitoring for the safety data will be 100%. Other data concerning secondary outcomes will be telemonitored and 25% will be monitored fully.

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper conduct of the research, for collecting and documenting, recording and reporting the data generated in writing, in accordance with the Standard Operating Procedures applied within the DRCI and in accordance with the French Good Clinical Practices as well as with the legislative and regulatory provisions in force.

The investigator and the members of the investigator's team agree to make themselves available during Quality Control visits carried out at regular intervals by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent
- compliance with the research protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

13.3 Case Report Form

All information required according to the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Each missing data item must be coded.
This digital case report form will be implemented in each centre thanks to a web-based data collection medium. Investigators will be given a document offering guidance in using this tool. When the investigators complete the case report via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. Thus, the investigator must validate any changes to the values in the case report form. These modifications will be subject to an audit trail. A justification can be added when applicable, as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the research. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance, by the investigator or any other individual involved in conducting the research, with the protocol, with the standard operating procedures, with the good clinical practices or with the legislative and regulatory provisions in force must be noted in a declaration of non-compliance addressed to the sponsor. As a first step, major or critical non-compliances will be reviewed and processed by the DRCI's medical coordinator in order to implement the necessary corrective or preventive actions. Next, the non-compliances will be sent to the Quality - Risk Management Division of the DRCI for verification and analysis. These verifications could result in the investigator in charge of the research location in question being asked for information or could lead to compliance or audit visits.

13.5 Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. Medical secrecy cannot be invoked in opposition to these audits and inspections.

An audit can be carried out at any time by individuals appointed by the sponsor and who are not associated with the research directors. The objective of the audit is to ensure the quality of the research, the validity of the results and compliance with the legislation and regulations in force.

The individuals who lead and monitor the research agree to comply with the sponsor's requirements and with the competent authority regarding research audits or inspections.

The audit may be applicable to all stages of the research, from the development of the protocol to the publication of the results and the organisation of the data used or produced as part of the research.

13.6 Primary investigator's commitment to assume responsibility

Before starting the research, each investigator will give the sponsor’s representative a copy of his/her personal curriculum vitæ, signed and dated, with his/her number in the RPPS (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will undertake to comply with the legislation and to carry out the research according to French GCP, adhering to the Declaration of Helsinki terms in force.

The primary investigator at each participating centre will sign a responsibility commitment (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their employees will sign a delegation of duties form specifying each person's role.

13.7 Pharmacist's commitment to assume responsibility

Each pharmacist will be responsible for the reception, the good storage and management of the experimental treatment according to the pharmacy manual (standard DRCI document). The employees of the parhamcy involve in the study, will sign a delegation of duties form specifying each person’s role.

14 ETHICAL AND LEGAL CONSIDERATIONS

This research will also be conducted in accordance with European laws and regulations, the principles of the World Medical Association (WMA) Declaration of Helsinki, established by the 18th WMA Assembly (Helsinki, 1964) and subsequent amendments, and current ICH GCP guidelines. It will be registered in European Medicines Agency (EMA) databases and other sites as appropriate, including the US Food & Drug Administration (FDA - clinicaltrials.gov) clinical trials database

14.1 Methods for obtaining information and consent from research participants

In accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research can be carried out on a person without free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code.

The informed consent will be obtained in the inclusion visit carried out by a physician who is part of the research team, in each participating centre. Consent could be obtained from the patient, or from a relative if the patient is unable to consent, or using the emergency clause according to French Law if no relative could be present within 24 hours. This third party must have no association with the investigator or with the sponsor If the patient was unable to consent, a pursuit consent will be sought as soon as the patient will be able to express its wills.

The subject will be granted a reflection period of 2 hours between the time when the subject receives the information and the time when he or she signs the consent form.

The information sheet and a copy of the consent form, signed and dated by the research subject and by the investigator or the doctor representing the investigator, are given to the individual prior to his or her participation in the research.

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining his or her consent or from his relative according to article L. 1122-1-1 à L. 1122-2 du CSP as well as the methods used for providing information with the goal of obtaining their consent. The investigator will retain the original signed and dated copy of the subject's consent form.

14.2 Subject prohibited from participating in another research or an exclusion period **anticipated after the research, if applicable**

The exclusion period specified for this is 6 months as the main outcome is collected at 6 months

During this period, the subject may not participate in other biomedical research protocols relating to medications until after 6 months, patients can nevertheless participate to observational protocol.

14.3 Legal obligations

14.3.1 The sponsor's role

GHU Paris Psychiatrie et Neurosciences is the sponsor of this research and by delegation, the Clinical Research and Innovation Office (DRCI) carries out the research's missions in accordance with Article L.1121-1 of the French Public Health Code. GHU Paris Psychiatrie et Neurosciences reserves the right to halt the research at any time for medical or administrative reasons. In this case, notification will be sent to the investigator

14.4 Request for an opinion from the Comité de Protection des Personnes (CPP, ethical review board)

Le GHU Paris Psychiatrie et Neurosciences, as sponsor, obtains for this biomedical research relating to a medication for human use and prior to starting the research, the favourable opinion of the appropriate CPP, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

14.5 Request for authorisation to ANSM

Le GHU Paris Psychiatrie et Neurosciences, as sponsor, obtains for this biomedical research relating to a medication for human use and prior to starting the research, authorisation from the ANSM, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

14.6 Commitment to compliance with the MR 001 "Méthodologie de Reference"

14.7 Le GHU Paris Psychiatrie et Neurosciences, the research sponsor, has signed a commitment to comply with this "Méthodologie de reference".

14.8 Standard declaration to the CNIL

This is a multicentric research taking place in 9 hospitals, Le GHU Paris Psychiatrie et Neurosciences as sponsor of the research will make a standard declaration to the CNIL.

14.9 Modifications to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to starting the research, a favourable opinion from the CPP and authorisation from the ANSM within the scope of their respective authorities.
The information sheet and the consent form can be revised if necessary, in particular if there is a substantial modification to the research or if adverse reactions occur.

14.10 Final research report

The final biomedical research report referred to in Article R1123-60 of the French Public Health Code is drawn up and signed by the sponsor and the investigator. A summary of the report written according to the competent authority's reference plan will need to be sent to the competent authority and ethical review board within one year after the end of the research, meaning the end of the participation of the last research subject.

15 FUNDING AND INSURANCE

15.1 Funding source

PHRC is the only funding office seeken for this trial. No complementary industrial funding is available at that time.

15.2 Insurance

For the duration of the research, the Sponsor will take out an insurance policy covering the sponsor's own civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide full compensation for all harmful consequences of the research for the research subjects and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the research cannot be invoked against said compensation.

Le GHU Paris Psychiatrie et Neurosciences has taken out insurance from Relyens Mutual Insurance (contract n°163543) located to 18 rue Edouard Rochet 69372 Lyon cedex 08for the full research period, covering its own civil liability and that of any agent (doctor or research staff), in accordance with Article L.1121-10 of the French Public Health Code.

16 PUBLICATION RULES

- A study group will be constituted for the publication. The main investigator will be listed as first author, the methodologist as second author, the scientific advisor last author, the investigators will be listed individually in order of inclusions number

16.1 Mention of the affiliation of Le GHU Paris Psychiatrie et Neurosciences for projects sponsored or managed by Le GHU Paris Psychiatrie et Neurosciences

- "The sponsor was Le GHU Paris Psychiatrie et Neurosciences (Délégation à la Recherche Clinique et à l'Innovation)"

16.2 Mention of the Le GHU Paris Psychiatrie et Neurosciences manager (DRCI) in the acknowledgements of the text

- "The sponsor was Le GHU Paris Psychiatrie et Neurosciences (Délégation à la Recherche Clinique et à l'Innovation)"

16.3 Mention of the financier in the acknowledgements of the text

- The research was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2023 (Ministère de la Santé)

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18 LIST OF ADDENDA

18.1 List of Investigators

National multicenter research

18.2 Form for reporting Serious Adverse Events

eCRF

18.3 Questionnaire or scale

Appendix 1 Modified Rankin with Structured Interview

The Modified Rankin Scale and Corresponding Sections of the Structured Interview

Modified Rankin Scale[3]	Structured Interview for the Modified Rankin Scale
5=Severe disability: bedridden, incontinent, and requiring constant nursing care and attention.	5=Severe disability; someone needs to be available at all times; care may be provided by either a trained or an untrained caregiver. Question: Does the person require constant care?
4=Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance.	4=Moderately severe disability; need for assistance with some basic ADL, but not requiring constant care. Question: Is assistance essential for eating, using the toilet, daily hygiene, or walking?
3=Moderate disability; requiring some help, but able to walk without assistance.	3=Moderate disability; need for assistance with some instrumental ADL but not basic ADL. Question: Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally?
2=Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.	2=Slight disability; limitations in participation in usual social roles, but independent for ADL. Questions: Has there been a change in the person's ability to work or look after others if these were roles before stroke? Has there been a change in the person's ability to participate in previous social and leisure activities? Has the person had problems with relationships or become isolated?
1=No significant disability despite symptoms; able to carry out all usual duties and activities.	1=No significant disability; symptoms present but not other limitations. Question: Does the person have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or coordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptom resulting from stroke?
0=No symptoms at all.	0=No symptoms at all; no limitations and no symptoms.

Pace A *et al* 2018: //doi.org/10.1093/brain/awy003

SAHOT
SubArachnoid Haemorrhage Outcome Tool

This form is designed to assess recovery following subarachnoid hemorrhage at this moment in time. The patient and their next of kin should fill in separate forms without consulting each other.

- **Please think back to how things were BEFORE the bleed, and compare this to how the following aspects of daily life are NOW (i.e. this week).**
- **Please circle the response that best describes this CHANGE for each aspect.**
- **If you have not yet tried an activity, or are unsure if you would be able to undertake a task, circle "large/severe change" for the purposes of this questionnaire.**
- **If you did not do an activity before the bleed, please select "N/A".**

Appendix 2 Subarachnoid hemorrhage outcome tool

SAHOT: SubArachnoid Haemorrhage Outcome Tool

Pace A *et al* 2018: //doi.org/10.1093/brain/awy003

1. General Aspects of Daily Life

OVERALL FUNCTION	No change	Some change	Large or severe change	N/A
Physical activities of daily life *(e.g. walking, climbing stairs)*	No change	Some change	Large or severe change	N/A
Socializing *(with people other than colleagues/family)*	No change	Some change	Large or severe change	N/A
Pursuing previous hobbies	No change	Some change	Large or severe change	N/A
Household chores	No change	Some change	Large or severe change	N/A
Days / evenings out	No change	Some change	Large or severe change	N/A
Quality of relationship with those closest	No change	Some change	Large or severe change	N/A
Tick if relationship is now better [ ] or worse [ ]				
Quality of relationships with others	No change	Some change	Large or severe change	N/A
Doing things on one's own *(e.g. shopping, going out)*	No change	Some change	Large or severe change	N/A
Coping in crowded, busy or noisy places	No change	Some change	Large or severe change	N/A
Sleep pattern *(day or night)*	No change	Some change	Large or severe change	N/A

SAHOT: SubArachnoid Haemorrhage Outcome Tool

Pace A *et al* 2018: //doi.org/10.1093/brain/awy003

Sex life	No change	Some change	Large or severe change	N/A
Basic self care *(e.g. ability to wash, dress)*	No change	Some change	Large or severe change	N/A
Recreational exercise	No change	Some change	Large or severe change	N/A

2. Physical Aspects

Physical fatigue / tiredness *(i.e. how much one can do before needing to stop to rest)*	No change	Some change	Large or severe change	N/A
Balance when walking	No change	Some change	Large or severe change	N/A
Clumsiness *(change in handwriting, difficulty with cutlery, knocking things over)*	No change	Some change	Large or severe change	N/A
Falls *(including trips / stumbling)*	No change	Some change	Large or severe change	N/A
Strength / coordination in arms and hands	No change	Some change	Large or severe change	N/A
Strength / coordination in legs	No change	Some change	Large or severe change	N/A
Pain	No change	Some change	Large or severe change	N/A
Urinary continence	No change	Some change	Large or severe change	N/A

Vision (excluding changes in prescription of glasses)	No change	Some change	Large or severe change	N/A
Hearing	No change	Some change	Large or severe change	N/A
Smell / taste	No change	Some change	Large or severe change	N/A
Swallowing food or water	No change	Some change	Large or severe change	N/A
Word finding when speaking	No change	Some change	Large or severe change	N/A

3. Cognitive Aspects

Mental fatigue *(i.e. tiredness with mental tasks)*	No change	Some change	Large or severe change	N/A
Short-term memory	No change	Some change	Large or severe change	N/A
Long-term memory *(i.e. remembering things that happened years ago)*	No change	Some change	Large or severe change	N/A
Learning a new skill	No change	Some change	Large or severe change	N/A
Concentration	No change	Some change	Large or severe change	N/A
Distractibility	No change	Some change	Large or severe change	N/A

Multitasking *(i.e. doing two or more things at the same time)*	No change	Some change	Large or severe change	N/A
Remembering names of familiar people	No change	Some change	Large or severe change	N/A
Recognising faces	No change	Some change	Large or severe change	N/A
Ability to get a point across in conversation	No change	Some change	Large or severe change	N/A
Ability to compromise in discussion with others	No change	Some change	Large or severe change	N/A
Ability to recognise danger	No change	Some change	Large or severe change	N/A
Navigational skills *(i.e. getting lost)*	No change	Some change	Large or severe change	N/A

4. Behavioural / Psychological Aspects

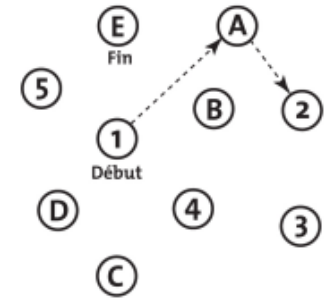
Low mood	No change	Some change	Large or severe change	N/A
Mood swings	No change	Some change	Large or severe change	N/A
Strength of emotions	No change	Some change	Large or severe change	N/A
Easily moved to tearfulness or laughter	No change	Some change	Large or severe change	N/A

Ability to control one's reactions	No change	Some change	Large or severe change	N/A
Irritability	No change	Some change	Large or severe change	N/A
Anxiety	No change	Some change	Large or severe change	N/A
Feelings of fear	No change	Some change	Large or severe change	N/A
Feelings of paranoia	No change	Some change	Large or severe change	N/A
Agitation	No change	Some change	Large or severe change	N/A
Restlessness *(inability to stand still)*	No change	Some change	Large or severe change	N/A
Self-confidence	No change	Some change	Large or severe change	N/A
Awareness of others' thoughts, feelings and/or needs	No change	Some change	Large or severe change	N/A
Motivation	No change	Some change	Large or severe change	N/A
Feeling comfortable in new environments	No change	Some change	Large or severe change	N/A
Apathy	No change	Some change	Large or severe change	N/A

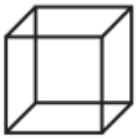
Appendix 3 MOCA Score

MONTREAL COGNITIVE ASSESSMENT (MOCA) NOM :
Version 7.1 **FRANÇAIS** Scolarité : Date de naissance :
Sexe : DATE :

VISUOSPATIAL / ÉXÉCUTIF — POINTS



Copier le cube



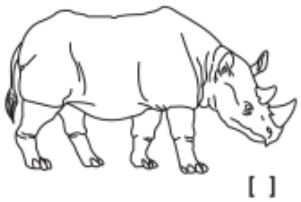
[ ] [ ]

Dessiner HORLOGE (11 h 10 min) (3 points)

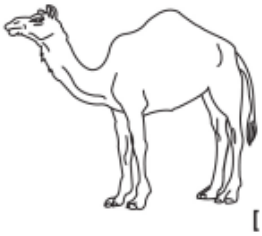
[ ] Contour [ ] Chiffres [ ] Aiguilles __/5

DÉNOMINATION

[ ]



[ ]



[ ] __/3

MÉMOIRE Lire la liste de mots, le patient doit répéter. Faire 2 essais même si le 1er essai est réussi. Faire un rappel 5 min après.

	VISAGE	VELOURS	ÉGLISE	MARGUERITE	ROUGE
1er essai					
2ème essai					

Pas de point

ATTENTION Lire la série de chiffres (1 chiffre/ sec.). Le patient doit la répéter. [ ] 2 1 8 5 4
Le patient doit la répéter à l'envers. [ ] 7 4 2 __/2

Lire la série de lettres. Le patient doit taper de la main à chaque lettre A. Pas de point si 2 erreurs
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Soustraire série de 7 à partir de 100. [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 ou 5 soustractions correctes : **3 pts**, 2 ou 3 correctes : **2 pts**, 1 correcte : **1 pt**, 0 correcte : **0 pt** __/3

LANGAGE Répéter : Le colibri a déposé ses œufs sur le sable . [ ] L'argument de l'avocat les a convaincus. [ ] __/2

Fluidité de langage. Nommer un maximum de mots commençant par la lettre «F» en 1 min [ ] ____ (N≥11 mots) __/1

ABSTRACTION Similitude entre ex : banane - orange = fruit [ ] train – bicyclette [ ] montre - règle __/2

RAPPEL

	Doit se souvenir des mots	VISAGE	VELOURS	ÉGLISE	MARGUERITE	ROUGE	Points pour rappel SANS INDICES seulement
	SANS INDICES	[ ]	[ ]	[ ]	[ ]	[ ]	
Optionnel	Indice de catégorie						
	Indice choix multiples						

__/5

ORIENTATION [ ] Date [ ] Mois [ ] Année [ ] Jour [ ] Endroit [ ] Ville __/6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30
Ajouter 1 point si scolarité ≤ 12 ans

Administré par : _____

Appendix 4 Activities of a daily living

24.10.2001

ECHELLE D'AUTONOMIE DE KATZ (A.D.L.)

(S'informer auprès de l'infirmière et de l'Aide-Soignante).

NOM : **Prénom :** **Date de naissance :**

ECHELLE A.D.L (Aide-soignante Infirmière)	1ère évaluation Date : Score:	2ème évaluation Date : Score:	3ème évaluation Date : Score:
HYGIENE CORPORELLE			
. autonomie	1	1	1
. aide	½	½	½
. dépendant(e)	0	0	0
HABILLAGE			
. autonomie pour le choix des vêtements et l'habillage	1	1	1
. autonomie pour le choix des vêtements, l'habillage mais a besoin d'aide pour se chausser	½	½	½
. dépendant(e)	0	0	0
ALLER AUX TOILETTES			
. autonomie pour aller aux toilettes, se déshabiller et se rhabiller ensuite	1	1	1
. doit être accompagné(e) ou a besoin d'aide pour se déshabiller ou se rhabiller	½	½	½
. ne peut aller aux toilettes seul(e)	0	0	0
LOCOMOTION			
. autonomie	1	1	1
. a besoin d'aide	½	½	½
. grabataire	0	0	0
CONTINENCE			
. continent(e)	1	1	1
. incontinence occasionnelle	½	½	½
. incontinent(e)	0	0	0
REPAS			
. mange seul(e)	1	1	1
. aide pour couper la viande ou peler les fruits	½	½	½
. dépendant(e)	0	0	0
TOTAL			

Département de Gérontologie – Hôpital NORD – CEBAZAT – CHU CLERMONT-FERRAND.

Appendix 5 Instrumental activities of a daily living

I.A.D.L (INSTRUMENTAL ACTIVITIES OF DAILY LIVING)

OBJECTIF
Les 4 items de l'échelle I.A.D.L de Lawton permettent de dépister les sujets qui présentent une démence non encore diagnostiquée, ou qui la développeront dans l'année.
DESCRIPTIF
Ces 4 items explorent l'autonomie ou le degré de dépendance du sujet par rapport à 4 activités pratiques de la vie quotidienne.

Ces 4 activités doivent faire l'objet d'une cotation de 1 à 2, 3, 4 ou 5 points selon les items. Vous devrez pour chaque item attribuer le score en fonction de la grille de cotation (ci dessous). La cotation est basée sur les réponses du patient et/ou en tenant compte de l'avis de la personne vivant avec lui au quotidien. Dans un deuxième temps, pour fonder votre décision pratique, vous simplifierez la cotation de chacun des items en codage binaire 0 ou 1.
Codez 0 : tout item pour lequel le sujet est autonome (la cotation ne dépasse pas 1).
Codez 1 : tout item pour lequel le sujet est dépendant (la cotation est supérieure ou égale à 2)

CAPACITE A UTILISER LE TELEPHONE... 0=autonome, 1=dépendant

1. **Je me sers du téléphone de ma propre initiative, cherche et compose les numéros, etc.**
2. **Je compose un petit nombre de numéros bien connus.**
3. **Je réponds au téléphone, mais n'appelle pas.**
4. **Je suis incapable d'utiliser le téléphone.**

MOYEN DE TRANSPORT 0=autonome, 1=dépendant

1. **Je peux voyager seul(e) et de façon indépendante (par les transports en communs ou avec ma propre voiture)**
2. **Je peux me déplacer seul(e) en taxi, mais pas en autobus.**
3. **Je peux prendre les transports en commun si je suis accompagne(e)**
4. **Je ne me déplace pas du tout.**

PRISE DE MEDICAMENTS 0=autonome, 1=dépendant

1. **Je m'occupe moi-même de la prise (dose et horaires)**
2. **Je peux les prendre moi-même, s'ils sont prépares et doses a l'avance.**
3. **Je suis incapable de les prendre moi-même.**

GERER SON ARGENT 0=autonome, 1=dépendant

1. **Je suis totalement autonome (budget, chèques, factures)**
2. **Je me débrouille pour les dépenses au jour le jour, mais j'ai besoin d'aide pour gérer mon budget a long terme.**
3. **Je suis incapable de gérer l'argent nécessaire a payer mes dépenses au jour le jour.**

RESULTATS

- 3 ou 4 items sont codes 1 : diagnostic de maladie probable
- 1 ou 2 items sont codes 1 :
  - *si la modification est intervenue dans l'année, envisager un Alzheimer*
  - *si la modification n'est pas intervenue dans l'année :*
    - il y a une plainte mnésique : envisager un Alzheimer
    - pas de plainte mnésique : refaire le test l'année suivante

Appendix 6 Charlson Score

Table 1. Charlson Comorbidity Index Scoring System

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.
Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Appendix 7 Therapy intensity level

TIL 0: No specific ICP directed therapy
TIL 1 – basic ICU care :
- Sedation for ventilator/endotracheal tube tolerance
- Volume/vasopressors for non-CNS cause (e.g. sepsis, myocardial injury)
- Head up positioning (ventilator bundle)
- Normocapnia ($PaCO_2$ ≥ 40mmHg)

TIL 2 – Mild :
- Higher levels of sedation
- Vasopressors/volume for CPP support
- Low dose osmotic therapy
- Mild hypocapnia ($PaCO_2$ 4.6-5.3 kPa; 35-40 mmHg)
- CSF drainage < 120 ml/day (<5 ml/hour)

TIL 3 – Moderate
- Higher doses of osmotic therapy
- Moderate hypocapnia ($PaCO_2$ 4.0-4.5 kPa; 30-35 mmHg)
- Mild hypothermia (> 35 °C)
- CSF drainage ≥ 120 ml/day (>5 ml/hour)

TIL 4 – Extreme
- Profound hypocapnia ($PaCO_2$ < 4.0 kPa; < 30 mmHg)
- Hypothermia < 35 °C
- Metabolic suppression for control of ICP
- Surgery for refractory ICP (decompression, lobectomy)

Appendix 8 Network meta-analysis for indirect treatment comparisons

Reference is made to a network meta-analysis [Dayyany, 2022] that tests the efficacy of prophylactic therapies for aSAH.

The literature search of the referenced network meta-analysis stopped in February 2020; therefore, an update was performed on Medline according to the same strategies from February 2020 to December 2022.

The search strategies are reported below.

Appendix 9 Fisher Scale

Fisher Grading Scale

Group	Appearance of blood on head CT scan
1	No blood detected
2	Diffuse deposition or thin layer with all vertical layers
3	Localized clot and/or vertical layers 1 mm or more in thickness
4	Intracerebral or intraventricular clot with diffuse or no subarachnoid blood

Fisher. Neurosurgery. 1980 Jan;6(1):1-9.

Search strategies

PUBMED

Search query:

((("clinical trial"[All Fields] OR "clinical trials as topic"[All Fields] OR "clinical trial"[All Fields]) AND ("intracranial aneurysm"[All Fields] OR ("intracranial aneurysm"[MeSH Terms] OR ("intracranial"[All Fields] AND "aneurysm"[All Fields]) OR "intracranial aneurysm"[All Fields])) AND ("subarachnoid hemorrhage"[All Fields] OR ("aneurysmal subarachnoid haemorrhage"[All Fields] OR "subarachnoid hemorrhage"[MeSH Terms] OR ("subarachnoid"[All Fields] AND "hemorrhage"[All Fields]) OR "subarachnoid hemorrhage"[All Fields] OR ("aneurysmal"[All Fields] AND "subarachnoid"[All Fields] AND "hemorrhage"[All Fields]) OR "aneurysmal subarachnoid hemorrhage"[All Fields])) AND ("vasospasm intracranial"[All Fields] OR ("vasospasm, intracranial"[MeSH Terms] OR ("vasospasm"[All Fields] AND "intracranial"[All Fields]) OR "intracranial vasospasm"[All Fields] OR ("cerebral"[All Fields] AND "vasospasm"[All Fields]) OR "cerebral vasospasm"[All Fields])) AND ((("clinical trial"[All Fields] OR "clinical trials as topic"[All Fields] OR "clinical trial"[All Fields]) AND ("intracranial aneurysm"[All Fields] OR

("intracranial aneurysm"[MeSH Terms] OR ("intracranial"[All Fields] AND "aneurysm"[All Fields]) OR "intracranial aneurysm"[All Fields])) AND ("subarachnoid hemorrhage"[All Fields] OR ("aneurysmal subarachnoid haemorrhage"[All Fields] OR "subarachnoid hemorrhage"[MeSH Terms] OR ("subarachnoid"[All Fields] AND "hemorrhage"[All Fields]) OR "subarachnoid hemorrhage"[All Fields] OR ("aneurysmal"[All Fields] AND "subarachnoid"[All Fields] AND "hemorrhage"[All Fields]) OR "aneurysmal subarachnoid hemorrhage"[All Fields])) AND ("vasospasm intracranial"[All Fields] OR ("vasospasm, intracranial"[MeSH Terms] OR ("vasospasm"[All Fields] AND "intracranial"[All Fields]) OR "intracranial vasospasm"[All Fields] OR ("cerebral"[All Fields] AND "vasospasm"[All Fields]) OR "cerebral vasospasm"[All Fields])))) AND (2020/2/1:2022/12/31[pdat])

Results 10

Ten new references were identified, none of which were suitable for the objective of the network meta-analysis.

Therefore, for the network meta-analysis, trials using nimodipine, cilostazol or fasudil (the usual comparator for cilostazol) as prophylaxis in at least one arm of the study were selected. Concerning the outcome as per the main objective of the CASH study (mRS assessed at six months, where the favourable outcome is defined as the mRS score of 0 to 2, and unfavourable outcome of 3 to 6) for the studies where the assessment was made using the GOSE scale, the results were converted as in Table S1. The meta-analysis was performed with MetaXL Version 5.3 (EpiGear International Pty Ltd -ABN 51 134 897 411 Sunrise Beach, Queensland, Australia, 2011-2016), a fixed-effects model was used, and the method for calculating the weighted average effect was the inverse of variance heterogeneity. The global heterogeneity of the model was assessed using the H inconsistency index H is the estimated residual variance of the standardized treatment effect estimates against the inverse standard error in each synthesis (Higgins and Thompson 2002); The interpretation is that H <3 indicates minimal inconsistency of treatment effects (the minimum possible H is 1). Values between 3 and 6 indicate modest network inconsistency and values > 6 suggest gross network inconsistency

Table S1: GOSE vs mRS conversion table

Modified Rankin Scale (mRS)	Glasgow Outcome Scale (GOS)
0 - No symptoms. 1 - No significant disability. Able to carry out all usual activities, despite some symptoms. 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.	4 - Moderate disability 5 - Low disability
3 - Moderate disability. Requires some help, but able to walk unassisted. 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted. 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent. 6 - Dead.	1 - Death 2 - Persistent vegetative state 3 - Severe disability

Tables S2a, S2b, S2c and S2d shows the characteristics of the trials included in the network meta-analysis and the risk of bias assessment.

Table S2a: Characteristics of the trials included in the network meta-analysis

Ref	Study (year)	Location	Setting	Age (yr)	Gender (female %)
1	Petruk (1988)	17 centers in Canada	Multicenter	54.9	66.6
2	Pickard (1989)	UK	Multicenter	47.0	60.1
3	Ohman (1991)	Finland	Single-center	45.1	51.4
4	Shibuya (1992)	60 centers in Japan	Multicenter	55.0	56.0
5	Zhao (2006)	5 centers in China	Multicenter	50.1	61.1
6	Zhao (2011)	5 centers in China	Multicenter	50.0	61.2
7	Suzuki (2011)	5 centers in Japan	Multicenter	63.0	76.0
8	Sembokuya (2013)	7 centers in Japan	Multicenter	60.6	62.4
9	Matsuda (2016)	5 centers in Japan	Multicenter	58.5	67.5

Table S2b: Treatment characteristics of trials and outcomes included in the network meta-analysis

Ref	Study (year)	Experimental arm	Pts. Nb	Dose	Duration (days)	Control arm	Pts. Nb	Dose	Duration (days)	Outcomes	Concomitant treatment	Length follow-up
1	Petruk (1988)	Nimodipine	91	90mg/q 4h	21	placebo	97	-	-	Mortality, Vasospasm, DCI, GOS	Hypervolemia and hypertension	3 months
2	Pickard (1989)	Nimodipine	278	30mg/q 4h	21	placebo	276	-	-	Mortality, DCI,GOS	-	3 months
3	Ohman (1991)	Nimodipine	104	Iv 5mcg/kg/min then 60 po	21	placebo	109	-	-	Mortality, DCI, GOS	-	3 years
4	Shibuya (1992)	Fasudil	136	30mg iv	136	placebo	140	-	-	Mortality, Vasospasm, DCI, GOS	-	1 months
5	Zhao (2006)	Fasudil	37	30 mg iv	14	Nimodipine	35	1 mg/h iv	14	Mortality, Vasospasm, DCI, GOS	-	1 months

6	Zhao (2011)	Fasudil	63	30 mg iv	14	Nimodipine	66	0.5-1 mg/h then 1-2 mg/h iv	14	Mortality, DCI, GOS	-	1 months
7	Suzuki (2011)	Cilostazol	49	200mg/d	14	Control	51	-	-	Mortality, DCI, mRS	Triple H therapy, fasudil hydrochloride and/orozagrel Na	14 days
8	Sembokuya (2013)	Cilostazol	54	200mg/d	14	Control	55			Mortality, Vasospasm, DCI, GOS	Fasudil hydrochloride	6 months
9	Matsuda (2016)	Cilostazol	74	200mg/d	14	Placebo	74			Mortality, Vasospasm, DCI, GOS	Fasudil hydrochloride	3 months

Table S2c: Summary of risk of bias assessment for included trials in the network meta-analysis

Ref	Study (year)	Sequence generation Study (year)	Allocation Concealment	Blinding of Participants	Blinding of health care providers	Blinding of Outcome Assessment	Missing participant data	Selective reporting	Source of Funding
1	Petruk (1988)	Low	Low	Low	Low	Low	Low	Low	No funding statement
2	Pickard (1989)	Low	Low	Low	Low	Low	Low	Low	Industry
3	Ohman (1991)	Low	High	Low	Low	Low	Low	Low	No funding statement
4	Shibuya (1992)	Low	High	Low	Low	Low	Low	Low	No funding statement
5	Zhao (2006)	Low	High	High	High	High	Low	Low	No funding statement
6	Zhao (2011)	Low	High	High	High	High	High	Low	No funding statement
7	Suzuki (2011)	Low	High	High	High	Low	Low	Low	No funding statement
8	Sembokuya (2013)	Low	Low	High	High	Low	Low	Low	No funding statement
9	Matsuda (2016)	Low	Low	Low	High	Low	Low	Low	No funding statement

Table S2d: Trials selected for network meta-analysis and events for each study arm favourable outcome at the longest follow-up

			Active			Control		
Active	**Control**	**Study name**	**Nb**	**Cases**	**Non-cases**	**Nb**	**Cases**	**Non-cases**
Nimodipina	Placebo	Petruk,1988	72	28	44	82	28	54
Nimodipina	Placebo	Pickard, 1989	278	223	55	276	185	91
Nimodipina	Placebo	Ohman, 1991	104	86	18	109	86	23
Fasudil	Placebo	Shibuya, 1992	136	98	38	136	95	41
Fasudil	Nimodipina	Zhao, 2006	33	27	6	34	28	6
Fasudil plus Nimodipine	Nimodipina	Zhao_2, 2011	55	49	6	60	48	12
Cilostazol plus Fasudil	Fasudil	Suzuki, 2011	49	39	10	51	24	27
Cilostazol plus Fasudil	Fasudil	Sembukuya, 2013	54	39	15	55	36	19
Cilostazol	Placebo	Matsuda, 2016	74	60	14	74	61	13
			855	**649**	**206**	**877**	**591**	**286**

The results of the network meta-analysis versus nimodipine are shown in Table S3 and Figures S1 and S2.

The model shows excellent consistency (H=1.0). The interpretation is that H <3 indicates minimal inconsistency of treatment effects (the minimum possible H is 1). Values between 3 and 6 indicate modest network inconsistency and values > 6 suggest gross network inconsistency.

Table S3: Network meta-analysis vs nimodipine

ID	Comparison	Active	Control	OR	LCI 95%	UCI 95%
	Direct estimates					
1	Nimodipine vs Placebo	Nimodipine	Placebo	1.655	1.226	2.235
2	Fasudil vs placebo	Fasudil	Placebo	1.113	0.659	1.879
3	Fasudil vs Nimodipine	Fasudil	Nimodipine	0.964	0.277	3.362
4	Fasudil plus Nimodipine vs Nimodipine	Fasudil plus Nimodipine	Nimodipine	2.042	0.709	5.880
5	Cilostazol plus Fasudil vs Fasudil	Cilostazol plus Fasudil	Fasudil	2.337	1.283	4.257
6	Cilostazol vs Placebo	Cilostazol	Placebo	0.913	0.396	2.105
	Indirect estimates (source IDs)					
7	Indirect Cilostazol plus Fasudil vs Nimodipine (5, 3)	Cilostazol plus Fasudil	Nimodipine	2.253	0.564	9.007

8	Indirect Placebo vs Nimodipine (2, 3)	Placebo	Nimodipine	0.866	0.224	3.357
9	Indirect Fasudil vs Nimodipine (2, 1)	Fasudil	Nimodipine	0.672	0.368	1.230
10	Indirect Cilostazol vs Nimodipine (6, 1)	Cilostazol	Nimodipine	0.552	0.227	1.340
	Result estimates (source IDs)					
	Placebo (1, 8)	Placebo	Nimodipine	0.614	0.458	0.824
	Fasudil (3, 9)	Fasudil	Nimodipine	0.720	0.418	1.240
	Fasudil plus Nimodipine (4)	Fasudil plus Nimodipine	Nimodipine	2.042	0.709	5.880
	Cilostazol plus Fasudil (7)	Cilostazol plus Fasudil	Nimodipine	2.253	0.564	9.007
	Cilostazol (10)	Cilostazol	Nimodipine	0.552	0.227	1.340

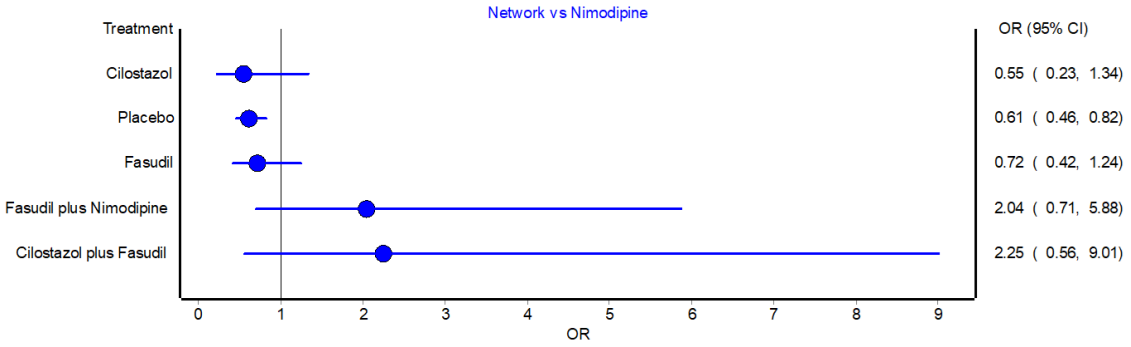


Figure S1. Forest plot

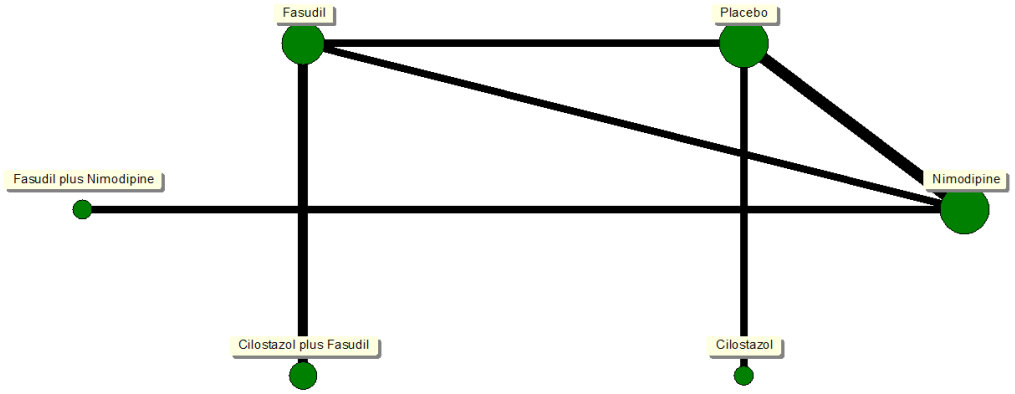


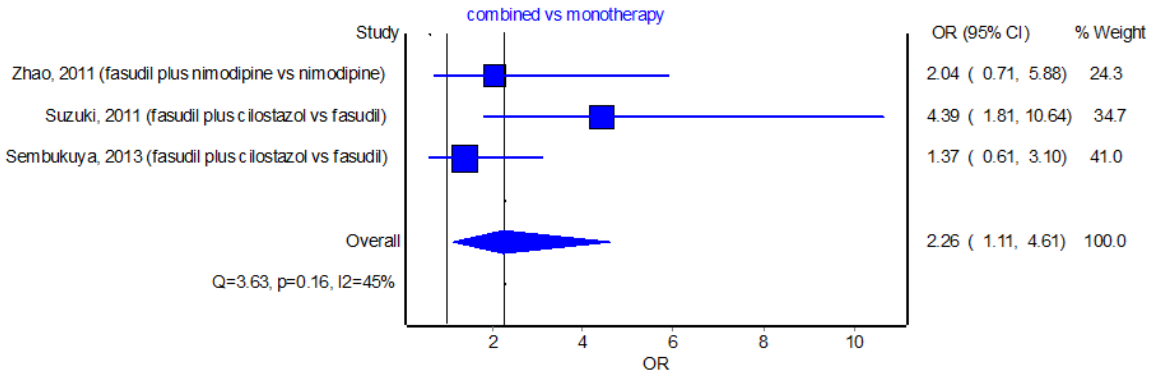
Figure S2. Network plot

The network meta-analysis versus nimodipine, where the outcome is the patient's status at six months, shows a non-inferiority of fasudil versus nimodipine (OR=0.720; 95% CI unilateral lower bound =0.050).

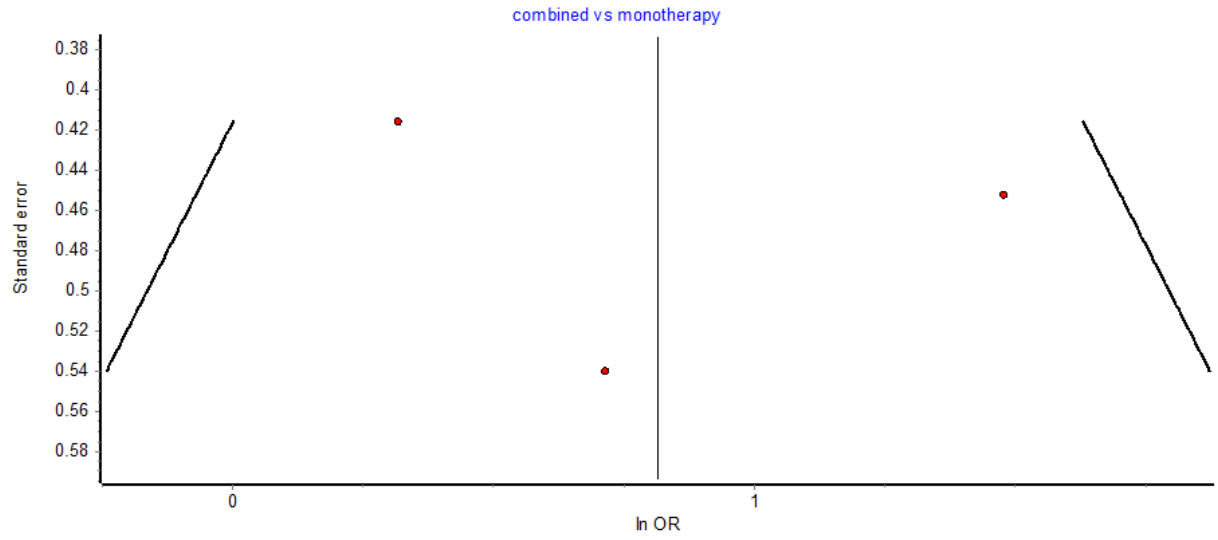
The efficacy trend of the combination of fasudil plus cilostazol (OR= 2.25; 95% CI unilateral lower bound=0.705) and fasudil plus nimodipine (OR=2.04; 95% CI unilateral lower bound=0.840) compared to treatment with nimodipine alone appears to be sharper.

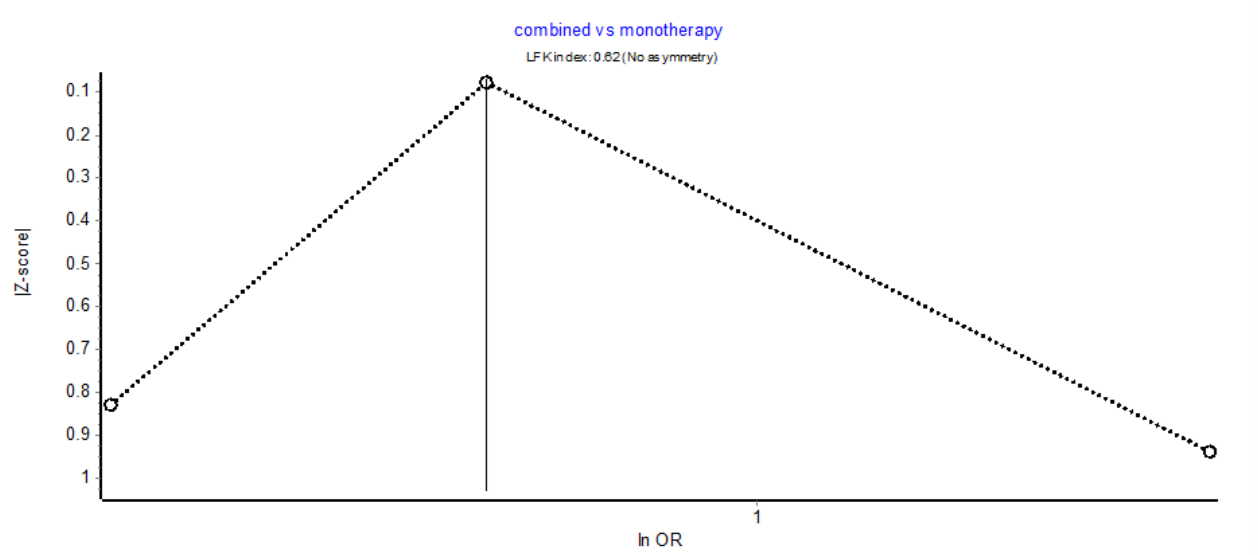
Considering that in both Japan and China, the standard prophylaxis after SAH is fasudil plus cilostazol, considering only trials evaluating combination versus monotherapy with nimodipine or fasudil, the greater efficacy of combination therapy is apparent.

The results of the meta-analysis and the forest plot are reported below. A low heterogeneity was found (I2=0.45; p=0.16); therefore, the inverse variance heterogeneity model was applied (Doi, 2015)



Study	OR	LCI 95%	UCI 95%	Weight (%)
Zhao_2, 2011 (fasudil plus nimodipine vs nimodipine)	2.042	0.709	5.880	24.322
Suzuki, 2011 (fasudil plus cilostazol vs fasudil)	4.388	1.809	10.641	34.665
Sembukuya, 2013 (fasudil plus cilostazol vs fasudil)	1.372	0.608	3.099	41.013
Pooled	2.261	1.108	4.614	100.000
Statistics				
I-squared	44.9			
Cochran's Q	3.63			
Chi2, p	0.163			





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